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We are Consistently Working on Building Contract Partnerships page 80

Theme of the Issue: **Pharmaceutical Market Potential**

No 1 (2) / Spring 2018

CIS GMP news

EAEU & CIS PHARMACEUTICAL INDUSTRY AND CURRENT GMP TRENDS REVIEW

Aspectus Pharma -
2 years from the idea and project to the enterprise ready for audit

see page 64

with the support of:

Pharmaceutical industry in Russia in 2017

As of the end of 2017, within the Russian Federation territory there were

540

valid manufacturing licenses*, which corresponds to

699

manufacturing sites in

71

regions

Out of them:

4

perform secondary packaging only

0,7%

** The license may be issued for several types of activities or for several sites (e.g. one license for manufacture of APIs and finished dosage forms)*

150

produce radiopharmaceutical products, medical gases or medical leeches

27,6%

Out of them:

129 medical gases only

8 leeches only

390

produce finished dosage forms and APIs

71,7%

Out of them:

342 finished dosage forms and APIs

48 APIs only

GMP news

Based on the results of license control and on the applications from drug manufacturers

130

licensees hold

148

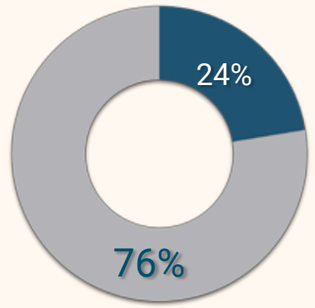
valid certificates of compliance with **GMP** at manufacturing sites

As per Rosstat Order No. 240 of of 14 April 2017

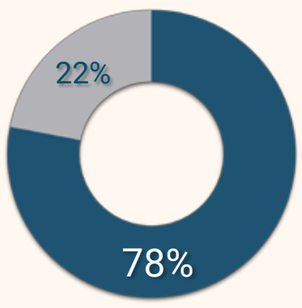
Legal entities (except small-business enterprises) holding a drug manufacturing license and performing drug release are to submit quarterly data about manufacture, shipment and prices for drugs as per form No. 2 LEC (ind.).

Manufacturing sites with a GMP certificate

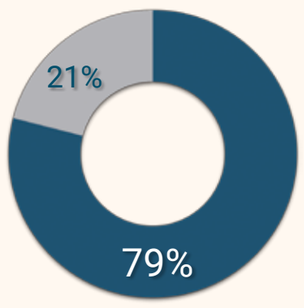
Manufacturing sites without a GMP certificate



Share of GMP certificate holders out of the total number of manufacturing license holders



Percentage of production volumes in monetary terms*



Percentage of production volumes in physical terms**

** assessment-wise, preliminary data for 2017. Russian GMP certificate only.

Information provided by Ministry of Industry and Trade of the Russian Federation and FSI "State Institute of Drugs and Good Practices"

MINPROMTORG RUSSIA

Pharmaceutical Industry Magazine

CIS GMP News

Specialized publication dedicated to Good Manufacturing Practice, modernization of pharmaceutical production, and modern pharmaceutical manufacturing technologies

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CIS GMP News
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Dear reader,

Pharmaceutical industry is one of the fastest developing sectors of industry in the whole world, including the EAEU countries. Events in EAEU region, and numbers characterizing national markets clearly show us that. This Spring issue of CIS GMP news delves into the current state of pharmaceutical industry, and is highlighting the achievements in the field of pharmaceutical production. On the pages you are holding in your hands, pharmaceutical experts try to uncover and point our attention to subjects of inspectorate, regulatory issues regarding the single market of medicines, API production, etc. We are going to keep current with the discussion in our forthcoming issues of CIS GMP news, also inviting other experts to join the conversation.

GMP inspections is a subject that is of interest to practically every our reader. This time, with the help of The State Institute on Drugs and Good Practices, we were able to publish an article about the international work of Russian inspectorate. It contains numbers, facts, and plans for the future. We are very grateful for the information given to us, and we are very glad to share it with you.

I would like to specifically acknowledge the interview with the Executive Director of Aspectus Pharma Valeriy Semenov. Aspectus Pharma is a new facility that was built from scratch in two years, and it deserves the highest mark of appreciation. The ambitious goals put forth by the "Euroservis" Group of Companies, subsidiary of which is Aspectus Pharma, are worth the attention, and from our side we are going to write about the accomplishments of the facility in the next issues of our publication.

Contract Manufacturing got its own category, and it is not for nothing. Throughout the whole world, contract manufacturing in pharmaceutical industry grows because of the need for modern GMP-compliant manufacturing capacities. We would like to welcome interested companies to tell us about their interests and opportunities. We are planning to expand and develop our contract manufacturing information platform with Pharmcontract GC, with support from our exclusive partner Rafarma.

On behalf of Editorial board, please allow me to say thank you to authors, experts, specialists, PR representatives of companies, translators, consultants, and everybody else who prepared and provided us with great, unique material to publish. Special thanks goes to my colleagues who helped to make the Spring issue of CIS GMP news happen.

Big thanks to our partners! It is very simple – without their help, the magazine issue could not come to life. We value our partnership very much, and we are sincerely hoping that this issue is going to be much better and more interesting than the previous.

We are looking forward to cooperating with you!

Vyacheslav Fedorenko
Editor-in-chief

Contents

Russia Pursues to Regulate Healthcare through Antitrust Instruments

What does the Roadmap for Development of Competition in Healthcare propose?

2 March 2018

Maria Borzova
Counsel, Trubor Law firm

INTRODUCTION

The regulatory ecosystem in healthcare is complex and requires careful approach. The existing experience in Russia is unique due to the strong position of antitrust service in the field of healthcare protection. Some market participants widely criticize such an approach, other – actively support the initiatives of the antimonopoly body. However, at the end of the day it is most importantly, whether the patients may benefit from the relevant proposals. Therefore, let's look at the announced regulatory scenarios in more detail.

On January 12, 2018 the Russian Government signed the Decree No. 9-r, which approves the Roadmap for Development of Competition in Healthcare (the Roadmap). Earlier in December 2017, the Russian President approved the National Plan for the Development of Competition, which created a pathway for adopting such sector specific documents.

The Roadmap covers 4 basic markets: medicines, medical devices, medical services, and food supplements. The Roadmap shows anticipated regulatory steps, form of amendments; stakeholders lists and timelines for elaboration of the relevant regulatory concepts.

In this article, we will focus on the most essential instruments suggested by the Roadmap in relation to medicines, as today the regulatory development of the pharmaceutical sector remains one of the governmental priorities.

For the purposes of the competition development on the pharmaceutical market, the Roadmap concentrates on the following key regulatory areas:

(a) improvement of the regulatory pathway for the registration of pharmaceuticals;

(b) alteration of the pricing regulations for vital and essential medicines;

(c) enhancing the functioning of interchangeability concept;

(d) alignment of the state procurement regulations;

(e) verification of the intellectual property regulatory framework.

Below we provide more detailed analysis of the outlined groups of the legislative proposals. Apart from describing the main regulatory steps set forth in the Roadmap in relation to pharmaceutical products, we will also look at the possible general implications of these initiatives for the pharmaceutical manufacturers, patients, and healthcare system as a whole.

SHORT-TERM AND MID-TERM COMPETITION DEVELOPMENT PLANS: WHERE ARE THE PITFALLS?

When reading the Roadmap, the pharmaceutical manufacturers should carefully study the background of each initiative for the purposes of risk assessment. Sometimes the background may provide the necessary details which may help to better understand the logic of the antimonopoly body which stands behind the relevant Roadmap provisions. The individual product profiles of the pharmaceutical companies may also influence the individual estimation of the Roadmap proposals.

The Roadmap suggests a number of other regulatory steps, which in conjunction with the listed proposals may influence the development of regulatory framework in the near future. Therefore, we recommend keeping an eye on the development of the relevant proposals by the responsible regulatory bodies inter alia through the Internet portal ***http://regulation.gov.ru***.

The Roadmap suggests certain additional regulatory initiatives, which in light of the pending regulatory

Key Roadmap suggestions covered by interchangeability umbrella.

REGULATORY ISSUE	TIMELINES	RESPONSIBLE STAKEHOLDERS	FORM OF AMENDMENTS	POSSIBLE IMPLICATIONS
Formation of register of template instructions for use (IFU) for interchangeable drugs	January'19	Ministry of Health Ministry of Industry and Trade Federal Antimonopoly Service	Draft Order of the Ministry of Health	May influence state procurement procedures as well as advertising practice. Therefore, we recommend closely monitoring the relevant developments
Obligatory alteration of all IFU within one INN[1] if the data on side effects and contraindications changes (respective liability for non-compliance)	October'18	Ministry of Health Federal Antimonopoly Service	Draft Federal Law	The proposals for the unification of instructions for use might in theory influence the purchasers' ability to describe the medicines in state tenders
Requirement for the EDL Formation Commission to analyze information on all medicines, included on the EDL[2], and having equivalent indications for use during consideration of new submissions	August'18	Ministry of Health Ministry of Economic Development Federal Antimonopoly Service	Draft Governmental Resolution	In theory, this may influence the patients' access to the second-generation products. However, at this stage, it is difficult to predict the possible practical effects
Determining the equivalence of the dosage forms, registered prior to approval of the Ministry of Health Order dated 27 July 2016 No. 538n, to prevent the unfair competition based on the differences in names of the dosage forms	December'18	Ministry of Health Ministry of Industry and Trade Federal Antimonopoly Service	Draft Order of the Ministry of Health	The list of equivalent dosage forms may be critical for application of the Ministry of Health Order dated 26 October 2017 No. 871n "On Approval of the Procedure for Determining the Initial (Maximum) Tender Price, Price of a Contract Concluded with a Sole Supplier (Contractor, Provider) During Procurement of Medicines" (i.e. application of "reference pricing" in state procurement). Therefore, we recommend to perform the risk assessment and verify the profiles of the individual products
Examination of the local registration files of the medicines for comparison with foreign registration files, as well as examination of the registration files for reference and follow-on products registered in Russia	August'19	Ministry of Health Ministry of Economic Development Federal Antimonopoly Service	Report to the Russian Government	The results of the relevant comparison may be used by the FAS[3] for the purposes of advertising control, state procurement control, and inclusion of the medicines into reimbursement lists (as well as further elaboration of associated amendments)

[1] International non-proprietary name of a medicine.
[2] Essential Drugs List.
[3] Federal Antimonopoly Service.

REGULATORY ISSUE	TIMELINES	RESPONSIBLE STAKEHOLDERS	FORM OF AMENDMENTS	POSSIBLE IMPLICATIONS
Compulsory Licensing: amendments to article 1360 of the Russian Civil Code to enable the Russian Government to authorize the usage of the invention without the consent of a patentholder in order to lower the prices for medicines, protected by patents, and necessary to defeat the epidemic, threatening the national security	December'18	Federal Antimonopoly Service Ministry of Health Ministry of Industry and Trade Ministry of Education and Science Rospatent	Draft Federal Law and Draft Governmental Resolution	Since 2014, the FAS has been actively discussing the compulsory licensing instruments. Moreover, on 26 July 2017, the Russian President signed the Federal Law "On Approval of the Protocol Amending the TRIPS" No. 184-FZ, which enables the usage of compulsory licenses for export purposes. Compulsory licensing remains one of the most controversial legal instruments, usage of which may be associated with various risks for the healthcare system and the whole economy. Therefore, we recommend the industry to take active participation in communicating and discussing the relevant risks
Verification of patentability criteria for medicines	September'18	Ministry of Economic Development Ministry of Education and Science Ministry of Industry and Trade Rospatent Federal Antimonopoly Service	Report to the Russian Government	The existing patentability criteria generally correspond to the international standards. However, the FAS believes that the "evergreening" issue exists in Russia, thus threatening the healthy competition. In FAS opinion, it is necessary to restrict the patentability criteria for medicines (incl. for new indications for use; therapeutic methods; pharmaceutical combinations; dosage forms; manufacturing methods). This, however, may impair the development of innovations and patients' access to new treatment options

Key Roadmap suggestions in relation to intellectual property (IP).

weaknesses in IP practice may adversely impact the existing regulatory environment for innovations. Therefore, the voice of the innovative manufacturers is critically necessary in the public discussions of the relevant proposals.

The Roadmap suggestions in relation to state procurement, in theory, may bring both positive and negative effect. It is difficult to make any predictions at this stage, as the actual outcome of the proposals much depends upon the wording of the relevant norms. At the same time, assessment of the listed initiatives must be complex as all the Roadmap suggestions are interconnected.

The Roadmap provisions must be also estimated in light of other regulatory initiatives developing in parallel in the Russian pharmaceutical sector. For instance, together with a number of other steps, the Roadmap suggests improving the procedure for registration of essential medicines prices; i.e. eliminate discriminatory approach to the domestic pharmaceutical manufacturers; update the pricing register; eliminate the prices for medicines, which were withdrawn from circulation; provide the up-to-date information on prices (necessary for determining the initial tender prices for medicines) to the state purchasers; elaborate the procedure for annulment of the prices registered on the basis of inaccurate submissions; prevent the unreasonable increases in budgetary expenses due to inclusion of new medicines on the EDL, etc. February 2019 is determined as a checkpoint for elaboration of the relevant proposals. However, these proposals repeat the earlier version of the Roadmap and therefore must be assessed within the framework of pending draft amendments suggested to the pricing regulations, including in terms of timelines.

The Roadmap also contains proposals on the creation of accelerated pathway for the launch of the original medicines, not tested in Russia, on the basis of foreign clinical trials in US, EU, and Japan. January 2019 is determined as a checkpoint for elaboration of the relevant draft law. Although theoretically this may be regarded as a positive plan, it is necessary to monitor the associated regulatory developments and the relevant wording.

CONCLUSIONS

Certain of the Roadmap proposals are already in the process of active discussions and implementation. The other are discussed in offline regime. One of the most important tasks of the industry and the governmental stakeholders is to secure the patients access to the necessary treatment and procure constructive dialogue during performance of the plan set out in the Roadmap. However, it might be not that simple, and strong efforts may be required from all sides to reach the compromise for the benefit of the healthcare system. ■

REGULATORY ISSUE	TIMELINES	RESPONSIBLE STAKEHOLDERS	FORM OF AMENDMENTS	POSSIBLE IMPLICATIONS
Determining clear criteria and conditions for approval of sole suppliers through President or Government regulatory act	February'19	Ministry of Industry and Trade Ministry of Finance Ministry of Health Federal Antimonopoly Service	Draft Federal Law and Draft Governmental Resolution	On the one hand, theoretically this may improve transparency of the state procurement procedures. On the other hand, if restrictively drafted, the relevant proposals may create significant risks for localization processes
Determining that the status of a sole supplier may be available only for medicines, not having analogues in Russia	February'19	Ministry of Industry and Trade Ministry of Finance Ministry of Health Federal Antimonopoly Service	Draft Federal Law and Draft Governmental Resolution	Today, the law does not restrict the sole supplier status to the medicines not having local analogues. Inter alia, the lack of such restrictions today is connected with the necessity to create incentives for the investors in the pharmaceutical sector. However, in theory, this proposal may lower the attractiveness of the localization and direct long-term supply agreements in Russia as well as generally affect the investment climate
Restricting the opportunities for entering into long-term supply arrangements, including the possibility of concluding a long-term supply contract only in relation to the medicines protected by patents, provided that significant rebates are set out in such contracts. Restricting the term of such a contract by the patent expiration date or the date of the market launch of a product, having the same indications for use	June'19	Federal Antimonopoly Service Ministry of Finance Ministry of Health Ministry of Industry and Trade	Draft Federal Law	Long-term supply contracts are widely regarded as a possible "ecologic" alternative to the restrictive governmental initiatives. However, these proposals of the Roadmap might lower the attractiveness of the relevant instrument and investment incentives

Key Roadmap suggestions in relation to intellectual property (IP).

Igor Falkovskiy
Head of Good Engineering Practice department, Ph.D
FSI "SID & GP"

2 April 2018

Anti – Counterfeiting of Medicines in Russia

Wordings and abbreviations:

- ***CIM – Control Identification Mark** – a carrier of information to be placed on a secondary pack within the Experiment which is generated in accordance with the Guide*
- ***CIM Emitent** – A participant of medicines circulation process who performs the entry of medicinal products into circulation and performs the medicinal products pack marking.*
- ***Circulation of drugs** – development, preclinical trials, clinical trials, expertise, registration, standardization and quality control, production, manufacture, storage, transportation, import, export, advertising, holiday, sale, transfer, use, destruction of drugs.*
- ***Circulation subject** each and every Circulation of drugs participant.*

Medicines falsification and counterfeiting is quite new challenge for Russia. Before 1991, Soviet pharmaceutical market was totally controlled by the state authorities with very few pharmaceutical manufacturers and state owned distribution system. Falsified and counterfeit medicines control was not a big problem. The first falsified medicine has been found on the Russian market in 1997.

The clear definition for the falsified medicine was given by WHO in 1992 which now says: "Medical products that deliberately/fraudulently misrepresent their identity, composition or source". In the Russian legislation, similar definition "falsified medicine" has been introduced in 2004 by an amendment to the Federal Act No. 86.

In 2002, Federal Act No. 184 on technical regulation has set mandatory certification of medicines, meaning that a declaration of conformity must be released by an authorized certification center for every batch. In April 2018, mandatory declaration is going to be canceled. According to the new legislation update, manufacturers will be responsible for introduction of all batches to the market and provision of quality passport and authorized person confirmation to the Federal Service for Surveillance in Healthcare. [1]

On 20 March 2018, Russia has ratified The "Medicrime Convention" signed in Moscow in 2011 by 27 countries. [2] "Medicrime Convention" – is the first international criminal law instrument to oblige States Parties to criminalize:

- the manufacturing of counterfeit medical products;
- supplying, offering to supply, and trafficking in counterfeit medical products;
- the falsification of documents;
- the unauthorised manufacturing or supplying of medicinal products and the placing on the market of medical devices which do not comply with conformity requirements.

The normative documents and their updates listed below regulate the **experiment** on **serialization** and **aggregation**, which is currently being run in Russia.

- Federal Act No. 61 of the Russian Federation of 12 April 2010 "On circulation of medicines" and its updates;
- Executive Decree of the President of the Russian Federation No. 85 of 4 February 2015 and MoH November 2015 Concept of the Federal Information System for Monitoring the movement of medicines from a manufacturer to a final customer by means of marking.
- Decree of the Government of the Russian Federation No. 62 of 24 January 2017 "On the experiment for marking certain types of medicines for medical use with control (identification) marks and their turnover monitoring".
- Methodical Recommendations (Guideline) on the conduction of the experiment for marking certain types of medicines for medical use with control (identification) marks and their turnover monitoring on the Territory of Russian Federation. Minister of Health of Russian Federation. 28 February 2017

According to the Federal Act No. 61 "On circulation of medicines", Chapter 8. Article 46. Point 2:

"…secondary (consumer) pack should contain readable Russian text indicating the name of the medicinal product (INN, or group, or chemical and trade names), the manufacturer name, **batch number**, date of release (for immunobiological drugs), MA number, **expiry date**, way of usage, dosage or concentration, volume, activity or number of doses per package, dosage form, terms of selling, storage conditions, warnings …"

The Federal Act No. 61 "On circulation of medicines" has been updated in the end of December 2017 with a substantial expansion of Chapter 14, related to the information on Medicines. Now, Chapter 14 determines the basics of **The system for medicinal products for medical use traffic monitoring**.

Four of these nine points are of vast importance. Three of them set the duty of the manufacturers and other players – subjects of circulation – to implement the serialization for all medicines starting from 1 January 2020 Application of Marks is mandatory, Info provision to the System is mandatory, and the violations will be prosecuted.

Point 12 says that the government keeps the right to set specific conditions for the System implementation, including deadlines, for the System implementation for the medicines related to the Essential Drug List and & High cost Nosologies program.

In February 2015, the President of Russia has issued the Executive Order for the Stepwise implementation of drugs Monitoring Automated System (from a manufacturer to a final customer) using identification of the drug packages.

In November 2015, MoH has developed the Concept of the Federal State Information System.

In October 2016, RF President Council for strategic development has approved the Passport of the Prioritized Project "Medicines. Quality and Safety".

Protection of the people against falsified medicines and prompt withdrawal of counterfeit and substandard drugs from the circulation are the main targets of the Prioritized Project "Medicines. Quality and Safety".

Governmental Decree No. 62 of January 2017 has officially started the Serialization Experiment in February 2017. Participants of the Experiment:

- Three federal ministries: Ministry of Health, Ministry of Industry and Trade, and Ministry of Finance,
- Three federal services: Federal Service for Surveillance in Healthcare, Federal Customs Service, and Federal Tax Service
- Other Participants of the medicines circulation.

The duration of the Experiment has been prolonged till 31 December 2018 by the Governmental Decree No. 1715 of 30 December 2017.

Therefore the currently set up Project phases are:

Phase I

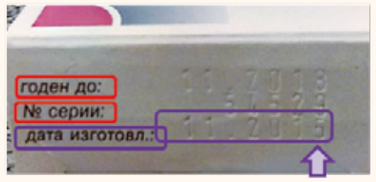
1 February 2017 – 31 December 2018

Serialization Experiment on voluntary basis for the medicines belonging to the group of 7 High Cost Nosologies (7HCN) mainly;

The targets of the ongoing Experiment:

- To determine the efficiency and effectiveness of the System
- To identify the changes that should be made in the legislation docs;
- To determine capabilities and need of further development of the System.

FEDERAL ACT 12 April 2010 No. 61-FZ "On circulation of medicines"



As a rule, manufacturers indicate the date of production (manufacture) as well, 3 requisites in total

FEDERAL ACT 12 April 2010 No. 61-FZ "On circulation of medicines"
Update in **December 28, 2017** via **FEDERAL ACT 425-FL**

Chapter 14.
INFORMATION ON MEDICINES

1. Info on Rx drugs sources specified for specialists in drugs circulation
2. Info on OTC drugs in widely accessed publications and advertisments
3. Info Carriers should provide storage and transmission without corruption

Chapter 14.
INFORMATION ON MEDICINES

THE SYSTEM for MEDICINS TRAFFIC MONITORING

+ nine more points:
4th to 12th

NO	SUMMARY	EFFECTIVE DATE
4	Marks of identification are mandatory	01.01.2020
5	Details of the Marks shall be determined by RF Government	
6	Monitoring System details and operation under Government control	
7	Medicines Circulation Participants provide Info to the System	01.01.2020
8	Interaction between the System and other State information systems	
9	Publicly available System information via Internet	
10	A manufacturer gets System Info related to his products free of charge	
11	Legal responsibility for violations: manufacture, sale without Marks, unreliable information	01.01.2020
12	Government has the right to set specific conditions, including deadlines, for Serialization of EDL & 7Nozologies drugs	!

Phase II
1 January 2018 – 31 December 2019
Mandatory marking of 100% of medicines brought into the Civil Circulation both produced in Russia & outside Russia for the Russian market. Excluding:

- Drugs for clinical trials,
- Drugs produced for export,
- Drugs which are not subjected for State Registration produced by a drugstore or veterinary as per receipt, purchased from abroad for personal usage, approved by authority for movement into RF for vital reasons of a certain person, API, radiopharmaceuticals produced in a hospital,
- Drugs aimed at usage in military actions, emergency situations, curing of chemical, biological and radiological factors

The application of CIM using 2D code is the duty of a manufacturer.

Russian Ministry of Health has developed the **Guideline for the Experiment** that determines and describes the topics listed below

1) The code structure and rules for the formation of the control (identification) marks;
2) Requirements for the equipment used for the application and reading of codes;
3) Requirements for the Information System;
4) The order of information transfer and exchange;
5) The order of interaction between the Information System and the existing resources;
6) Applicants registration procedure
7) Participants interaction including the list and the order of information entering into the system, etc.

The first three items are briefly described below.

1) The code structure and rules for the formation of the control (identification) marks

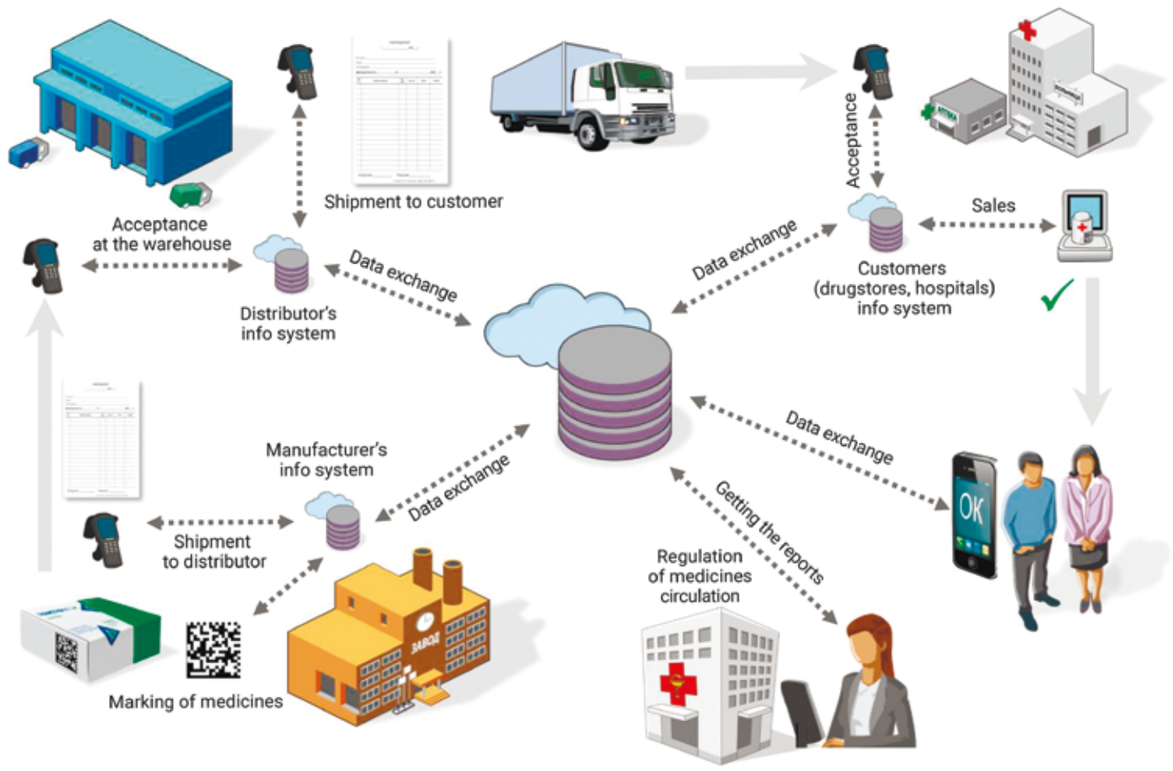
2D DataMatrix code should contain 3 necessary data groups:

- *The first data group* is (GTIN) preceded by the application identifier (01). (14 characters)
- *The second data group* is an individual serial number of a pack preceded by the application identifier (21), randomly generated (14 characters)
- *The third data group* is the FEAC (Foreign Economic Activity Code), preceded by the application identifier (240). (4 characters i.e.-> first 4 symbols of 10-digit FEANC code).

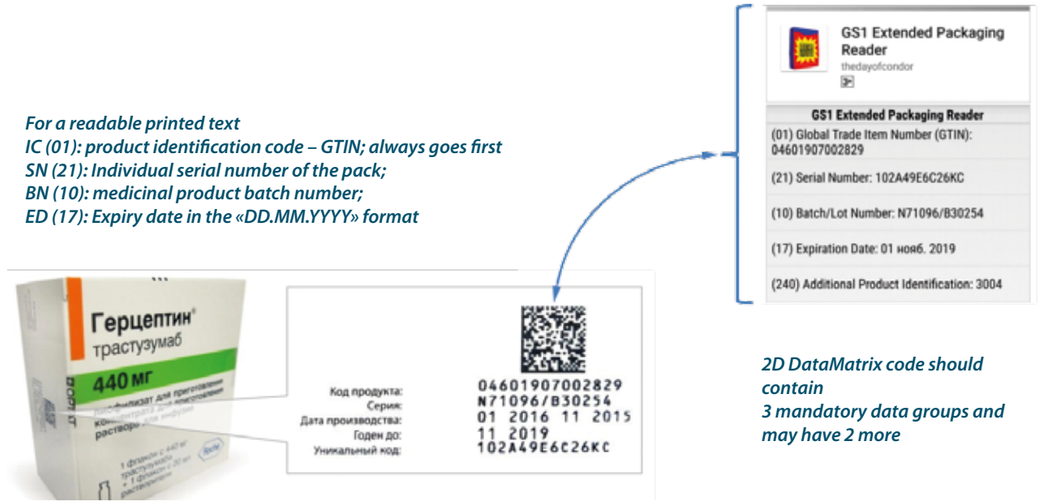
Not necessary are:

- *The fourth data group* is the medicinal product batch number preceded by the application identifier (10)
- *The fifth data group* is the expiry date, which is preceded by the application identifier (17)

For a readable printed text on the



The scheme of interaction between the state authorities, manufacturers, distributors, customers (hospitals & drugstores), and final customers



For a readable printed text
IC (01): product identification code – GTIN; always goes first
SN (21): Individual serial number of the pack;
BN (10): medicinal product batch number;
ED (17): Expiry date in the «DD.MM.YYYY» format

2D DataMatrix code should contain
3 mandatory data groups and may have 2 more

secondary packaging it is recommended to use the following data format:

- C (01): medicinal product identification code – GTIN;
- SN (21): Individual serial number of the secondary pack;
- BN (10): medicinal product batch number;
- ED (17): Expiry date in the DD.MM.YYYY format

In the context of the Experiment, it is acceptable to duplicate the DataMatrix information

As mentioned earlier, Manufacturers often indicate date of production (manufacture) - see pink arrows on the insert. They still keep indicating manufacturing date which makes the number of readable information lines to be five

2) Requirements for the equipment used for the application and reading of codes

- Either printing or labeling
- Upon opening the secondary pack, the organization must register the withdrawal of the medicine out of Circulation. The withdrawn CIM must not be re-used
- Recommended dot size for 2D code is 0,255 – 0,615 mm

CIM application quality

- Application quality should be class C or higher in accordance with ISO 15415 (GOST R ISO/MEK 15415-2012)
- For printing, ECC-200 mistakes correction method should be used
- ASCII codification based on ISO 16022 (GOST R ISO/MEK 16022 -2008) should be used

Equipment for reading must allow reading the codes applied in accordance with ISO 15415 (GOST R ISO/MEK 15415-2012) with dot size for 2D code of 0,255 – 0,615 mm

3) Main requirements for the Information System:

Track & trace System developed by the Federal Tax Service of Russia will be used.

Main Principles:

- Unique CIM for secondary packs of medicines
- Full traceability of a medicine batch, information should be signed with enhanced qualified electronic signature
- Information on each medicine movement from one Circulation subject to another must be accepted (confirmed) by each participant

Medicines Movement Monitoring Component of Information System should:

- allow free Software usage,
- allow all participants the access to information with the possibility of expansion
- storage of all transactions throughout a 5-year period of time
- servers must provide the availability level of 99,9 % (not more than 9 hours of disconnection (shutdown) per year) with 24 hours/7 days per week regime
- recovery time after a shutdown not more than 45 min under the condition of elimination the shutdown cause and keeping the integrity of the software and databases installed on the server (working station)

Governmental Decree No. 189 of **23 February 2018** "On the rules of subsidy to the Russian Foundation For Technological Development for the pharmaceutical manufacturers serialization projects" sets the terms and conditions that must be included into the agreement between the Foundation and a manufacturer who is applying for the subsidy. Necessary subsequent documents are currently being developed.

From the practical point of view the current situation looks as follows:

- The number of Circulation subjects that has joined the Information System has increased from more than 1,380 in the end of January to more than 2,760 in the end of March 2018, including local and international manufacturers, wholesalers, networks, and hospitals.
- More than 9 Mio packs have been already marked within the experiment.
- The overall number of Circulation subjects is 370 thousands. More than 6 Billion packs of medicines circulate on the Russian market annually.

https://pharmvestnik.ru/publs/lenta/v-rossii/kolichestvo-uchastnikov-markirovki.html

- Serialization of medicines will be mandatory for all manufacturers in 2020, but for some types of drugs, including expensive, may become mandatory in 2018. This applies primarily to drugs for seven high-cost nosologies and some expensive medicines for which targeting is important. The relevant Governmental decree is currently being prepared.

http://tass.ru/obschestvo/4877072

International Activities of the Russian GMP Inspectorate

16 March 2018

Results of the GMP inspections of foreign manufacturing sites in 2017

GENERAL INFORMATION ABOUT INSPECTIONS CARRIED OUT IN 2017

In 2017, FSI "SID & GD" carried out inspections for the total of **545** foreign manufacturing sites. As compared with the results for 2016 (**188** inspections in total), the number of the inspections carried out almost tripled.

Based on the results of the inspections carried out, the total number of positive decisions resulting in issuance of the certificate of compliance with GMP requirements was **347**, as of beginning of January 2018. The total number of refusals of issuance of the certificate of compliance for the same period was **103**, while it should be noted that some decisions on the inspections carried out are still being discussed, so the results will only be available later.

The geography of the inspections carried out in 2017, as compared with the previous year, also expanded: the number of countries where inspected manufacturing sites were located increased from 40 to 56. Sampled information about the statistics of the inspections carried out is given in Table 1.

It can be seen that India came down in the list of countries hosting the largest number of inspections making way to Germany. Besides, the number of US-based inspected sites significantly increased as compared with 2016.

RESULTS OF INSPECTIONS

In total, during inspections of foreign manufacturing sites in 2017, **3503** nonconformities were found, including: 266 critical (8%), 1,644 major (47%) and 1,593 minor (45%) nonconformities. The diagram representing classification of nonconformities found in 2017 as per their criticality as well as the relevant data for 2016 are given in Fig. 1.

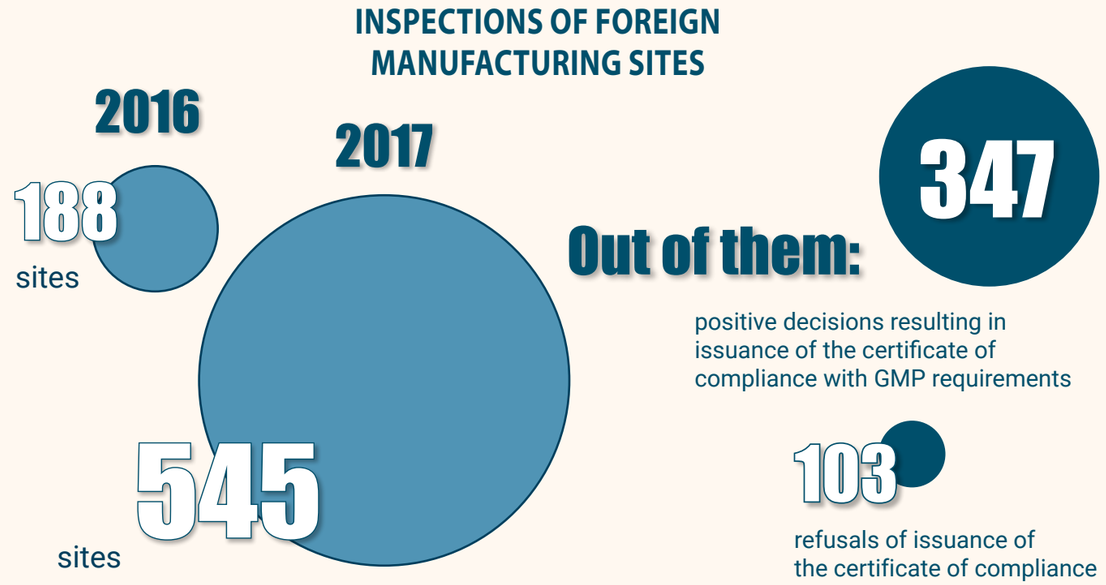
As compared with the results of inspections carried out in 2016, the share of major nonconformities in 2017 obviously increased, while the percentage of detected critical nonconformities remained relatively the same.

CATEGORIZATION OF DETECTED NONCONFORMITIES

Examples of nonconformities detected in 2017:

We would like to focus on the nonconformities which can be found almost at every second manufacturing site. Unfortunately, we still find the cases when the drug product is released by the Qualified Person against the approved normative documentation registered in the Russian Federation. With that, such findings are surprising even for inspection participants responsible for registration activities.

Inspectors continue to detect cases when either finished or intermediate products may be manufactured at sites which are not listed in registration documents. A large number of observations is related to non-fulfillment of process validation principles (initial validation not performed on three consecutive batches, no stability study results, use of not listed process lines for validation).



We witness a rather simplified approach to organization and monitoring of sterile processes (non-fulfillment of the requirements of Annex 1 on particles and bioburden monitoring) as well as execution of a media fill test.

Quite often our foreign partners share the view that the nonconformities detected during inspections of foreign manufacturers differ from the approaches adopted by other countries. If we dig into the process of preparing for an inspection and conducting it by Russian inspectors, we will see that the approaches utilized by the Russian inspectorate are fully in compliance with regulations and standards of the well-developed countries from a regulatory point of view (EU, USA, Japan).

The documents and internal regulations (SOPs) of the Russian GMP inspectorate were created based on PIC/S recommendations and established standards. However, rights of the Russian GMP inspectorate are somewhat different from those possessed by our foreign colleagues. For instance, we cannot immediately stop manufacture in case we find some serious violations. Non-resolved is also the issue of consequences and the actions to be taken by GMP inspectors in case they are denied an access to certain documents, objects, or rooms during a GMP-inspection.

There are also differences in the requirements of Russian Pharmacopeia which impact the results of inspections. Thus, if we compare the most frequent nonconformities with American ones, we

2016		2017	
COUNTRY	NUMBER OF INSPECTIONS CARRIED OUT	COUNTRY	NUMBER OF INSPECTIONS CARRIED OUT
India	31	Germany	108
Germany	14	India	81
Hungary	11	France	45
Slovenia	10	USA	40
Poland	8	Italy	35

Table 1. Statistics for the leading inspection-hosting countries.

can see that the difference is about 30%. Below are the examples of critical and major nonconformities detected during inspections:

- drug product release against the requirements of the registration dossier (e.g. drug release to the market based on the analytical results for the in-bulk product);
- non-correspondence of internal methods used at the facility with the methods listed in the drug registration dossier;
- absence of dedicated isolated areas for storage of rejected / recalled products, as well as of rejected starting materials and excipients (including cases with fully computerized storage systems);
- absence of traceability of the quantity of printed packaging materials with applied variable data destructed during production;
- absence of bioburden control for primary packaging materials (production of non-sterile solid dosage forms) with absence of batch-wise control of finished products as per this parameter;
- non-fulfillment of the requirements of normative documentation for the registered drug product for the conditions of storage of the finished products warehouse (e.g. requirement for a "dry" place in Rus. Ph. 13);
- absence of verification (validation) of time intervals between the end of the production process and equipment cleaning, as well as between the executed cleaning and the start of the next process (dirty hold time / clean hold time).

On the whole, based on the results of inspections, measures are taken to eliminate nonconformities, including activities in the legislative and law-enforcement directions, as well as awareness-building and educational sessions for pharmaceutical manufacturers. In specific critical cases, preventive measures taken by the Russian Ministry of Industry and Trade may include a request to Roszdravnadzor with the recommendations to recall drug products from the Russian Federation market.

PRIORITIES OF GMP INSPECTORATE DEVELOPMENT

At the very beginning of activities by the Russian inspectorate, we could see insufficient preparation for an inspection by manufacturing sites. For many manufacturers, this resulted in refusal of issuance of the certificate of compliance with GMP requirements. Now, inspectors witness more profound preparation by manufacturing sites, which translates into the number of issued GMP certificates. It justifies the importance of an inspection – if a manufacturer holds a certificate issued by experts to support the quality of its products, it is deemed reliable, and the drugs can be used without any doubt.

GMP standards have existed in the world since 1963. Adherence to these principles guarantees that drugs will be manufactured and delivered to consumers with strict abidance by established technologies, meaning that these drugs will be of reliably high quality. This implies that the need in activities by the Russian GMP inspectorate will always be acute as they, firstly, secure provision of patients with safe drugs, and secondly, prove Russia's commitment to drug efficiency objectives.

LEGISLATION OF EAEU COUNTRIES

An important mission of the Russian GMP inspectorate is to implement good practices, and create a professional system of values with experts in the pharmaceutical industry. Besides, we make determined efforts to support Russia's integration to the global pharmaceutical community. Harmonization of EAEU legislation with the best world practices and accession of inspectorates of EAEU member states to PIC/S remain the overarching priorities for the GMP inspectorate development.

It is known that, within the Eurasian Economic Union, the intention is to create a common market of drugs. Russia entered the EAEU on 1 January 2015.

Today, apart from Russia, the EAEU includes four more countries – Belarus, Kazakhstan, Armenia, and Kyrgyzstan.

In December 2014, Russia, Belarus, and Kazakhstan signed the Agreement for Unified Principles and Rules of Drugs Circulation Within the Eurasian Economic Union. In 2015, Armenia and Kyrgyzstan entered into the agreement as well. The agreement establishes unified principles and rules of drugs circulation within the EAEU territory, and creates the basis for functioning of the common market of drugs.

The important measures provided for by this agreement include:

- establishment and implementation of good practices based on the main stages of drugs circulation;
- creation and provision of controls in the field of drugs circulation by means of pharmaceutical inspections;
- creation and maintenance of the common EAEU Pharmacopeia;
- maintenance of the key element of GMP compliance supervision – attestation of Qualified Persons of manufacturers and keeping the register of attested Qualified Persons;
- establishment of unified rules of registration, expert evaluation, etc.

In August 2016, as part of the meeting of the Eurasian intergovernmental council, the leaders of EAEU member states approved the set of documents regulating the field of drugs circulation. In particular, EAEU Good Manufacturing Practice, which is in concordance with EU GMP, was approved.

Creation of the common market of drugs suggests recognition of the results of inspections throughout the EAEU territory.

In this regard, all EAEU member states face major efforts to harmonize the legislation, train inspectors, experts, market players on good practices, create the inspectorate, apply and enter PIC/S, invest in technological advancement of the resource base for testing of drugs.

Implementation of the common inspections system within the EAEU territory is preceded by a transition period. Thus, until the end of 2018, it is allowed to submit a "national" document (i.e. the document issued by the national authority of a EAEU member state) to confirm compliance with GMP, instead of the Union's GMP. Until the end of 2018, it is

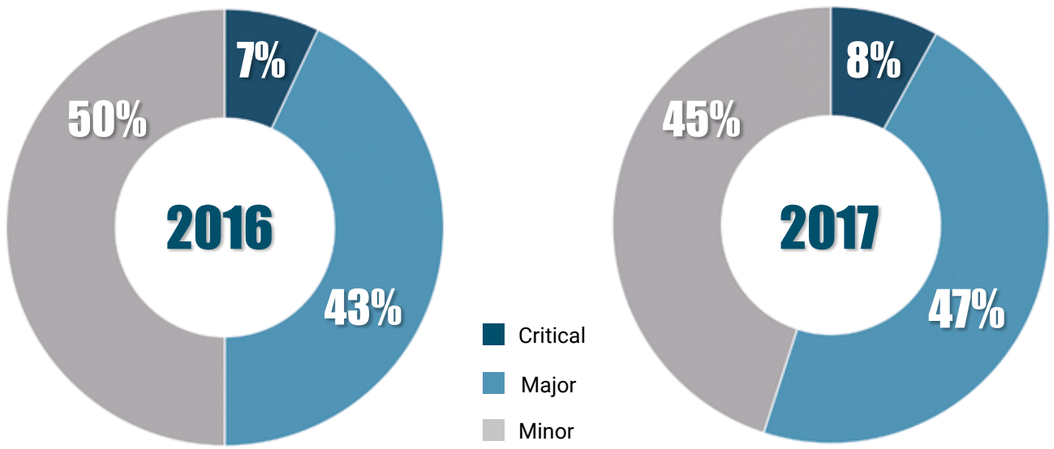


Figure 1. Diagrams of criticality of nonconformities detected in 2016-2017.

CATEGORY	CLASSIFICATION OF DETECTED NONCONFORMITIES	
	CRITICAL	MAJOR
Pharmaceutical quality system	13	66
Personnel	2	20
Procedure of product release by the Qualified Person	3	19
Complaints and recalls	1	14
Facilities and equipment	47	294
Documentation	1	107
Production processes	32	203
Quality control	29	285
Process validation and equipment qualification	51	138
Cross-contamination prevention measures	17	77
Microbial contamination and sterility provision	39	323
Compliance with registration dossier requirements	31	98
Total	266	1644

Table 2. Categorization of critical and major nonconformities detected in 2017 according to Good Manufacturing Practice (GMP).

Vladislav Shestakov
Director of FSI "SID & GP", Deputy Head of State GMP Inspectorate

It is important to expand the horizons, leverage effective experiences, strive for development, and use the best practices. However, it is essential to keep in mind that everybody has one's own path, and it does not matter where this path runs, in which structure it is laid, and which peculiarities it possesses. What is most important is its capability, efficiency, and performance, which can be observed only through practical activity, when all the details of how it works from the inside have been explored.

The reality today is deep consolidation of regulatory experience and its continuous sharing between interested countries and associations. Our Institute, in particular, besides its direct duties, initiates cooperation with inspectors from other countries. For instance, this year a continuously acting working group of EAEU inspectorates is going to launch its operation. Moreover, we continue our teamwork with BRICS countries and activities on Russian inspectorate accession to PIC/S. Formation of mutual trust between inspectorates internationally is the basis stimulating global development and implementation of good manufacturing practices in the pharmaceutical industry throughout the whole world, which is the essence of the GMP philosophy.

also possible to conduct parallel inspections of manufacturers for compliance with the Union's GMP for the purposes of drugs registration.

And by the end of 2020, national manufacturers, within national registration procedures, will be able to confirm GMP-compliance in two ways – both by the document issued by the national authority of the EAEU member state and by the Union's document.

HARMONIZATION ISSUES

Even with availability of a robust and thoroughly controlled system of the drug manufacture quality, today it is impossible to secure 100% control of all pharmaceutical manufacturers globally and hereby provide patients with safe drugs. It is often caused by the impact of various approaches to GMP regulation in different countries, including national pharmacopeias, which complicates recognition of the results of inspections in different countries. When entering new markets, manufacturers are forced to be inspected again and again.

This points to the fact that the current international system of GMP inspections is not perfect.

There is a pressing need in reduction of export-import barriers, a need in harmonization of approaches and standards, as well as in activities aimed at mutual recognition of the results of inspections. In this regard, very important is cooperation between different states aimed at joining the efforts on creation of common global markets of drugs, with the unified quality system controlled by several parties at the same time.

It appears that the key priorities in development of GMP inspections are accession of regulatory authorities of EAEU member states to PIC/S and harmonization of the EAEU legislation with the best global practices.

PIC/S ACCESSION

All EAEU member states, except Kyrgyzstan, in one way or another made attempts to access PIC/S – applications to join this international association were submitted by Belarus, Kazakhstan, Armenia, and Russia.

Belarus is now in the process of joining the inspectorate (the most advanced among all EAEU member states). Together with the EU, Belarus managed to develop a vast program covering advancement of laboratory facilities and changes in the structure of the pharmaceutical regulatory framework.

Having submitted the application, Kazakhstan implemented organizational and staff-wise changes in the structure of the Ministry of Health and the Pharmaceutical Inspectorate. The structure of the regulatory authority is intended to become similar to the US FDA, although it will report to the Ministry of Health, while inspections and expert evaluation of drugs will be carried out by a separate expert authority.

Armenia also has plans on re-organizing the drugs circulation regulatory framework. In the near future, a regulatory authority will be created. It will report directly to the Prime Minister of the country and be responsible for carrying out inspections, issuance of the registration dossier, expert evaluation of drugs and medical devices, etc. – similar to the US FDA.

Kyrgyzstan made no attempts to access PIC/S, although there are plans to change the inspectorate structure and make it similar to that of Kazakhstan. As the pharmaceutical market in this country is rather small and there are few pharmaceutical manufacturers, the number of inspectors is not big.

Finally, Russia submitted a PIC/S pre-accession application in August 2017. Now, major efforts are being made to harmonize the approaches. The authority was pre-audited by independent experts for compliance with PIC/S requirements. The internal documentation and SOPs are now exhibiting high readiness. To implement the plans on PIC/S accession, it is necessary to make amendments to federal legislation.

HARMONIZATION WITHIN EAEU

As noted above, at the end of 2016, EAEU member states approved the standards and principles of the common pharmaceutical market shared by the Union member-states. On 3 November 2016, a set of documents regulating the common market was signed (Decision by the Eurasian Economic Commission No. 73-93).

The adopted common market regulations include the following:

- Rules for registration and expert evaluation of drugs;
- Good pharmaceutical practices in the sphere of drugs circulation;
- Rules for carrying out pharmaceutical inspections;
- Procedure for carrying out joint pharmaceutical inspections;
- General requirements for the quality system of pharmaceutical inspectorates.

Key challenges faced by pharmaceutical inspectorates

At present, there is a need in:

1. Further advancement of joint GMP-regulation in EAEU countries;
2. Establishment of unified approaches to regulation and positions on inspection issues, both on the internal market, and globally:
   - Unified approaches of carrying out inspections;
   - Unified classification of nonconformities;
   - Unified educational standards, training programs for preparation for inspections;
3. Cooperation of inspectorates (carrying out joint inspections, conduct of joint training sessions, consultations on application of GMP-regulations);
4. Drawing up recommendations for inspectorates of EAEU member states;
5. Initiation of improvements of GMP regulations under a simplified procedure in relevant EAEU authorities;
6. Exchange of inspection reports, and creation of a unified base of such reports.

Based on the meeting of the Eurasian Economic Commission held on 16-17 November 2017, a decision was made to create a standing Pharmaceutical Inspections Working Group under the Eurasian Economic Commission.

This Working Group will facilitate:

1. Strengthening of trade, economic, and professional relationships between EAEU member-states.
2. Market curing from disreputable manufacturers.
3. Provision of drugs safety in the countries by improving the quality of manufacture.
4. Creating conditions to increase export opportunities.
5. Enhancing the quality of inspections.
6. Transparency in mutual GMP recognition issues.
7. Decrease of the load on pharmaceutical manufacturers.

The EAEU rules and procedures were initially developed on PIC/S requirements. Nowadays, a Working Group is being formed within the Eurasian Economic Commission on the issues of conducting pharmaceutical inspections for compliance with GMP in the sphere of drugs circulation.

The first meeting of the working group was held on 1 February 2018. Further on, it is planned to hold quarterly enlarged sessions and monthly briefing sessions. The task of this Working Group is to coordinate the activities and harmonize and develop procedures and methods (detailed SOPs). For the time being, what it involves is only GMP documentation, while in the long run similar work is planned to be done for all good practices. ■

ABOUT TRAINING OF INSPECTORS

Training step 1 *– a program of additional professional re-training of experts.*
1. Advanced professional development program "Good Manufacturing Practice – Theory and Practice of GMP/GDP Inspections/ Audits". The program includes theoretical and practical sessions in total of 280 hours.

Steep 2 *– international-level training.*

2. Training at Pharmakon, Danish College of Pharmacy Practice – Collaborating Partner to WHO (Copenhagen), course: "Training of Pharmaceutical Inspectors", including 3 modules: 1 – theory and 2 practical modules at manufacturing sites.

Step 3 *– self-training, continuous training of experts according to approved annual plans. Includes weekly internal workshops and periodic (at least once per quarter) external workshops on specific areas and topics.*

ABOUT INSPECTIONS WITHOUT PRIOR NOTICE IN RUSSIA

Inspections without prior notice in Russia are not provided for by the actual RF legislation.

The exception is cases of unscheduled on-site inspections without listing the scheduled inspection in the annual plan of inspections (uploaded to the RF Prosecution Office web-site) and without notifying the legal entity, provided for by Article 10 and Article 12 of Federal Act No. 294 of 26 December 2008 "On Protection of Rights of Legal Entities...".

QC System of FSI "SID & GP"

Conforms to International Standards

FSI "SID & GP" certified for conformity of the quality control system to international standard requirements ISO 9001:2015 (GOST R ISO 9001-2015)

Source: *gilsinp.ru*

Certificates for conformity of the quality management system accepted by FSI "SID & GP" to international standard requirements ISO 9001:2015(GOST R ISO 9001-2015) were handed out in a ceremony held on February 9, 2018. Vladislav Shestakov, director of the FSI "SID & GP", received the certificates from Natalia Prokofyeva – a representative of the country's largest licensing and expert organization "Russian Register" and head of the Russian Register – Baltic Inspection LLC.

The issued ISO certificates are internationally recognized by the Dutch Council for Accreditation (an IAF member) as well as the International certification network IQNet which includes 37 world's leading certification regulators.

Russian Register's auditors carried out a two-fold certification of the Institute's quality management system in November-December 2017 which demonstrated that the system has been successfully developed and implemented in accordance with the annual plan.

"Leadership of your director who ensured effective interaction and involvement of the entire staff in achieving mutual goals, active teamwork aimed at the analysis, and improvement of every process in the Institute ensured successful certification and conformity of the Institute's quality management system with the requirements of ISO 9001: 2015 (GOST R ISO 9001-2015): it is now properly implemented and fully operational", – said **Natalia Prokofieva** at the ceremony.

In his turn, **Vladislav Shestakov** reiterated the significance of this event for the Institute, *"This step that we just made on the road to the Institute's excellence will no doubt take us to a higher quality level. The certification audit has proven we are moving in the right direction. Let us not forget ,however, that we are only in the beginning of the journey: now that the system has been implemented it is of great importance to ensure its seamless operation and integration in all internal processes"*. ■

National GMP Inspection Practice

for Biotech Pharmaceurticals: Commonalities, Differences, Opportunities

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23 March 2018

The public health policies require regulators in the pharmaceutical environment to ensure all pharmaceuticals on their local market to be manufactured according to Good Manufacturing Practice (GMP) standards. In recent times, emerging countries are setting up their regulatory systems in order to regulate terms and conditions for establishing GMP inspections. Most of the regulations therefore also stipulate an oversight of foreign-based manufacturers supplying pharmaceuticals for the local market.

This article describes the similarities of GMP requirememts and highlights some scientific aspects on recent inspection observations. It complements the global benchmarking, convergence, and mutual reliance / recognition article [1] by discussion of the result of a survey that was performed in summer 2017 on the regulatory systems enabling inspection oversight. It can be demonstrated, that the different agencies are on a journey, which usually ends up in implementing risk based approaches, as it is realized that not every single manufacturing site can be inspected frequently. The reliance on GMP-certificates by recognized domestic inspectorates appears to be the best-in-class procedure in mid and long terms.

1. PROBLEM STATEMENT

In recent times, emerging countries are setting up their regulatory systems in order to regulate terms and conditions for regulatory GMP inspections.

The public has driven regulators in the pharmaceutical environment to ensure all pharmaceuticals on their local market are manufactured according to Good Manufacturing Practice (GMP) standards. Most of the regulations therefore also stipulate an oversight of manufacturers based in foreign countries. Even if it is not explicitly stated, this is done by onsite inspections rather than reliance on inspections by locally recognised authorities. This article complements the global benchmarking, convergence, and mutual reliance/recognition article [1]. It also describes the results of a survey that was performed in 2017 on the regulatory systems enabling inspection oversight.

The aim of this article is to clarify that different stages of development and deployment of regulatory GMP inspections allow for safe and on-time access of medicines in the respective country, and satisfy expectations of public health authorities. It also highlights specific elements in biotech manufacturing.

2. SPECIFIC AREAS FOR CLARIFICATION

We have made a variety of observations in inspections. Different inspectorates rank them differently. Furthermore, some inspections' observations can be a surprise for manufacturers. This article lists examples of scientific interpretations.

Manufacturers often host inspections at a single site multiple times. This usually happens if there are different addresses / company names mentioned in the regulatory dossier of different products, and/or that the scope of an inspection does not include all products at this manufacturing site.

There had also been reports that for a sterile drug products, the API must also be sterile. There are cases known where the registration document indicated that the API is a sterile substance. The root cause here often can be a translation issue.

2.1. Inspections methodology: Harmonized risk assessment and classification of observations

Inspection reports should indicate how the criticality level of each observation relates to compliance issue with the potential impact to patient safety. In the absence of a globally harmonised approach, EFPIA assessed the available definitions of risk classifications by PIC/S, EMA, ISO 13485, Health Canada, Australia, China, South Korea, LRQA, TUEV Sued, and BSI [3]. It is understood that they follow principles of Quality Risk Management set in ICH Q9.

The basic principle in ICH Q9 says that *the evaluation of the risk to quality should be based on scientific knowledge and ultimately link to the protection of the patient*. There are different interpretations according to which the risk ranking does not link to the protection of patents, but just focuses on compliance with the text in the submission.

Analysing literature results in very similar levels of classifications. This can be summarised as follows [3]:

Risk level 1: Critical observation

- A deficiency that has produced, or leads to a significant risk of producing a product which is harmful to the user or patient, and/or
- The manufacturer has engaged in fraud, misrepresentation, or falsification with respect to the product or supporting data.

Risk level 2: Major observation

A non-critical deficiency that:

- Has produced or may produce a product that does not comply with its marketing or manufacturing authorization and/or established specifications;
- Indicates a major non-compliance (e.g. a repetitive or permanent departure from a GMP provision or regulatory expectation);
- Indicates a failure to follow satisfactory procedures for release of batches, or a failure of the authorized person or quality unit to fulfil their required duties; or
- Is a combination of individual deficiencies, none of which may be major on their own, but which may together represent a major deficiency and should be explained and reported as such.

Risk level 3: Other (minor) observation

- A deficiency that cannot be classified as either critical or major, but which indicates a departure from GMP (e.g. isolated instances of non-compliance).

In addition, "recommendations" can be addressed, and should consist of every other notes the inspector may wish to offer with respect to best practices to potentially improve any procedures or processes. These recommendations should not be considered observations, and no formal response from the inspected party is to be required [3].

2.2. Hazards to be addressed in API Biotech manufacturing

In contrast to small molecule, a typical API upstream manufactuing process starts with a working cell bank, which is done in a cascade of serveral steps in the so-called fermentation tank (fig. 1). This needs to be processed under low bioburden conditions, which can be interpreted as "sterile" conditions.

supported by GXP SIDI GP State Institute of Drugs and Good Practices

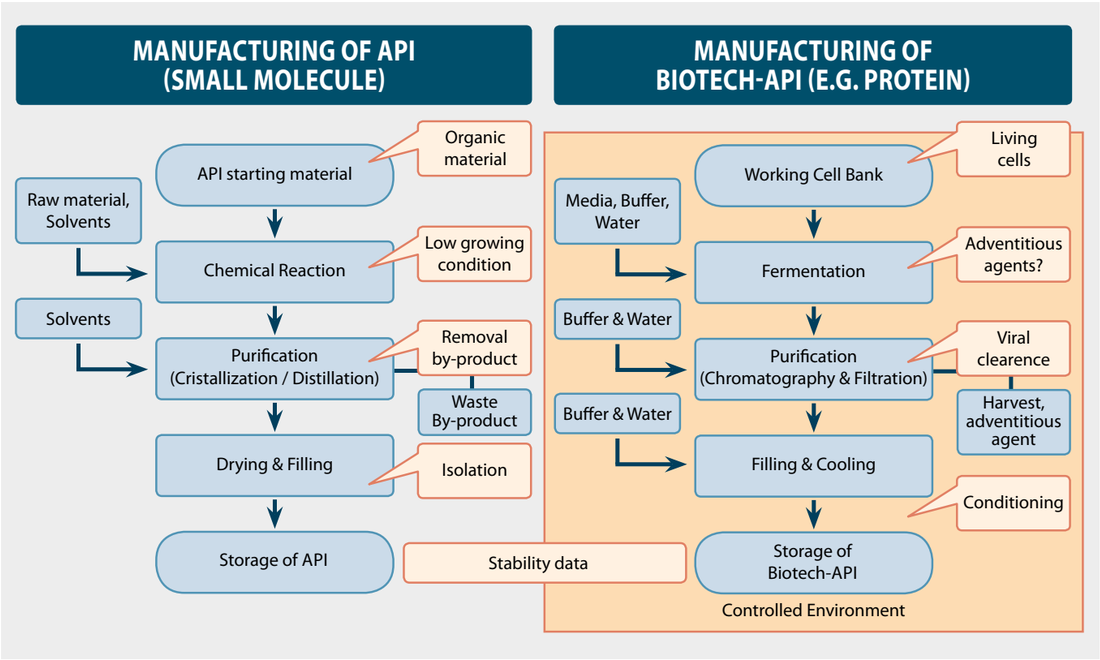

Fig. 1. Differences between a small molecule and biotech process.

Because of these circumstances, some inspectors argue to apply regulations and guidance for sterile products. This section will demonstrate that there can be a misunderstanding on the reason why low bioburden conditions are nessessary.

The applicable regulations and guidance are focusing on the GMPs for API described in Chapter 18 of the ICH Q7 guideline [4]. The ICH Q7 Basic training material developed and performed by the Parenteral Drug Assocuatons (PDA) and the Pharmaceutical Inspection Co-operaton Scheme (PIC/S) describe a risk-based approach on what to consider for such a manufacturing step [5].

The hazard for this fermentation step is the potential growing of adventitious agents, which may be neither detected, nor removed later in the process. Therefore, the risk control strategy needs to address the fact that working with cell banks, media, and buffer represents optimal growth conditions for microorganisms. For this control strategy, low bioburden conditions during manufacturing are required (fig. 2).

Further analysing this potential risk levels which can be addressed at the fermentations step are protection of the patient (level A), protection on manufacturing using working cell bank (level B), and protection of employee and environment (level C). The hazards to be addressed to protect the patients include that impurities need to be reduced, adventitious agents and risks for contamination are controlled, and the Biotech-API (e.g. protein) is stabilized. The protection on manufacturing using working cell bank is fundamental to running the process at all. Without that, the microorganism does not produce the API, and there will be up to no product received. It is also evident that for this risk level, an appropriate control of the master cell bank (see ICH Q5D) and working cell banks needs to be established. Finally, the protection of employee and environment will need to be addressed.

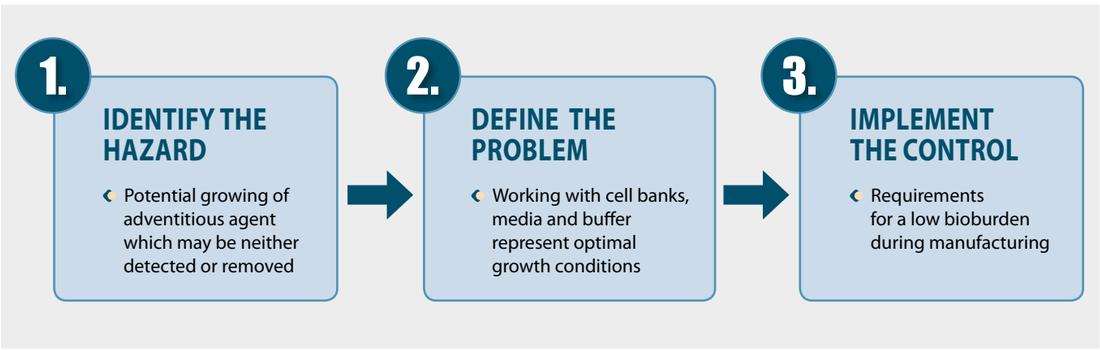

Fig. 2. Hazards and controls in an API biomanufactuing process.

These hazards can represent a risk, which needs to be controlled. Academia and industry have innovated technical solutions, which demonstrated a successful risk control. These measures include, for example:

- Protection of patient on manufacturing of the API-Bulk (level A): Sterility of the (drug (medicinal) product) ensured by the quality built in during manufacturing of the API-bulk (low bioburden)
- Protection on manufacturing using working cell banks (level B): Ensure that the cells are producing the right product by an adequate level of purity and freedom from contamination (low bioburden), e.g. controlling the environment (e.g. physical containment), and
- Protection of employee and environment (level C): By clean room concept, airlocks, and gowning the operators and the environment protections is ensured.

While the risk level C applies thoughout the whole API manufactuing process from the working cell bank towards the API, the protection level B is only applicable in the upstream part of the API manufatcuing (Fermentation), and the level A only in the downstream part starting with the sterile filtration step (fig. 3).

2.3. Disclosure of internal audit reports

Some jurisdictions allow inspectors to have full visibility of all documents related to quality. There is an experience that internal audit reports are demanded to be studied in detail. However, such internal audit reports represent a tool for continuous improvement. It is a common understanding that the entire document is only disclosed, if there are major doubts that the system does not work, and / or to verify due diligence for outsourced activities.

In case the requirement for a Quality Agreement with another legal entity of the company or a contractor applies, the QA should have a right for an audit by the QA for all suppliers of concern. It can be specified in the QMS that this right is usually not executed. However, the access to respective audit reports should be guaranteed.

It is best practice for the format of an internal audit report that there is one cover page with a summary (to show to an inspector) providing, for example:

- A statement that the auditee is accepted, or not
- A list of topics in scope of the audit, which can include e.g., products/group of products, elements of the quality systems etc.
- A signature of the auditor and QA.

Some companies also list the number and ranking of observations with a reference that they are usually followed up in a CAPA system.

3. ABOUT INSPECTION PRACTICES

A small group of colleagues from some Eastern Europe based training programmes, and one info resource on GMP initiated a survey focused on GMP inspection practice worldwide. The questionnaire was circulated in two versions: Russian and English. Accordingly it could be filled in one of the two. It was preceded by a review of the situation (*http://gmpnews.ru/2017/04/praktika-inspektirovaniya-po-gmp/* and *https://gmpnews.net/2017/04/gmp-inspection-practice-a-case-for-global-benchmarking-convergence-and-mutual-reliancerecognition/*). Experts from EFPIA participated in the preparation of the background review and in the development of the questionnaire. The present analysis ought to be considered in conjunction with the above-mentioned publication.

A survey was conducted by the First Moscow State Medical University, Moscow, Russian Federation in 2017. The survey covered the core group of countries forming the Eurasian Economic Union (Russia, Belarus, Kazakhstan), and also important neighbors to EEU: Ukraine and Uzbekistan, as well as countries with stringent sectoral

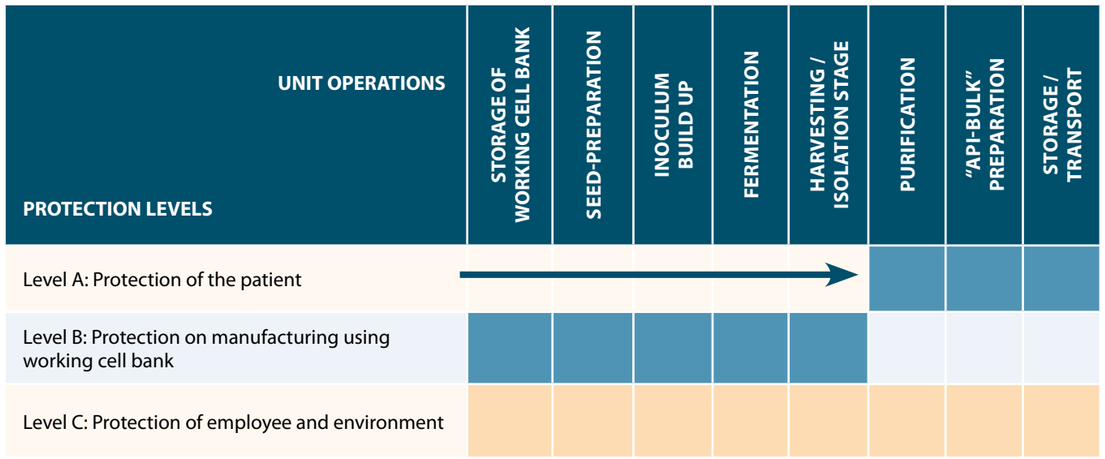

Fig. 3. Level of protection of patient in the Biotech manufacturing, and the protection of employee and environment.

regulatory requirements represented by France and Switzerland. The diversity of approaches is assured by data from two small Central European countries on one side, and India from the Asian area. The authors understand that this is not a statistically significant number of responses. However, it represents a variety of different levels of maturity of the inspectorates as WHO recently highlighted this system [6]. We understand that the elements of the survey can be helpful for emerging inspectorates to get an idea about the pros and cons when optimizing their inspections capacity.

National inspection systems, which in principle operate in accordance with internationally recognized guidelines, differ in fact in many details regarding administrative structures and procedures.

The inspectorates, if established, are organized either in the national government (e.g. as a deparment of the ministry of health or ministry of industry and trade), or in an autonomous structure of an agency reporting to the government. They are financed by the budget of the respective organization and more or less by inspections fees paid by the inspected manufactung sites. About 25% of the inspectors are dedicated to GMP inspections, while most of them are also inspecting GDP, and other GxP areas.

All of the inspectorates perform inspections at API manufacturers; 40% occasionally, or if there is a cause.

3.1. Internal procedures at inspectorates

It is a common understanding that all actors in the regulated environment need to be appropriately trained. The survey results indicate that diverse approaches are used to achieve this goal. Most inspectorates covered by the survey organize in house training programmes. In addition to that, in some cases, extramural educational activities are conducted, e.g. through universities.

Depending on the country, the inspectors either have the obligation to do less than 10, or more than 20 inspections per year. The authors further investigated and concluded that the limited workload of the respective inspectors can be explained by the additional responsibilities the inspectors have in their jurisdictions.

We have seen in 60% of the countries that inspectors have regular meetings with the respective reviewers of the regulatory dossier. Relations of inspectors with product registration body are assured mostly through joint internal meetings. Internal exchange of product-specific information between the registration group and inspectors is part of the preparation of a GMP/GDP inspection in one inspectorate only. Some inspectors have assessors included in inspection teams, or inspectors participate in the review of applications. However, none of the countries established that the inspectors have an advice function for the reviewer.

3.2. Procedural aspects on inspections

Risk-based approaches are established, or on the way to be implemented by 60% of the inspectorates. 40% do not follow any risk-based approaches so far. 25% of the inspectorates establish risk-based approaches as they, for example, accept GMP certificates / Certificates of Pharmaceutical Products (CPP) issued by stringent regulatory authorities and do not perform their own inspection. We understand that Mutual Recognition Agreements (MRA) can, but not necessarily have to represent the legal bases for that. 50% of the inspectorates in the survey do not consider such documents. However, Certificates of Pharmaceutical Products (CPP) are recognized by 50% of the inspectorates in the survey.

60% of the inspectorates in this survey collect documents from the site prior to an inspection. None of them is currently prepared, or legally allowed, to waive an inspection based on the documents submitted prior to an on-site inspection.

All combinations have been reported from inspectorates regarding inspection of overseas sites. These foreign inspectons are performed by dedicated inspectors, but also by those performing domestic inspections, in addition. In half of the countries, there are different fee structures for domestic versus foreign inspections. Further investigations demonstrate that fees for foreign inspections can be many times higher than those needed to cover additional foreign travel and time.

None of the inspectorates conduct unannounced inspections as a routine. However, if there is a reason, they may show up without prior notification.

3.3. Onsite inspections

Detailed checklists developed by their own inspectorate are used in inspections by 40% of the inspectorates. Another 40% are using such lists occasionally. There was no inspectorate which indicated using 'aid memoirs' from the Pharmaceutical Inspection Co-operation Scheme (PIC/S).

The access to companies internal audit reports is a standard approach in inspections by 20% of the inspectorates. Only one agency checks, if there is evidence, that the system is functioning.

At the time of the survey, 50% of the inspectorates were using such approaches to determine the scope and length of inspections.

Daily wrap-up meetings, in which the inspectors provide information on the findings as the inspection progresses, are a standard procedure for 50% of the inspectorates. Written information on potential observations after inspection are issued directly, or shortly after an inspection by 80% of the inspectorates. The purpose is to allow companies for editorial feedback. Companies are receiving inspections reports. However, 80% of the inspectorates do not publish inspection outcomes, or a status of a site.

4. OPPORTUNITIES IN INSPECTION MANAGEMENT

There are several areas which emerging regulatory inspectorates can consider to improve their processes. Besides getting involved in collaboration and learning from other recognized inspectorate, like those organised in PIC/S, here are some ideas for further opportunities.

4.1. Interactions between inspectors and reviewers

As in none of the countries there is an advice function of the reviewer by the inspector established, the authors see opportunities for improvements. Industry is faced with GMP related question by reviewers. This is usually demonstrating a lack of knowledge of the operation at a manufacturing site. As a result, industry has to submit specific documents from the Quality System, which in most countries are added to the commitments companies are providing with the regulatory filing. However, these documents represent procedures in the day-to-day operations and are continuously improved. Doing this as described results in an unnecessary regulatory scrutiny. The best practice would be that reviewers exchange info with inspectors in order to increase their knowledge, and let inspectors participate in the process to come to a conclusion to accept a regulatory filing and grant the marketing authorization.

4.2. Inspection resources

All inspection costs (both domestic and foreign), including salaries of inspectors, might be financed by regulated industry (UK is an example) using fees. Also, industry invests in inspections. For foreign inspections, additional costs related to travel and accommodation of the inspectors have to be compensated. Industry is quite open about the fact that costs incurred are transferred to consumers, which results in reduced affordability of medicines. 20 years ago, the practice of user fees for regulatory activities was supported in a WHO publication [7]. It can be calculated that the costs of one inspection is about EUR 1,000 for a manufactuing site. This estimation includes, beside the inspection fee, the costs for the dedicated staff actively involved in inspections, or on standby, as well as the preparation work and the follow up after the inspection.

Nowadays, there are opportunities to use the resources in a more focused way. Last year, Australian inspectors were promoting a risk- and reliance-based approach in planning of GMP inspections [8]. The same volume contains a reference to a draft WHO document on a paper-based inspection approach in the area of GMP, GLP, and GCP (Working document QAS/17.713 of May 2017).

4.3. Potential to waive inspections: review of documentation

Companies see an increasing number of requests to submit more and more detailed documentation to regulatory agencies prior to an inspection, and/or for paper-based inspection. Companies have to deal with agency specific requests and questionnaires resulting in administrative issues. Furthermore, translation into local language is occasionally requested, which is regarded as leading to a high risk of misunderstanding and misinterpretation.

What inspectors want to know about a site? Usually, they request site- and product-related information. An overview of the Quality Management System allows an insight into the operations on the site. Standardized preparation of such documentation packages are recommended by the European Federation of Industry and Associations (EFPIA) [2]. EFPIA suggests using existing reporting tools [2]:

- Site-related: Site Master File (SMF) according to PIC/S for information about the site, including the facilities, products, validation concepts, people, and organization.
- Product-related: Annual Product / Annual Quality Reviews of product(s) within the scope of inspection. These include information about recalls / withdrawals, product complaints, change control and validation assessments.
- Quality System related: Quality Manual with an appropriate overview of the Quality System and its elements implemented at the site.
- Additional compliance information: valid GMP/GDP certificates for the site; list of inspections, list of internal audits, and a number of customer / contractor audits.

This allows for faster provision of information and better utilization of resources. They help to tailor inspections with regard to their depth, breadth, and duration, or can even trigger waiving of an inspection.

5. CONCLUSION

Further convergence of GMP inspection practices towards a harmonized understanding of interpretations of GMPs seems to be advisable. This would both support strengthening regulatory mechanisms at national level, and promote trust and reliance between GMP inspectorates from different countries. These objectives may be achieved either by countries, e.g. by benchmarking, or through developing recognized guidelines and stewardship offered by competent international organizations such as WHO, PIC/S, or International Coalition of Medicines Regulatory Authorities (ICMRA).

We understand that implementing best practices as described might be positively considered by other countries in the course of benchmarking, or reflected in updated, internationally recognized interpretations. This will facilitate the communication of alternative approaches that might be more effective, even though they are not in line with the mainstream approaches. ■

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Prospects of Pharma Markets in CIS Region

9 April 2018

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CIS MARKETS IN THE GLOBAL CONTEXT

CIS (Commonwealth of Independent States) region includes former Soviet republics outside Russia and Baltics, namely: Kazakhstan, Uzbekistan, Turkmenistan, Kyrgyzstan, Tajikistan, Azerbaijan, Armenia, Belarus, and Moldova. From the market perspective, the region includes ex-CIS countries such as Ukraine, Georgia, and Mongolia that have never been a formal part of CIS, but have been an integral part of the economy of a bigger region. The subgroup of CIS countries (Kazakhstan, Kyrgyzstan, Belarus, and Armenia) also form Eurasian Economic Union (EAEU) together with neighboring Russia.

The outlined region refers to the extreme part of "Pharmerging" group of markets, the markets representing high potential and lucrative perspectives, but that are accompanied with high risks and volatility for pharmaceutical companies. Pharmerging CIS region market is forecast to grow at 6-9% CAGR in USD in 2018-2021 (see Fig. 1), in comparison with 5-8% growth in the USA, and 2-5% growth in European countries, so overall, the region might represent growth opportunities for companies looking for higher growth (see Table 1).

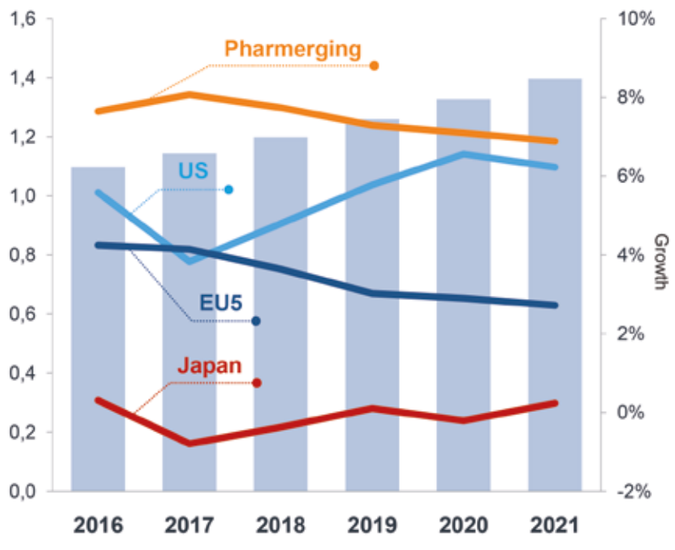


Fig. 1. Global sales (2016-21) Trillions of Constant USD.

At the same time, EAEU and CIS countries are starting to play a more significant role in the "Pharmerging" segment: in 2016, Kazakh market entered the top-20 list among other emerging markets. Moreover, overall CIS market is expected to grow at the highest end of the world rates: 7.6% per annum vs. 4.9% growth of the world market, which makes this region interesting for a deeper analysis.

Developed	2-5%
US	5-8%
Japan	(-1)-2%
Germany	2-5%
UK*	2-5%
France	2-5%
Italy	2-5%
Spain	1-4%
Canada	2-5%
Pharmerging	**6-9%**
China	6-9%
Brazil	6-9%
India	10-13%
Russia	6-9%
Turkey	10-13%
Mexico	3-6%

Table 1. CAGR 2016-21

Notes:
*Subject to PPRS rebate;
Ex-manufacturer price levels, not including rebates and discounts.
Contains Audited + Unaudited data;
Growth considered on par if the there is overlap between country and region CAGR ranges

Source:
IQVIA Market Prognosis March 2017

Higher than region CAGR
On par with region CAGR
Lower than region CAGR

ECONOMY PROSPECTS

CIS pharmaceutical markets continue to grow despite worsening economic situation: most of the countries in the region have suffered from local currency devaluation driven by global price fall of oil and other commodities in 2014. Because of external commodities price shock, both state and population faced lower purchasing power and squeezing ability to pay. Kazakhstan's gross domestic product growth slowed down from 8.3% in 2012-2014 to 3.1% in 2014-17; Azerbaijan's – from 5.7% to 0.4%; Uzbekistan's – from 11.1% to 2.2% in the same period. Some countries allowed the currencies to follow commodity price fluctuations (Ukraine), others tried to smoothen external price shocks on the internal markets (Kazakhstan, Azerbaijan, Uzbekistan) by keeping the price / currency levels, but eventually they reached nothing more than exhaustion of national funds trying to keep the exchange rates. Finally, over the period from 2014 to 2017, almost all the countries allowed their currencies to adjust to new reality. Lowering purchasing power and currency devaluations led to a 1.5- to 2-fold pharma markets contraction in USD terms in most of regional markets in 2014 to 2017. After clearing up all the imbalances, the region is now set for growth.

HEALTHCARE SYSTEM AND PHARMACEUTICAL MARKET

The region inherited soviet healthcare system and lived with it in from 1990s to 2000s. Some resource-rich (Kazakhstan, Azerbaijan) or socially-oriented (Belarus) countries continued to invest in state healthcare by expanding funds available for purchasing new drugs, or modernization of medical facilities (Kazakhsan with Salamatty Kazakhstan program). Some countries (Georgia) have made a bet on the private system with a gradual increase in state financing, others (Ukraine) have experienced a major overhaul of healthcare principles system in 2017.

Despite some regional programs, overall healthcare system in the region suffers from long-time underfinancing and has a huge unmet market potential in both retail, and state segments in major therapeutic areas, such as cardiology, commutable disease, diabetes, and oncology.

Though the biggest pharmaceutical markets in CIS kept experiencing issues with currency exchange rates, EAEU and CIS Pharma market evolution in 2017 showed solid performance of local manufacturers, with 3% growth in 2016-2017, both in value and volume (see Fig. 2). Ukraine, Kazakhstan, and Belarus were the major drivers of this increase, with 95% share in total growth of the region in 2017.

Most of the value growth is attributed to the OTC market growth, which grew by 6% in 2017 (see Fig. 2), while volume was driven mainly by Rx products (+5% growth in 2017). Many regional countries (Ukraine, Kazakhstan, Uzbekistan, Belarus) keep attempts to develop localized production and give preferences for localized manufactures; EAEU countries implement the rules favoring cross-EAEU localized policy (i.e. manufacturers in Kazakhstan and Belarus can obtain price and participation preferences in Russian state tenders being a part of EAEU common market). Overall, localized products in the region showed 9% growth in value in 2017, reaching 24% of total CIS region pharma market.

We expect that overall CIS pharma market would grow at 7-8% per annum in 2018-2020 vs. 4-5% growth of the world market. Major drivers of region growth include coverage of huge unmet medical need driven by better access and availability of products, healthcare reforms, and increase in state funding.

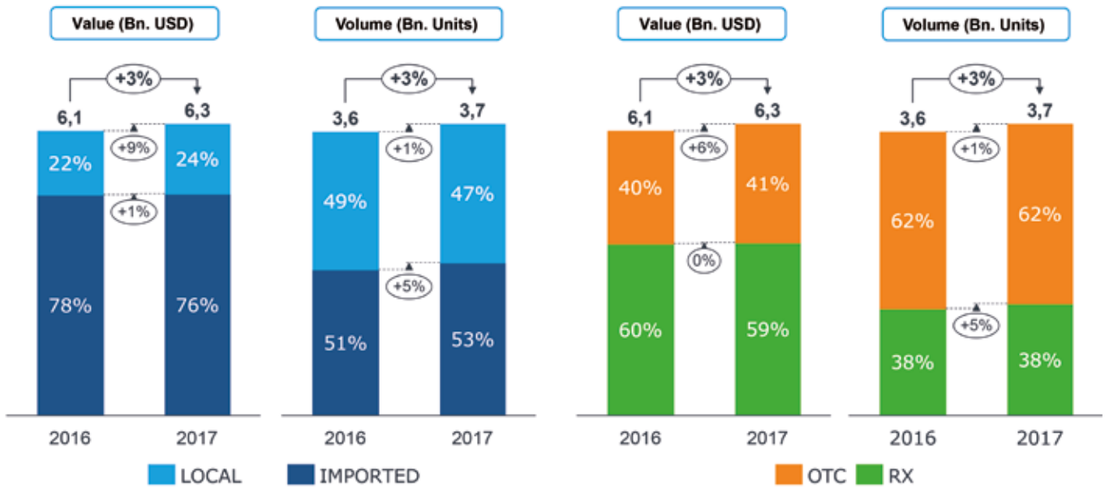


Fig. 2. EAEU & CIS Pharma market evolution in 2017/16 showed solid performance of local manufacturers, primarily in OTC area.
Though the biggest markets in CIS kept experiencing issues with currency exchange, rates the consumption helped to sustain the currency issue.

KEY MARKET HIGHLIGHTS

Ukraine

Continued macroeconomic and political instability, war in the east, tensions with Russia keep uncertainty for economic situation, and impose threats for further market development in 2018-2019. Some stabilization is expected after presidential elections in 2019. Ukraine's healthcare system is currently under significant overhaul including implementation of reimbursement for cardiology, diabetes, and asthma which has been the major market driver in 2017. Increased financing and coverage by the government would allow reimbursement, implementation of clear rules (e-health system) would allow to maintain market growth for 2018-2020.

Uzbekistan

Uzbekistan's pharmaceutical market was marked by one of the strongest increase of consumption. Devaluation of natural currency in 2017 provided the volume growth in Uzbekistan; in local currency terms, its market has been growing at 27% in 2017, while in USD, the market sharply declined.

There is strong competition from cheap products from India and low-income level among population create limitations for launching expensive retail products. While Government introduced the program for import substitution and localization for international players which is relevant not only for pharmaceutical industry, but became overall trend for other sectors. Overall, Uzbekistan's market is one of the most promising in CIS in terms of growth.

Kazakhstan

Kazakhstan pharmaceutical market has been growing at 16% CAGR in 2012-17 period and showed one of the highest growth rates among CIS markets. It is currently ranked #3 among other countries in this group (right after Ukraine and Uzbekistan). Kazakhstan pharmaceutical market is expected to grow by 10% per 2018-2020, driven by government initiatives, and growing purchasing power of population.

At the same time, there is a price pressure expectations caused by upcoming regulatory changes in 2018-2021 when Kazakh government is going to introduce stricter price controls. Harmonization of EAEU would present another pulldown effect on the Kazakhstan's prices in generics, and is going to free up the budgets for newer inclusions.

Azerbaijan

Due to government price regulation policy, Azerbaijan market has been falling sharply (in USD) since 2014, by 22% per annum. The government pushed for price / margin controls that led to a huge spike of smuggling market with products coming from neighboring Turkey, Iran, Russia, and Georgia. Many international players have left the market. After stabilization of the currency we expect slow market recovery maintaining relatively strong state purchases and smaller retail market.

Additionally, implementation of compulsory medical insurance is expected to happen not earlier than in 2020, which might increase the budget segment and replace some retail purchases.

CIS region does not present an obvious potential that is easy to catch: there is indeed a lot of diversity, complexity, and uncertainty. However, it is hard to skip such a huge unmet need in the region, which might represent one of the world's highest untouched growth rates for the next 3-5 years available for risk-tolerant players looking for great growth opportunities. ■

Program for the Development of the Russian Pharmaceutical Industry:

Main Results of Implementation and New Horizons

21 March 2018

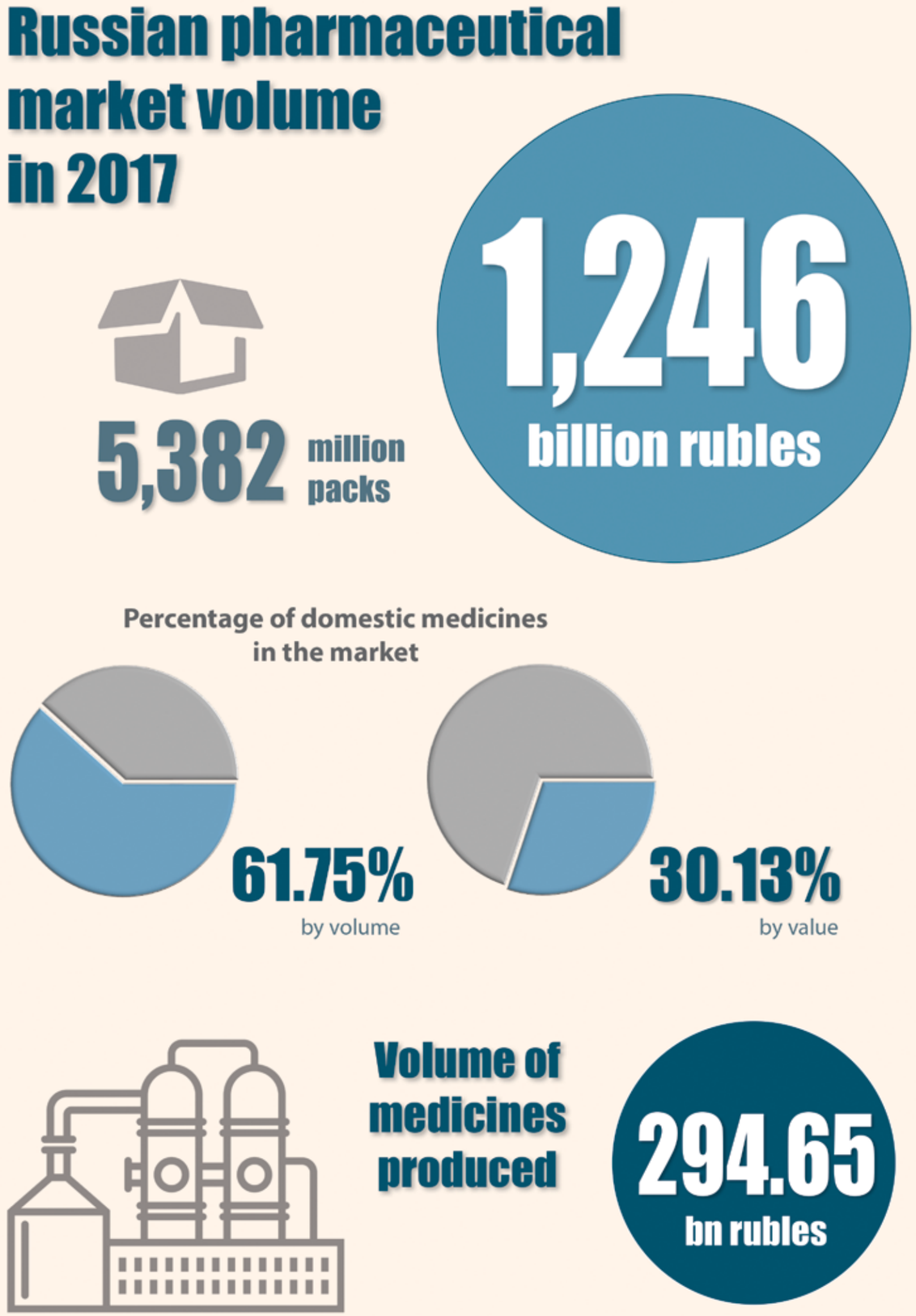
In 2011, a strategy was developed and a federal special-purpose program for the development of the pharmaceutical and medical industry until 2020 called "Pharma 2020" was launched. There is not the slightest doubt that it laid the foundations for innovative development of the industry: during its implementation, the domestic industry of pharmaceuticals and medical equipment has reached a new level, and is now showing high growth rates. Thus, the results of 2017 indicate that the volume of production of medicines according to the Federal State Statistics Service increased by **12.3%** in comparison with 2016 and amounted to **294.65 billion rubles**. As a consequence, the share of Russian-made drugs on the domestic market is constantly growing. According to analytical agencies, the volume of the pharmaceutical market in 2017 was **1,246 billion rubles** (+ 7.27% as compared to 2016), and 5,382 million packs (+ 1.67% as compared to 2016). The share of home-produced medicines in the total market volume was **61.75%** in physical terms, and 30.13% in value terms. As a result of the implementation of the State Program, **70** medicinal products were registered by the end of 2017. It is safe to say that it is thanks to the activities under "Pharma 2020" over the past 5 years that Russian producers have new opportunities and they are constantly expanding their sphere of influence in the pharmaceutical market.

During the implementation of the "Pharma 2020" program, domestic companies have learned to produce the most high-tech biopharmaceuticals, which previously were represented exclusively by imported products. According to the Presidential Decree of 7 May 2012, the volume of domestic production of medicines included in the list of vital and essential drugs should be brought to 90% by 2018. Our industry shows impressive results: as of 1 January 2018, 468 international non-proprietary names (INN) were registered from that list, which represents **84.2%** of the total number of registered medicines. As of 1 January 2018, in the period from 2013, **50** import-substituting vital and essential drugs (VED) were registered.

As an example of high-tech products, one can mention genetically engineered protein molecules: monoclonal antibodies, cytokines, recombinant coagulation factors. Also, in Russia began the production of modern cytostatics for cancer treatment, drugs for pulmonary diseases, and new hormonal drugs are being developed.

Over the past 5 years, the sales of Russian medical drugs have increased almost threefold in monetary terms. And now virtually **every second cancer drug is of Russian origin**. There is a similar situation with tuberculosis, where the share of Russian drugs also increased to 73.51% in monetary terms, and up to **85.79%** in terms of the number of packs. A qualitative leap occurred in HIV therapy: 5 years ago, less than 10% (in monetary terms) of medicines were domestic, and at the end of 2017, their share was already over 28%.

In 2017, as compared to 2016, an increase in the production of medical drugs was registered for the majority of the most important pharmacotherapeutic groups, namely: medicines for the treatment of digestive and metabolic diseases, up to 115.0% in terms of ampoules; products influencing hematopoiesis and the blood formula, up to 102.4% in terms of vials, and up to 132.5% in terms of ampoules; medicines for the treatment of the cardiovascular system, up to 113.5% in terms of packs, and up to 129.3% in terms of vials; hormonal products for



systemic use, except for sex hormones, up to 112.2% in terms of packs; antitumor drugs and immunomodulators, up to 146.4% in terms of packs; medicines for the treatment of the nervous system, up to 109.9% in terms of packs, and up to 117.7% in terms of ampoules; drugs for the treatment of respiratory system organs, up to 109.7% in terms of packs; medicines for the treatment of sensory organ diseases, up to 131.8% in terms of packs; drugs for the treatment of skin diseases, up to 103.5% in terms packs.

The pharmaceutical industry development program provides support for the development of original domestic medicines. During the implementation of the state program, **more than 400 innovative projects in the pharmaceutical field were supported**, more than 100 of them are currently at the stage of clinical trial. So there are clear prospects for efficient and safe original Russian products appearing on the market in the nearest future. And already there are tangible examples of that. A domestic drug for the treatment of hepatitis C, a new drug for the treatment of diabetes, an original Russian medicine for the treatment of HIV infection are already on the market.

Many foreign companies are localizing their production in our country, actively investing in the creation of new production facilities. Recently, some of the largest pharmaceutical companies have started production in Russia, such as Novartis, Sanofi, AstraZeneka, Teva, Takeda, and many others. Foreign pharmaceutical companies have built **8** new plants in Russia since 2010. Nowadays, more attention is given to ensuring that the level of production and quality of products in Russia is not inferior to the standards that are used by advanced manufacturers in the global pharmaceutical industry. Over the past 4 years, **19** new production facilities have been set up in our country that adhere to the most advanced international standards of manufacturing: Good Manufacturing Practices (GMP).

Russian pharmaceutical companies have a significant export potential. The figures speak for themselves: according to the Federal Customs Service of Russia, the volume of pharmaceutical products exports in 2017 increased by **16.6%** as compared to 2016, and amounted to 688.4 million of US dollars. This is a very high growth rate for a high-tech industry.

The rapid development of the pharmaceutical industry in recent years made it necessary to have a concept for the development of the industry for the long term. The work on drafting new strategic documents for the development of the pharmaceutical and medical industry until 2030 (Pharma 2030) is now at the stage of gathering data from all interested executive authorities and market participants. By the end of April, the Interdepartmental Working Group on Strategy Development will have the first Draft of the document, which, prior to being submitted to the Government, should be subject to public discussion, and should be approved by the federal executive authorities. The new strategy takes into account the results of the implementation of the previous state program and lays down clear priorities for the long term development of the industry. In this regard, the Ministry of Industry and Trade of Russia faces a difficult task: to take into account the interests of all stakeholders: scientists, manufacturers, patients, regulators, venture investors when defining priorities. At the moment, the following priorities of the new government strategy have been identified: support for original Russian research & development; search for new medicinal targets and molecules; development of pharmaceutical substances production; activities to support the export potential of the pharmaceutical and medical industry; development of the intellectual property market; manufacturing of cellular products; development of personalized medicine. ■

PharmMedProm - 2018,

a Strategic Discussion on the Future

Constant interaction between the practitioners, the medical community and the manufacturers is key to the success of a new pharmaceutical or medical product on the market. A considerable part of the activities under the State Program for the Development of the Pharmaceutical and Medical Industry are dedicated to ensuring the participation of domestic manufacturers that are receiving support in specialized medical congresses and exhibitions. One of the key industry events is the annual exhibition and scientific and practical conference "PharmMedProm", which the Ministry of Industry and Trade of Russia organizes at the end of each calendar year as part of the scientific and practical forum "RUSSIAN HEALTHCARE WEEK". "PharmMedProm" is an effective platform where current trends in the development of world medicine, national healthcare are examined and new medical equipment and modern medicines are demonstrated. The goal is to present the domestic industry to practitioners, the medical community, the patient community, the general public, to show the successes achieved under the State Program in the period that has elapsed since the previous event.

The new industry strategy "Pharma 2030" aimed at achieving leadership positions in the domestic and global markets provides for more active interaction with the practitioner community, the creation of patient-oriented healthcare and many other important tasks that can not be accomplished without improving the regulatory framework and developing cooperation between all potential players in the industry: from students to global manufacturers, from executive bodies to each individual patient. That is why it became an urgent necessity to maintain a constant dialogue between all players and stakeholders.

In 2018, it is planned to transform "PharmMedProm" into a permanent discussion platform for professional dialogue between manufacturers, the global industry, representatives of all ministries and departments involved in the program implementation, investment funds and private investors, developers, representatives of educational organizations, medical and scientific community, representatives of patients' organizations. During 2018, it is planned to hold a series of events in various formats as part of specialized conferences and forums and a concluding event under the "PharmMedProm" brand. ■

Kaluga Pharmaceutical Cluster

Successfully Develops International Cooperation

Irina Novikova
Executive Director of "Kaluga Pharmaceutical Cluster" Association

13 March 2018

Since its establishment in 2012, "Kaluga Pharmaceutical Cluster" Association has been systematically developing two directions in expanding international cooperation. The first one is facilitation in promoting the cluster participants to external markets through development of international cooperation and attraction of direct foreign investments. The second one is internationalization through development of links with other clusters, which gives additional opportunities for expansion of scientific cooperation, and it provides access to new competencies and knowledge, and it allows to take part in the exchange of better practices.

A.D. Artamonov, Governor of the Kaluga Region, and Philippe Saurel, President of the Montpellier Méditerranée Métropole (France), signing a cooperation agreement between the two regions (October, 2017)

Since 2014, the Association is a member of the European Cluster Collaboration Platform uniting more than 200 leading European clusters, and as of today, being the only cluster in the Russian Federation integrated into the European professional community with the **European Cluster Excellence Initiative Silver Label** status.

COOPERATION WITH FRANCE

Active mutually beneficial cooperation between Kaluga Region and France started at the beginning of the 90s; the closest ties have developed with the Montpellier City Agglomeration and the province of Limousin. In 2012, we signed an agreement with the leading French cluster in the field of life science **EUROBIOMED** (Montpellier region, Marcel, Nice), and in 2013, a delegation from the Limousin province (France) headed by its President Jean-Paul Denanot visited Kaluga Region; during the said visit, one more cooperation agreement was signed. As a result, in the territory of the Limoges city business incubator a mutual Russian-French enterprise was established for development and production of an innovative medical and pharmaceutical waste disinfection facility, allowing to process up to 30 tons of infected waste a year. In 2014, the certification of the produced installation in the EU territory was completed, and in 2015, it was already sold in the EU as well as exported to Russia, Belarus, and Kazakhstan in the number of more than 1,000 items annually.

Last year, our cooperation with France got to a new level. In October of 2017, during the visit of a delegation from Kaluga Region headed by the region Governor A.D. Artamonov, Memorandums of Scientific Partnership in Healthcare were signed between the organizations of Montpellier City Agglomeration and Kaluga Region. That time, the parties highlighted such innovations in medicine as active compounds

synthesis, development of new drugs to treat socially significant diseases, expansion and exchange of knowledge of modern technologies application as the key directions. Precisely in these directions scientific cooperation is planned between the **University of Montpellier** and the Alliance of Competences "Park of Active Molecules" (PAM). As a part of the specific programs of operational cooperation, the Alliance of Competences "Park of Active Molecules" signed agreements with **CILcare** – a leading global company rendering services related to development of therapeutic solutions for patients suffering from hearing disorders, with ChainOrchestra – an operator of the BNO-blockchain network and with ChainHero – an expert in the field of blockchain editors. PAM and CILcare partnership is forged to verify the efficiency and safety of new molecules – clinical candidates to treat hearing loss and tinnitus. Cooperation with **Chain Orchestra** and **ChainHero** is aimed at creation and implementation of an information platform for bio-pharmaceutical projects with an integrated decentralized autonomous system of interaction between the biotechnological environment participants, regardless of their location.

According to **Celia Belin**, Head of CILcare: *"The goal of alliance of France and Russia is, among other issues, development of solutions aimed at improving people's quality of life and correction of age-related changes. As of today, 15% of the world's population, i.e. 1 in 3 adults over 65 years of age suffers from hearing loss. At the same time, more than 1 billion of younger people are exposed to risk of loss of hearing due to excessive noise impact. Taking into account the irreversible nature of this disease and the fact that there are no efficient drugs on the market to treat hearing loss, the market prospects of new efficient methods of treatment in this field are rather high.*

When CILcare, the leading global servicing company specializing in hearing disorders, obtained access to the portfolio of molecules developed by the Alliance of Competences "Park of Active Molecules", several innovative clinical candidates with a great potential in treating inner ear diseases were determined. Both companies decided to join their efforts to satisfy the patients' needs and promote innovative products on the market. We are proud of this alliance and very glad that we were joined by the National Center of Scientific Research that has brought its experience in 3D molecule modeling to optimize the molecules and their interaction with the target, respectively."

Irina Novikova, Executive Director of Kaluga Pharmaceutical Cluster, and Bertram Lohmüller, Director of Steinbeis Global Institute, Tubingen, signing a cooperation agreement

PARTNERSHIP WITH GERMANY

Germany can easily be called the leading partner of our Association. As far back as in 2013, a cooperation agreement was signed with the **Bavaria's Chemical Cluster** (Munich city). Last year, participants of "Kaluga Pharmaceutical Cluster" Association conducted a business mission to Baden-Wurttemberg during which a cooperation agreement between "Kaluga Pharmaceutical Cluster" Association and **Steinbeis Global Institute Tubingen** at the Steinbeis University Berlin was signed. The agreement was signed by Irina Novikova, Executive Director of the Association, and Bertram Lohmüller, Professor and Director of the Institute. This agreement provides for implementation of a number of mutual programs of training of specialists and advance training in the interests of the "Kaluga Pharmaceutical Cluster" participants in programs such as "Global Technology Management" (master's degree), "Production and Entrance to Global Markets" (MBA), "Technology Transfer and Business Development" (MBA), and other programs in the field of healthcare and pharmaceutical production.

"According to our agreements, Steinbeis Global Institute will provide consulting and organizational support to small and medium businesses – cluster participants in search for partners in Germany and product launch on the European market. In our turn, we will become the 'point' of entrance for German pharmaceutical and biotechnological companies to the Russian market", said **Irina Novikova**.

COOPERATION WITH FINLAND

Annual organization of business missions and internships for the cluster participants allows us not only to take part in international events, but also to obtain access to technologies, expand scientific cooperation, and search for partners abroad. Thus, the main goal of a cooperation agreement with **BIOTURKU** Finnish cluster is to ensure interaction in the field of creation and development of infrastructure, implementation of mutual training programs, cooperation in scientific and technical activities, including such areas as:

- development of technologies and pilot production of original pharmaceutical substances,
- modeling of the structure and effect of chemical drugs,
- engineering and scaling of pharmaceutical production.

INTERACTION WITH ITALY

In October 2016, within an official visit of a delegation of the Russian Ministry of Industry and Trade to Italy, a cooperation agreement by and between "Kaluga Pharmaceutical Cluster" Association and one of the largest clusters in Italy, **C.H.I.C.O.** was signed. (CLUSTER OF HEALTH, INNOVATION AND COMMUNITY).

This agreement provides for cooperation in a number of cluster priority areas, such as:

- development of technology and production of pharmaceutical substances;
- modeling of the structure and effect of chemical drugs;
- computer design of medicines;
- licensing and production of finished dosage forms;
- services of disinfection of pharmaceutical substances and finished dosage forms;
- possibility to organize contract manufacturing.

This agreement will be implemented through exchanging of advanced experience, participation in mutual projects aimed at economic development, information exchange, development of cooperation between Russian and Italian universities, research institutes, healthcare institutions and specialized companies in life science and healthcare.

Today we can say with great confidence that the work on internationalization of Kaluga Pharmaceutical Cluster will be continued. Our short term plans include organization of a business mission to the **Republic of Serbia** and a visit of an official delegation of the **Tehran Pharmaceutical Cluster** (Iran) to Kaluga Region. ■

AstraZeneca Industries LLC plant in the "Vorsino" Industrial Park, Kaluga Region

Berlin-Pharma LLC plant in the "Grabtsevo" Industrial Park, Kaluga Region

Hemopharm LLC plant (STADA group) in the Obninsk Municipal Industrial Area, Kaluga Region

From Creation (Manufacturing)

to Consumption (Patient)

Girish Malhotra
CPhI Expert and President, EPCOT International

20 March 2018

Since the beginning of 2018, "doing something" to curb ever increasing drug prices has picked up steam. I call two recent announcements [1-4] to be "constructive destructionist" [5] and if successful they could have an everlasting impact and game changing influence on the pharma landscape. With their success we should expect additional entrants.

Till recently, many have talked and proposed legislations, but whenever rubber has met the road the tires have gone, or went flat and the blame games started. We have to accept the fact that anything being proposed by the legislators or put on the ballot box is not going to come to fruition. This is due to pharma lobby having significant influence on the electability of the legislators who want to stay in office for eternity. This combination has been deadly against the needs of the constituents who want justifiable lower drug prices.

Recent initiatives are opportunities worth a review. Each presents a game changing opportunity to improve drug affordability, improve product quality, revenue and profits for the pharma landscape. In the United States, drugs are acquired through two major systems, Veteran's Affairs is for the veterans and rest of the country through mutually subsidized healthcare systems, which include Medicare. Veteran's Affairs along with selected Health Systems [1] (VAH) and Amazon, Berkshire Hathaway, and JPMorgan [2-4] (ABM) are set to cause a perturbation to the existing mutually subsidized system when it comes to their employees. They could be the start of a revolution against ever increasing drug prices. I am presenting my perspective and opportunities they present.

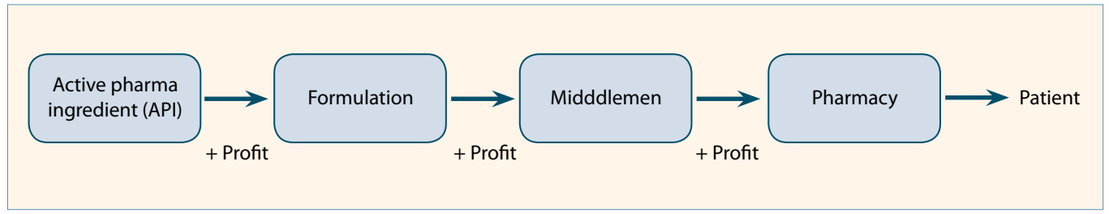


Figure 1.

VETERAN'S AFFAIRS

There are about seven million participants in the Veteran's Affair (VA) system. Some of us may not know, but VA has its own methods for acquiring drugs at discounted prices [6]. Its drug acquisition plan is unique and most likely is not entertained by the pharmaceutical companies because number of drugs offered is restricted and pharma and supply chain profits are lowered. However, pharma companies have acquiesced to avoid wrath of the US government and the country. Following guidelines have to be followed.

"Unlike Medicare, in which beneficiaries can choose drug plans, each with its own formulary, the VA offers no choice. Serving as the sole purchaser of drugs, the VA maintains a single national formulary that physicians must follow. The VA formulary is created through access restrictions on drugs. For drugs to be covered on the formulary, their makers must list all of their drugs on the Federal Supply Schedule (FSS) for federal purchasers at the price given to the most-favored non-federal customer under comparable terms and conditions. Additionally, drug makers must offer the VA a price lower than a statutory federal price ceiling (FPC), which mandates a discount of at least 24 percent off the non-federal average manufacturer price (NFAMP), with a rebate if price increases exceed inflation."

Even with VA's restrictive purchasing program, February 2018 announcement [1] presents generic drug producers to capitalize on an opportunity to expand their markets (other Mutually Subsidized and Medicare systems) and increase profits and revenues. Since the healthcare systems are going to be directly working with the manufacturers, it is a unique opportunity for them to capitalize on values economies of scale and innovative manufacturing technologies [7, 8].

MUTUALLY SUBSIDIZED SYSTEMS

VAH and ABM alliances [9] should use reverse calculations [10] to encourage manufacturing companies to innovate. Economies of scale and "what if" analysis can be used to improve manufacturing processes. Upside of the effort is going to be higher revenues, higher profits and lower drug costs. FDA and other regulators will have to be open-minded and proactive to make sure innovative manufacturing practices are adopted on a timely basis and commercialized [11, 12].

Figure 1 is a schematic of the supply chain that is applicable to patients in Medicare and mutually subsidized healthcare systems.

Pharmacy benefit managers (PBM) [13], for simplicity I call them middlemen, facilitate distribution of drugs to most outside the VA system. Manufacturing and cost of API and their formulations are simple to understand [10, 14]. However, under the current system, pricing from formulations to the patients becomes murky and complex. However, the mystery is being slowly unraveled [15-19]. States are also taking steps to contain rising prices [20, 21].

PBMs have made every attempt to make sure that the cost details are not readily available and the patients pay the highest drug prices. UnitedHealth [22] has announced a possible peak in the PBM "Black box". However, till the beans of this initiative are counted and everything is black and white, it is too early to grasp the impact.

It is interesting to note that PBMs block direct import of drugs by the patients from e.g. Canada and other countries, but the same drugs are imported and sold at a significantly higher price in the United States. Explanation given is the safety of the drug. This also could be considered an artificial way to keep prices up by using scare tactics. Uniform global drug standards will greatly help but they would be a challenge to establish.

From drug price information collected in India and in US [14] (with regular insurance, Medicare, and NO insurance) one can easily see the reasons why PBMs have discouraged ABM Alliance [2] to take a peak in the "Black Box". Most can conjecture that PBMs do not want anyone to negotiate and jeopardize their profits. Sood etal [16] and Grant [17] have done an excellent review of the PBM price structure. Price multiples of between 100-1500 times from manufacturing to patients [14, 16], Table 1, should be an eye opener for the negotiators in VA and ABM Alliance. As has been said earlier, economies of scale and better technologies can significantly lower these multiples.

Table 1.

DRUG	DOSE, MG	PRICE PER TABLET IN INDIA, USD *: ~RS. =65 TO 1 USD	WITH INSURANCE ***		MEDICARE D [23] ***	NO INSURANCE [24] ***
			DRUG PRICE PER TABLET IN US, USD **	% OVER INDIAN PRICES	PRICE RANGE PER TABLET, USD	PRICE PER TABLET IN US, USD
Lasix	40	0.01	0.13	1300%	0.05-0.13	0.67
Metformin	500	0.06	0.07	117%	0.05-0.08	0.73
Atorvastatin	10	0.08	0.43	538%	0.03-0.18	3.90
Levothyroxine	0.112	0.03	0.13	433%	0.03-0.50	1.10
Omeprazole	20	0.04	0.5	1250%	0.10-0.30	2.83
Nexium	40	0.15	1.33	887%	1.57-6.83	8.33
Ciprofloxacin	500	0.05	0.17	340%	0.28-0.67	4.77

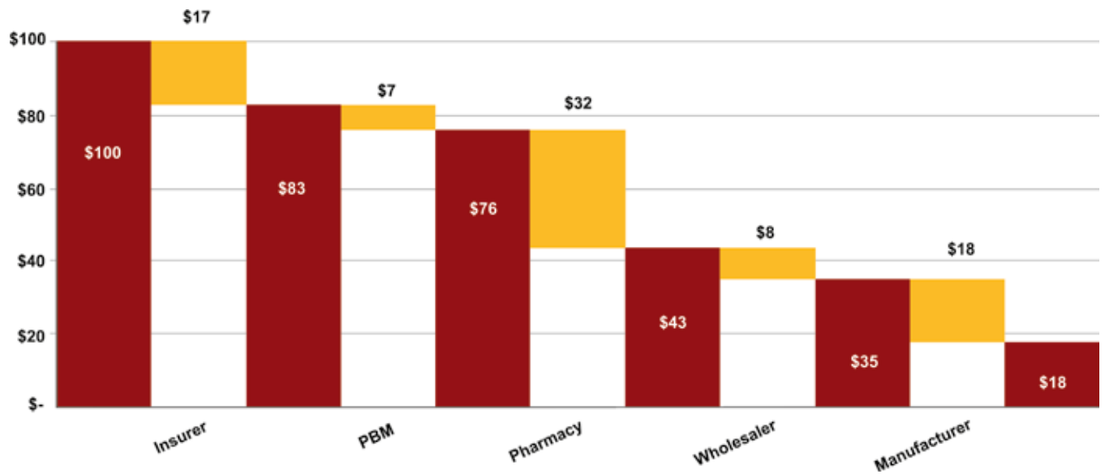
** Price has ~35% profit margin*
*** US prices are from Walmart, Costco, Walgreens, and GoodRx using non-Medicare insurance*
**** Have prescription*

DRUG PRICE REDUCTION OPPORTUNITIES

Using Panel B for the money flow [16] illustration, it is interesting to note how an $18.00 drug gets to the patient in the current system and sells for $100.00.

Using sound principles of economics, chemical engineering, chemistry, economies of scale, and good manufacturing practices a 20% reduction in manufactured cost will translate to about $80.00 to the patient if no improvements are done to the current PBM supply chain "Black Box". 20% or better cost reduction in the supply chain should not be considered an out of reach of possibilities. Combined cost reductions in manufacturing and supply chain would mean that a current $100.00 drug would cost about $65.00 to the patient. I am sure $35.00 cost reduction is worth the effort. 20% cost reductions in manufacturing and in the supply chain each are not out of the realm of reality. Effort would be needed. Everyone from "Creation (manufacturing) to Consumption (patient)" will benefit financially.

Panel B is Courtesy Sood etal [16].



Panel B: Expenditure on generic drugs.

BUSINESS MODEL CHANGE

Accelerated 2018 chatter is not going to let up. It seems that the pressure to make drugs affordable or lower drug prices will continuously increase. Dan Akerson, ex CEO of General Motors, said it well that If you don't attack your own business model, trust me, somebody else will.

So far pharma companies and PBMs have stuck with their models of creating new drugs and along with PBMs selling them at the highest price participants can afford in mutually subsidized systems. Essentially no effort has been made to improve their methods to lower drug costs. In the last few years, big pharma companies have relied on orphan drugs or marginally better drugs to improve their revenues and profits. These are not going to sustain major pharma companies for the long haul.

Since generic drugs, an ever-increasing need, in the United States are distributed through PBMs, in our mutually subsidized healthcare systems even they are priced at the highest level (Table 1). We have to recognize that Pharma/PBM's major customer base is dependent on affordable drugs. Pharma/PBM business model has to change. It is time.

There is a need and it seems that PBMs and associated companies are trying to cater to the shareholders [25] rather than the patients who are the basis of their existence. With success of VAH and ABM Alliance, we could see spread of drug price reductions. Pace could accelerate. As they say "cat is out of the bag" and the question is how pharma industry and PBMs are going to participate for everyone's benefit. My conjecture is outliers will cause a change and it will happen sooner than expected. ■

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What the Hell is Blockchain

and What Does It Mean for Healthcare and Pharma?

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medicalfuturist.com

20 March 2018

Blockchain already earned the buzzword of the year award, so it is high time to address the elephant in the room. Is it really there? If it is, will it really change everything? How will it impact healthcare?

BLOCKCHAIN: MORE TRANSFORMATIVE THAN TRUMP ON TWITTER

Don Tapscott, author of the book entitled Blockchain Revolution said in his superb, no-frills TED Talk that blockchain is the technology that is likely to have the greatest impact on the next few decades. No, it's not social media. No, it's not big data, not robotics, not even artificial intelligence. It's the technology behind the cryptocurrency, Bitcoin.

Stop there for a moment. So, blockchain will have more transformative power on our lives than Facebook, Instagram, and Donald Trump using Twitter for diplomacy? How? Why? When? Is that true, or is it another bubble shaping up in front of our eyes?

When looking at how fast companies in various industries are adopting blockchain, the latter question is certainly worth considering. According to Transparency Market Research, the global blockchain technology market is expected to be worth $20 billion(!) by the end of 2024 as compared to $315.9 million in 2015. The overall market is anticipated to exhibit a 58.7 percent annual growth between 2016 and 2024. Moving faster than Elon Musk's red Tesla Roadster in space. And the drivers of this massive expansion are innovators, start-ups, bold companies in finance, retail and manufacturing, government – and healthcare.

Due to blockchain's ties to cryptocurrencies, most people believe that the financial system will adopt the technology soonest, but healthcare's speed of leveraging blockchain seems to actually surpass it. A new IBM Institute for Business Value blockchain study, Healthcare Rallies for Blockchain, surveyed 200 healthcare executives in 16 countries. They found that 16 percent aren't just experimenting; they expect to have a commercial blockchain solution at scale in 2017. Moreover, according to IBM's estimation, another 56 percent will follow the first adopters until 2020. That means within 2 years!

Thus, it is high time to have a look at how and why the technology behind Bitcoin, the cryptocurrency in a great part powering criminals trading on the darknet could become the cornerstone of future healthcare. More briefly, let's see what the hell blockchain is!

BLOCKCHAIN IS THE NEW WORD FOR TRUST ONLINE

On the Internet, nobody knows that you're a dog. Although Peter Steiner's cartoon drawn for The New Yorker in 1993 is mostly associated with the issue of anonymity on the Internet, it highlights deeper problems in relation to trust, credibility, security, and privacy. In the era of fake news and online scam, it does not come as a surprise to anyone that it is difficult to secure information, communication processes or trade online. And it is especially important in case of such sensitive information as money or healthcare data.

In case of money, trust and credibility have long been established by central intermediaries, such as banks and other types of middlemen. You transfer money via your online bank account knowing it's safe and secure because you trust the financial institution behind it. And in the case of online transactions, there has been another problem for which trustworthy intermediaries have meant the solution for years. The problem of duplications. When you send an e-mail with an attached cat photo, the image will automatically be copied. So, how do you make sure that doesn't happen with your money? That the well-earned dollars that you spend on books will actually disappear from your bank account and appear on Amazon's. In the case of digital assets like money, stocks or intellectual property, not to speak about electronic health records, authentication and accountability are key elements.

Still, middlemen such as banks are too slow. And too expensive. While an e-mail arrives in seconds in another person's mailbox, an international transfer could take several days, even weeks. And it is not even that secure, as it could be hacked more easily due to the banks' centralized nature. As a response to all these issues, Satoshi Nakamoto, a mysterious Japanese programmer or a group, worked out the world's first digital currency, Bitcoin and its underlying, supporting system, the blockchain. Since then, several types and modified versions of the technology appeared. As The Economist explained, blockchain enables an economy where trust is established not by central intermediaries but through consensus and complex computer code. It lets people who have no particular confidence in each other collaborate without having to go through a neutral central authority. Simply put, it is a machine for creating trust.

BLOCKCHAIN IS LIKE A SCARF KNITTED BY YOUR GRANDMOTHER

The concept and the operation of the technology are rather difficult, but it is perhaps easier to imagine with a nicely-put metaphor by The New Yorker's Nathan Heller. In his article about Estonia as a digital republic, he said that a blockchain is like the digital version of a scarf knitted by your grandmother. She uses one ball of yarn, and the result is continuous. Each stitch depends on the one just before it. It's impossible to remove part of the fabric, or to substitute a swatch without leaving some trace: a few telling knots, or a change in the knit.

When The Medical Futurist asked Ivo Lohmus from Guardtime, an Estonian company developing K.S.I. blockchain technology, he said it is to be imagined as a shared book of records, or in more technical terms, a distributed database that's designed in such a smart way that whatever is added to this database, that's immutable. As if it's carved into stone. Any change becomes immediately evident. Another aspect of the system is that there is no central authority to decide what's right or wrong. The participants need to come to a consensus, to articulate some shared view of the world.

There are several methods for making a decision about a new entry based on the particular consensus, Medium's Collin Thompson explains the proof of work process used by Bitcoin as the following: when a digital transaction is carried out, it is grouped together in a cryptographically protected block with other transactions that have occurred in the last 10 minutes and sent out to the entire network. Miners (members in the network with high levels of computing power) then compete to validate the transactions by solving complex coded problems. The first miner to solve the problems and validate the block receives a reward. The validated block of transactions is then timestamped and added to a chain in a chronological order.

New blocks of validated transactions are linked to older blocks, making a chain or blocks that show every transaction made in the history of that blockchain. The entire chain is continually updated so that every database in the network is the same, giving each member the ability to prove who owns what at any given time.

THE BENEFITS OF BLOCKCHAIN

The technology has numerous benefits for online transactions, especially in the field of digital assets, such as health data. Blockchain's time-sensitive nature allows any data to move around in that particular format only once in the network. The blocks are impossible to change; only new entries can be added to the network. This is critical in case of health data. Just imagine what might happen if someone could change a patient's blood type in the health record system without anyone noticing it.

Moreover, Ivo Lohmus said that many times, as in the case of the K.S.I blockchain which is used for the Estonian medical records system, the blockchain does not directly deal with

the data. Through the cryptographic process, a unique identifier of the data, a hash, is created, which functions similarly to the biological fingerprint. While you can identify anyone based on his or her fingerprint, you cannot "reconstruct" the whole person. And finally, as the blockchain is based on the consensus of network participants, access to data can be linked to permission.

Beyond ensuring authentication and credibility, blockchain also brings unprecedented security benefits. Hacking attacks that commonly impact large, centralized intermediaries like banks would be virtually impossible to pull off on the blockchain. For example – if someone wanted to hack into a particular block in a blockchain, a hacker would not only need to hack into that specific block, but all of the proceeding blocks going back the entire history of that blockchain. And they would need to do it on every ledger in the network, which could be millions, simultaneously.

BLOCKCHAIN IN HEALTHCARE – LONG INSTEAD OF BIG DATA

Blockchain has immense potential in healthcare. According to the IBM Institute for Business Value blockchain study, new adopters of the technology expect the greatest blockchain benefits across time, cost, and risk in three areas: clinical trial records, regulatory compliance, and medical / health records.

It is capable of transforming the entire system of medical records, just as Estonia has already done. In March 2017, the Baltic country's eHealth Authority signed a deal with Guardtime to secure the health records of over a million Estonians. Patientory, a start-up helping hospitals to secure their patient data while enabling patients to follow the fate of their own data, has urged the British government "to get behind a blockchain-enabled national IT health system" at the time of the NHS ransomware attack. If there were political will and comprehensive financial support, other countries could also follow Estonia's as well as Dubai's lead. The latter has also started to test blockchain technology for securing its electronic medical records.

Due to its time-sensitive nature, blockchains shift the lens from disparate bits of information held by a single owner, to the lifetime history of an asset. Instead of big data, capturing long-term data becomes more easily possible. And that's exactly why it is the perfect solution when we need to document a patient's health record to set up reliable vaccine registries or to secure the movement of drugs through the supply chain.

BLOCKCHAIN IN PHARMA

The issue of counterfeit medicines, as the dark side of networked markets and globalization, has become increasingly pressing, both in terms of the economic cost of this global black market and the risk to human life that comes from taking counterfeit drugs. In many developing countries in Asia, Africa, and South America, counterfeit drugs comprise between 10 percent and 30 percent of the total medicines on sale.

Cindy Greatrex, Vice President of The National Alliance of Research Associates Programs remarked that for combatting fake pharmaceuticals a solution needs to be employed that stops the counterfeits from contaminating the supply chain. The best solution is to track pharmaceuticals so that digital systems linked to medication moving in the physical world are established. This is important because when you have a unique digital reference to a drug and a physical copy of that drug, it is much harder to erase or duplicate one without the other.

Blockchain offers security through transparency. It might work as follows: barcode-tagged drugs could be scanned and entered into secure digital blocks whenever they change hands. This ongoing real-time record could be viewed anytime by authorized parties and even patients at the far end of the supply chain. This would make it much more difficult for criminal networks to sell their counterfeit drugs on the market.

However, the advantages of blockchain for pharma does not stop there. Drug developers running clinical trials might be able to share clinical data and medical samples more securely. And while blockchain underpins the digital currencies demanded in ransomware attacks, the technology could also play a role in securing sensitive industry data from malicious attack.

It's clear that blockchain will have a massive impact on dealing with healthcare data. It's also worth looking at news about blockchain differently than those related to Bitcoin. The blockchain is a technology, Bitcoin is a product of it. As it is going to be more and more widespread in the future, we'll keep on writing about the many ways blockchain can support healthcare and pharma. ■

It is Important that Foreign Companies

Understand the Rules of the Game in the Long Run

Nikita Ivanov
Senior Director Government Affairs, Health & Value and Business Development, Pfizer Russia

23 March 2018

Nikita, how would you describe the route the Russian pharmaceutical industry has been taking recently? Could you highlight the key points?

The direction for the development of the Russian pharma was set about ten years ago when the national program "Pharma-2020" was introduced. The focus on localization and import substitution gave its results; according to the Ministry of Industry and Trade, the share of essential drugs produced domestically accounts for 84% of the Russian market. Today, the vector is changing; the "Pharma-2030" program discussion is focused on the development of the export potential and R&D. To address the new and ambitious tasks set by the state, international producers need a sustainable business climate conducive to growth and investment. They also need an insurance of a certain level of predictability, stability, and transparency of state regulation of the industry. The most important issues for producers are the protection of future investments in the form of providing new measures of state support. This agenda also includes issues of protection of intellectual property rights, and new conditions for medicines market access.

Since we are discussing the localization, could you please tell us about Pfizer localization projects implemented in Russia, please? Which of them, in your opinion, proved to be the most successful?

Since 2011, Pfizer has been implementing its "More than" investment strategy in Russia, main focuses of which are localization, educational programs in cooperation with leading universities, and support of Russian research projects.

At present, Pfizer has several localization projects at different stages of implementation. One of them is the transfer of manufacturing technology with a full pharmaceutical cycle of Prevenar® 13, an innovative pneumococcal vaccine to Petrovax Pharm company. This project has been successfully completed. The second project is local production of three drugs at POLYSAN company plant. These medicines help extend the expectancy and quality of life for patients with such diseases as atherosclerosis and rheumatoid arthritis, and save lives of patients with severe hospital-acquired infections. The third and our most ambitious project for today, is the localization of production of more than 30 INNs in partnership with the Russian company "NovaMedica". The portfolio includes drugs for the treatment of severe bacterial and fungal infections, cardiovascular, inflammatory, and cancer diseases. Most of them are on the essential drug list (EDL), some are also included in the Russian list of essential drugs (ONLS), and in the "7 Nosologies" program.

To implement this project, a new plant will be built in Vorsino Technopark, Kaluga Region.

I would like to highlight that Pfizer applies the local content policy not only to manufacturing. Great attention is given to development of educational programs and social responsibility initiatives. In 2017, our "More than education" program marked five years since its start. Over this period, more than 1,500 students from subject-oriented universities gained the most up-to-date knowledge in various pharmaceutical areas, and many of them now apply it at Russian enterprises. The program has become successful and now it is rolled out in the EEU countries; students from Belarus and Kazakhstan have joined the program.

Within the framework of the social initiative "More than rehabilitation", rehabilitation cabinets for children with musculoskeletal disorders and rheumatoid arthritis have been established in regional children clinical centers. As of today, there are seven cabinets equipped in various Russian regions where about 10,000 little patients have been supported by rehabilitation.

You are doing a great job!

Thank you. We keep on working on the program, three other cabinets to be equipped in Ulyanovsk Region, the Republic of Sakha (Yakutia) and Khabarovsk Region.

Today, another Russian pharma trend gains pace – contract manufacturing. Does your company management consider the opportunities that Russian manufacturers can offer?

Yes, we keep considering various opportunities for the local production of Pfizer's drugs in Russia, and our task is to support the improvement of patients' access to quality treatment. We have been pondering various localization strategies, including partnership with existing production sites, or activities aimed at construction and establishment of new ones. However, it is important that foreign companies thinking about localization understand the rules of the game in the long run, and opportunities that a stable legal framework with transparent and friendly regulation can offer. The efficiency of investment attraction and support mechanisms on the national level and the strength of the local intellectual property protection system are of key importance in making investment decisions about the technology transfer.

The violation of the patent law with respect to original drugs of some foreign companies in Russia has been widely discussed recently. Did your company face such an infringement?

Yes, Pfizer is one of the innovative pharmaceutical companies that faced the problem of generics of their original medicines coming into civil circulation before the patent term expiry. Recently, Pfizer has filed a patent infringement claim with respect to its original product Sutent®. The claim is in the court at its early stage of consideration. Pfizer has filed multiple preliminary injunction motions that were all dismissed by the courts without consideration of legal arguments, leaving Pfizer without any tools to protect their violated rights. It is especially dangerous for such drugs as Sutent®, which is purchased via government procurements.

What is the reason of such situation?

According to the current legislation, generic drugs can be put into circulation immediately after state registration of their price, even if the original product is protected by a patent. Generics take advantage of this and participate in procurements and win contracts.

Gaps in the legislation that allow generics entering the market during the effective period of the patent for the original product combined with inability to get injunction motion from courts raise a serious concern among innovative companies and investors. They want to be confident that their investments, including those in the projects on transfer of technologies to Russian partners, will be protected under an effective system that promotes investments rather than deter them, as a potential for further developments and investments will undoubtedly influence the availability of new innovative medicines for Russian patients.

What kind of innovative products can Pfizer offer to Russian customers in the near future?

Pfizer focuses on research and development of drugs and therapies that will benefit patients all around the world. Currently, our global portfolio of advanced developments contains 80 new molecules and indications, ten of which are at the marketing authorization stage. The goal is to make new innovative drugs available to Russian patients as soon as possible, like we did for the drug for treatment of metastatic breast cancer Ibrance® that was registered in Russia just 18 months after the FDA approval, i.e. earlier than in European countries. ■

The Delayed Effects

of the Pharmaceutical Price Regulation: Experience of the CIS and Baltic States

Oleg Vrazhnov
Director for CIS & Baltic states of the Russian STADA AG office

9 April 2018

Over the past few years, caused by economic crisis and national currency devaluation, the pharmaceutical price regulation changed in several countries of the former Soviet bloc. Have the changes in regulation been implemented successfully? Do they meet the purpose, which is to make the pharmaceuticals more affordable? **Oleg Vrazhnov**, the Director for CIS & Baltic states of the Russian STADA AG office, will answer these, and other questions.

ON THE "PLUS" SIDE

To evaluate the effectiveness of the change in government regulation, let us use the example of such countries as Azerbaijan and Moldova. In Moldova, the national price catalogue was developed and implemented. Margins of price mark ups were limited. In Azerbaijan, the prices for all pharmaceuticals on the national market have been re-evaluated in stages, and referenced pricing, which takes into account prices in the markets in other countries, was introduced. The changes in regulation are still being implemented there, but we can already see that there are many more positive than negative results. The state has benefited too, because now the budget funds are used more effectively, whilst patients have access to affordable pharmaceuticals.

COMMON SENSE

A regulatory body's influence on the market should be within reasonable limits. When controlling the pharmaceutical prices strictly, it is important for them to realize that every pharmaceutical company has a certain "margin of safety" based on economic criteria in relation to each product. If they do, then the manufacturer is unlikely to leave the market whilst the prices are being controlled. There is a number of examples when a socially significant and affordable medicine was withdrawn from the market, following which the manufacturer and the regulatory body held negotiations and the product was re-introduced to the market after the price was increased.

What other negative effects can a regulatory body's pressure on the pharmaceutical market bring? Let us consider not one, but two medications, for example, for the treatment of the benign prostatic hyperplasia. If the prices for these products are set at a low level, one medication can be withdrawn from the market, whilst the manufacturer of the second one can stop its marketing and educational activities in relation to this medication. As a result, the products that do not treat the condition, such as dietary supplements or medicine, effectiveness of which is not investigated fully or proved at all, will become prominent on the market. When the price is not regulated, the manufacturer of such products can have an exorbitant margin, and use prohibited, often unethical, methods when promoting the products. In the end, is a patient better off? Certainly, not.

What follows is that implementing changes should be evaluated together with the regulatory body that controls the market of dietary supplements and medical products.

It is clear that it is difficult to foresee all the potential issues which can arise in the market when the changes are implemented. Nevertheless, through a thorough analysis of the rules and principles, which will be used to calculate the highest (maximum) price, it is sometimes possible to foresee which undesirable situations may arise. For example, in Azerbaijan, various principles of price calculation based on the medicine's country of origin were used. As a result, the maximum prices for the same medicine produced in two different countries were significantly different. For example, the maximum retail price of the popular STADA nasal spray produced in Germany is 5.72 manats in Azerbaijan, whilst the price of the one produced in Spain is 5.26 manats. If STADA produced this medicine in Russia, the price would be much lower, which most probably would cause the company to leave the market. The discrimination on the basis of geography is clear: such an approach can automatically result in favorable conditions created for a certain manufacturer, or even a whole group of manufacturers operating in the same country. We have investigated whether this approach contradicts the rules set by the World Trade Organization and found serious inconsistencies.

In addition, it is important to take into consideration the difference in the US Dollar and Euro exchange rates. The prices set in the local currency should be indexed according to the Euro exchange rate, not the rate of the US Dollar, as the largest market share belongs to the manufacturers located in Europe, and not the USA. Such situation arose in Azerbaijan. Regulatory bodies allowed for the indexation of the maximum prices for a catalogue of pharmaceuticals only in case of the significant change in the US Dollar exchange rate (more than 5%), whilst indexation of prices in case of the change in the Euro exchange rate was not foreseen. What happened was that over just a few months, the Euro to US Dollar exchange rate improved by about 15% and some products from European manufacturers could not remain in the market because of the low prices set in the local currency.

OPTIMIZE THE APPROACH

The approach to setting the price for pharmaceuticals can and should be optimized.

In the countries of the European Union, where health indicators of the population are high, the coordinate system which is used almost always is when the maximum price is set based on the data taken from the group of reference countries; this is the so-called indicative pricing method. Some countries have an even simpler approach that utilizes the experience of the neighbor countries. For example, in Lithuania the maximum price of any subsidized medicine cannot be higher than that in Latvia or Estonia.

In my view, the method of setting the price based on the indicative prices in other countries is the most reasonable. In such a case, the risk that the situation, in which a price is set at too low a level and the manufacturer is forced to forgo deliveries of certain medicine when there is information available that the product of the same value exists on another market, is low. Besides, it is important to confirm this by checking the data available on the websites of official bodies, and not the open resources on the Internet: the price indicated in the catalogue does not guarantee that this product is used by the market participants. There is a risk of taking the so-called "exception price" as a basis for the calculation, for example, when the low price in the market is the result of the temporary factors like the residual stock of the products with the expiry date due soon, promotions of the manufacturer when the seasonal residual stock of the products is high, etc.

Today, in the Russian Federation, a new method of pricing in the segment of the vital and essential medicine is being actively discussed. The shift from the cost method to the indicative method is planned. It is important to prepare a solid ground for its implementation, if the change is to be effective. A team of analysts, capable of modelling the situation, should be formed; it is necessary to use the databases of data analytics companies, cooperate with specialists in the field of pharmacoeconomics, and maintain a continuous dialogue with manufacturers. This will allow for the main goal of the proposed change to be achieved, that is to not only make medicine more affordable, but to create the necessary conditions for the complete and mutual understanding between a patient and a doctor with regards to the medicine prescribed, which will lead to the improvement of the health indicators of the nation in general. ■

Privacy of Patient

Data in a Clinical Trial Framework

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Clinical trials are quite complex and heavily regulated event with a lot of data accumulated through the process by the operator of such trials. Most of such information has legally privileged status with restraints on its distribution. Large volume of various information which is necessary for conduct of the process is gathered from the patients. This data is generally circulated within the researchers' and sponsor team, and the hospitals involved in the conduct of clinical trials. The number of the patients participating in the trial may be rather high; correspondingly, each patient's personal data shall be rendered in accordance with the current legislation restrictions. After the trail, some data is used in the scientific publications, and sometimes in several research and development activities. Existing restrictions do not provide the unequivocal answer to the questions regarding the possibility or impossibility of data processing that arise due to the specificity of the clinical trials, which lead to several legal defects of the results of trials report and liability risks.

GENERAL LEGAL REQUIREMENTS FOR DATA RENDERING IN CLINICAL TRIALS

The participation of patients in the clinical trial is directly related to the necessity to provide information to the clinical trial sponsor, as well as to the research team and other parties who, according to current legislation and generally accepted standards, shall have access to such information. In particular, when collecting the data from the patients, which is necessary for the full and effective conduct of the clinical trial, researchers may face at least two types of data protection:

a) the protection of personal data of a special category, stipulated by Art. 10 of Federal Law No. 152-FZ "On Personal Data" of 27 July 2006), and

b) the protection of physician–patient privilege, provided by Art. 13 of the Federal Law N 323-FZ "On the basis for protecting health of citizens in Russian Federation" of 21 November 2011.

Personal data is defined rather widely according to the current Russian law. Concerning clinical trials name, age, contact info of the participant are "regular regime" personal data, and all health data is "special regime" personal data and has even more restricted regime of circulation.

Physician–patient privilege is any data transferred from the patient to a doctor including information on the fact that a citizen applies for providing medical assistance, the state of his health and the diagnosis, other information obtained during his medical examination, and treatment etc. This data has restricted use and circulation, but unlike some common law countries, there is no legal immunity against using this info in court.

Potential liability for the breach of personal data legislation can be up to 50,000 rubles (700 euro) for legal entities, and 10,000 rubles for senior officers (general manager in most cases) for each offence committed. Each invalid patient information sheet can be potentially taken as single offence by regulatory authority, so total fine amount can be rather high.

According to the current practice, patient data in clinical trials includes both personal data and physician–patient privilege, which might not be the regulation purpose, but it reflects the current situation in the sphere.

CONSENT ON DATA TRANSFER

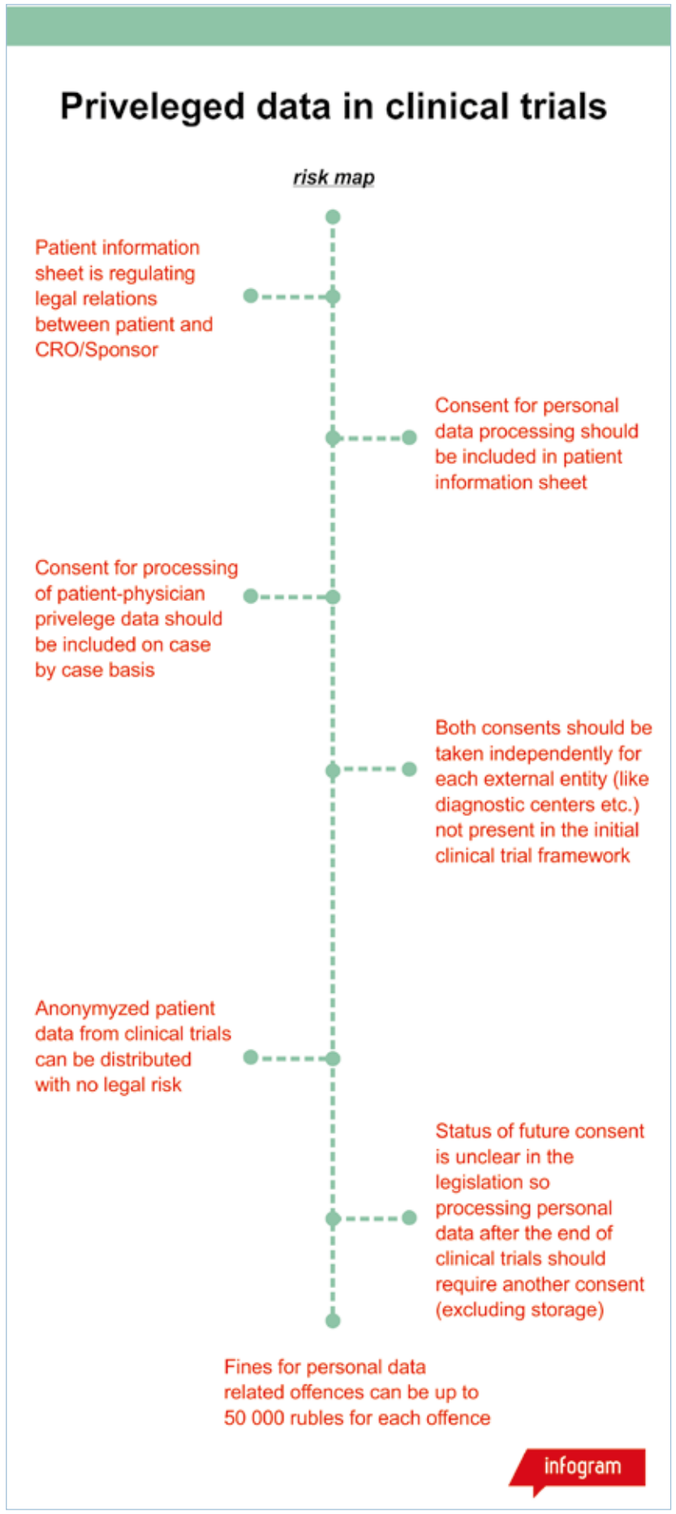
Both physician–patient privilege and personal data are inadmissible for disclosure without the written consent of the patient. It is important that the current legislation does not allow the transfer of physician–patient privilege to any legal entities. In other words, physician–patient privilege arises only when the healthcare professional is engaged in the processing and, correspondingly, the dissemination of data. The provision on medical confidentiality shall not be applied, provided information is disclosed to legal entities, as well as to the persons who are not HCPs, since the provisions regulating the personal data shall be applied in the relations of these subjects. Current law also requires consent for personal data processing, and this rule is applicable to both natural persons, and legal entities. Thus, on one hand, the data on the state of health of the patient participating in the clinical trial remain personal data of a specialized type and, along with that, having entered into the medical community; this data acquires a special protection regime in the form of consent to personal data processing. Such consent provisions exist in patient information sheet and generally cover personal data and dome patient information. In the trials according to good clinical practice rules all patient data are randomly anonymized and in most cases data exists in an anonymous form from then on. So the exact content of consent should be defined on case by case basis depending on the subjects involved in further circulation of the data.

Certain complex cases:

1. Validity of the consent after the end of clinical trial.

As a rule, patient information sheets contain a provision that the patient's consent to the processing of personal data is valid for an unlimited period of time. At the same time, clinical trials, a legally regulated action, is officially over after the submission of the report on the results of the trials. In this connection, it is unclear whether the patient's consent to the processing of his data obtained during the trial should be qualified as exhausted after the end of clinical trial. If it is necessary to use such data after the end of the trial due to some reason, should the operator of the trials obtain the consent to the processing of personal data from patients again, or future consent is possible. In other words, the initial consent may include wording, that extends its validity to some period of time in the future, and a repeated obtainment of the consent is not required. Since there is no specific regulation on data processing after the end of the clinical trial, it seems that in the described case, the consent in the patient information sheet covers the period after the end of the trial, if data processing is performed with respect to the same information and for the same purposes. If new data should be collected after the completed clinical trial, it is necessary to obtain new consent from patients.

2. Access to the data should be



obtained by an outside organization that does not constitute a research group and is involved, for example, to conduct a re-monitoring of a clinical trial.

By signing the patient information sheet, the participant of the clinical trial consents on transferring his data to the investigator, investigator institution, trial site, CRO, and sponsor which are usually named in such consent. An open question is whether all this subjects should be named in this consent, and whether the new subject should obtain the consent even if all actions are in the field of clinical trials. Current legislation does not give a clear answer to this question, however, it seems that the extension of the patient consent to the described cases would mean an excessively broad interpretation of it and regulatory trends comply with this conclusion. Therefore, in this case, a new data processing is performed by the new subject and it is required to obtain a new patient's consent to such actions, which may be not possible at the moment.

CONCLUSION

We suppose that the current Russian and the EAEU legislation concerning the clinical trials, personal data, and physician–patient privilege should define clinical data of patients as a special data sui generis having implied consent on processing both personal data, and physician–patient privilege (when necessary). Such consent should cover both clinical trials period timeframe, and R&D actions in the future connected with the results of such clinical trials. For insuring privacy of patient data and preventing its unlawful distribution, all such operations should be backed up with liability for the breach of personal data legislation (such offence already exists). Elimination of such uncertainty will benefit the further development of clinical trials market. Currently, to avoid that current point, pharmaceutical companies and CROs should tailor their patient information sheets and clinical trial agreements very carefully, minding all regulatory and privacy law details. ■

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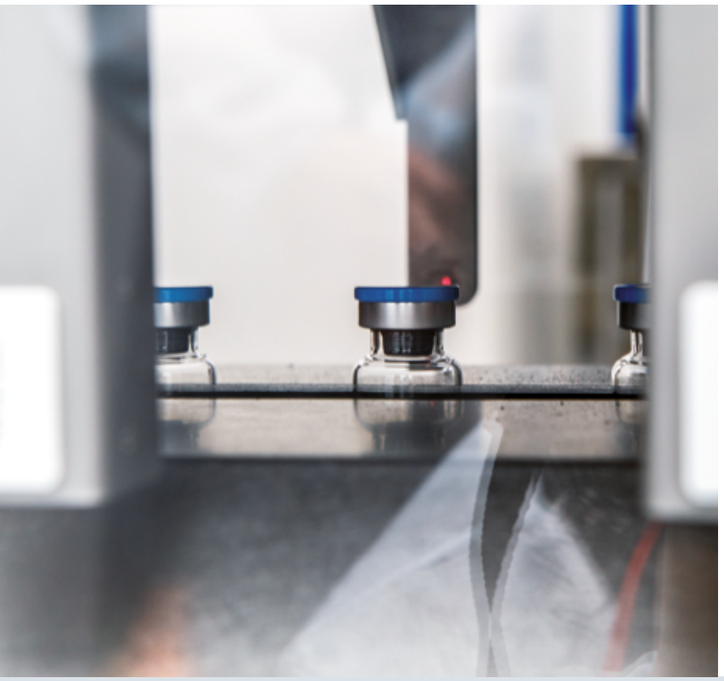
Nacimbio

Launches a Production Site for Preparation of Botulinum Toxins

National Immunobiological COMPANY

6 April 2018



Microgen, incorporated in Nacimbio, launches a new modern site for preparation of unique Russian-made botulinum toxin type A – drug called Relatox. It will be brought into production by the end of 2018.

Thanks to new production capacities, it will become possible to produce up to 200 thousand drug packages a year.

The drug is prepared in the full cycle process in Russia at the Ufa Microgen – Immunopreparat enterprise. The new site will be used only for preparation of botulinum toxin type A. Relatox is used in cosmetology for correction of facial wrinkles in adults, treatment of blepharospasm, as well as in neurology for several indications. The project, in terms of which the stages of qualification and validation of the production site have been already completed, is implemented in accordance with GMP standards, which are compatible with the requirements for facility management and quality control of medicines at the international level.

A complex of production facilities will be available on the new production site, including cool dehumidification machine, aseptic filling monoblock unit and decontamination sluice, which provides a full cycle of decontamination of bottles before marking and packaging.

"Launching a new production site will increase the company's performance related to the implementation of import substitution policies in pharmaceutical industry, in such segments as cosmetology and neurology. High-tech equipment will ensure the production quality control at the highest international level", – said **Sergey Goryunov**, the first Deputy General Director of Microgen.

An automated polyparametric inspection system will become available too. The system with a conveyor line in automatic mode can perform total monitoring of the quality conformity of the finished product in bottles (up to 800 units per minute) with the established requirements, including check of the filling level, circular inspection of caps, detection of scratches and cracks. The system's pulsed x-ray technology also provides automatic identification of tightness, compositional uniformity of the finished product, foreign inclusions and, in case of their presence, rejection of bottles.

The world demand for botulinum toxins increases every year. According to various estimates, the world market volume may amount to USD 7.3 billion by 2025. For comparison, it was estimated to be twice as little in 2015 – USD 3.4 billion. It is expected that its average annual growth rate may amount to 7.9% from 2013 to 2025. Experts associate the upward trend with the increasing number of consumers in the age group from 25 to 65 years, and the growing popularity of non-invasive and minimally invasive procedures.

Russia is one of the largest consumers of cosmetology injections. According to market representatives' estimates, the registered drugs (Botox, Dysport, Xeomin, Lantox, and Relatox) brought more than 4.7 billion rubles in 2016. The market is characterized by the predominance of sales of drugs related to "gray area segment". According to the analytical center Vademecum, there were about 280 products for cosmetic injections in the domestic aesthetic medicine in the first quarter of 2017, and it should be noted that more than half of them did not have registration certificates.

Botulinum toxin sales geography covers all regions of the country. In 2017, the Russian drug enjoyed the greatest popularity in the Central Federal District. The share of sales in the region amounted to about 32% of the total volume in packages. The second and third place in the rating belonged to the Volga Federal District (about 26%) and the Southern Federal District (about 14%).

30% of world sales of botulinum toxin drugs account for injections in neurology. According to various estimates, the average annual growth rate in Russia

amounts to 11-15%. The country continues to study the properties of botulinum toxin type A in order to identify new mechanisms of action in neurology.

For example, since 2016 it is approved to use the drug Relatox for indications of upper limb spasticity muscles after a stroke. In December 2017, clinical tests of the drug for treatment of spastic forms of ICP (infantile cerebral paralysis) at the age from 13 to 17 years were completed. Before that, all means for treatment of these diseases in Russia were represented by foreign developments. Already this year, the producer has completed clinical tests on expanding the indications for use of Relatox for treatment of axillary hyperhidrosis. It is planned to further increase indications for use of the drug for therapeutic purposes.

The annual increase in the number of physically challenged persons with ICP is about 2%. In Moscow there are about 10 thousand physically challenged persons with the consequences of ICP, half of them are children. In the Moscow Region, there about 5 thousand disabled persons. Totally, in Russia there are about a million disabled persons as a result of ICP. The frequency of stroke varies in different regions from 460 to 560 cases per 100 thousand people. About 36 thousand strokes occur every year in Moscow, in St. Petersburg – 12 thousand cases per year. In recent years, the frequency of the disease has become 2-3 times higher than the frequency of myocardial infarction. According to statistics, 85% of people, who suffered a stroke, need an intensive course of functional changes recovery. The frequency of stroke significantly increases with age, starting from 30 years. Old age is the most significant risk factor for stroke. 95% of strokes occur at the age of 45 years and over, two thirds – over the age of 65 years. Hyperhidrosis affects 3 to 15% of people in the world. ■

ABOUT THE DRUG

Relatox drug, the only Russian alternative to imported products, was introduced to a professional audience in 2014, and for some neurological indications such as treatment of spastic forms of infantile cerebral paralysis (ICP), hyperhidrosis, and a number of other diseases, it only approaches the market. According to experts, the drug has broad prospects of taking a significant market share both in cosmetic and neurological segments. Relatox is cheaper than foreign analogues and its quality characteristics meet the world's requirements. The difference in the average package price for Relatox compared to some other drugs registered in Russia can reach almost 50%.

The enterprise started its development in 2001. In March 2017, Microgen received a registration certificate on the entry of Relatox in the State Register of Medicines on a permanent basis.

DIFFERENCES FROM IMPORTED PRODUCTS

All botulinum toxin drugs are based on protein complexes of various sizes with a complicated structure. In contrast to chemically synthesized drugs, botulinum toxins are produced by living organisms. This peculiarity does not allow producers to obtain identical drugs, so all existing botulinum toxins are unique and have individual properties and characteristics. Doctors and cosmetologists are aware of these distinctions and consider them in their practice. Relatox, in particular, has the following properties that distinguish it from other drugs: it has limited diffusion in tissues. This property insures the targeted effect of the drug on muscle fibers in those areas where it was injected, with minimal impact on neighboring tissues. Thus, it has potential to provide greater security in use.

The duration of therapeutic efficacy and relaxing effect of the drug compared to biosimilars is distinguished by a slightly higher intensity. In contrast to imported competitors that use lactose and sucrose in the production of drugs, Microgen added other disaccharide into Relatox – maltose. Maltose intolerance is less common in people than lactose and sucrose intolerance, so the risks of allergic reactions in patients are relatively lower.

There are no facts of production and distribution of counterfeit Relatox, while among the imported botulinum toxins there is a great number of "gray area" drugs and counterfeits. Relatox has a special protective container that provides safe storage and use of the drug after opening its original package. ■

Aspectus Pharma -

2 Years from the Idea and Project to the Enterprise Ready for Audit

Interview with Valery Semenov, Executive Director of Aspectus Pharma

1 March 2018

Valery, could you please tell us a little about the history of the newly organized enterprise Aspectus Pharma.

Aspectus Pharma is a young company established on 26 January 2016 as part of the Euroservice Group of Companies, which has been providing healthcare facilities of the Russian Federation with highly effective hospital pharmaceuticals and healthcare products for more than 20 years. In order to, firstly, provide citizens and healthcare institutions with medicines from the list of domestically produced vital and essential medicines (VEMs), whilst also considering the direction of the "Development of the pharmaceutical and medical industry" state program for the period from 2013 to 2020, the company management decided to set up its own pharmaceutical production facility. I'd like to point out that we managed to create the manufacturing complex in as little as 2 years! We initially set ourselves an ambitious task: to organize a complete production cycle from developing modern, high-quality, and safe medicines to producing them. The company plans to manufacture non-sterile medicines like capsules, uncoated tablets, and coated tablets. We intend to obtain the appropriate license this year.

Could you tell us what products and in what quantities will you produce them in more detail?

If we are talking about a complete cycle production program, our goal is to produce at least 20 million tablets and 50 million capsules per year. What are these preparations? First, we plan to start producing medicines for the treatment of diseases of the cardiovascular system for the following indications: acute myocardial infarction; ischemic stroke; encephalopathy; recovery period after cerebral circulation disorders; violations of peripheral circulation (intermittent claudication, Raynaud's disease, trophic ulcers). According to ATC classification, these preparations are as follows: angioprotectors and microcirculation correctors, medicines for the heart treatment.

The next important part of our production program will be to manufacture products together with our contract manufacturing partners. The production capacity of the packing and labelling stage site is planned to be at least 12 million packs of tablets and capsules and 3 million of pre-filled syringes per year.

Aspectus Pharma positions itself as a full production cycle enterprise. Why have you done it? Isn't it cheaper to purchase substances on the Asian/Indian markets?

Today, many enterprises use purchased substances and a few use their own. We pay attention to the tasks that the state sets before the pharmaceutical industry, and, following the import substitution policy, Aspectus Pharma plans not only to pack, but to make products starting from the very chemical

synthesis, synthesis of substances. In addition to maintaining existing processes, if we are talking about generics, our company plans to have original preparations in our portfolio developed scientifically by our own efforts. At the outset, in order to achieve the maximum economic efficiency, we set the following as priorities for ourselves:

- Development, production, storage, and sale of pharmaceutical substances;
- Development, production, storage, and sale of pharmaceuticals, including on contract basis;
- Testing and research in scientific fields

Aspectus Pharma is currently at the final stages of completing the preparatory work for obtaining the licence to manufacture medicines for medical purposes from the Ministry of Industry and Trade of Russia.

As soon as we are granted the licence and certified on GMP compliance, we will be ready to proceed with the synthesis of the substance, and to produce the final medicine on its basis, and introduce it on the domestic market. Among the company's plans are certainly also the export programs, but they will not be effected during the first years of the full-scale functioning of the production facility.

What is the substances synthesis laboratory busy with today?

The initial substances we are working on are not currently registered on the territory of the Russian Federation. Both for the Regulatory Authorities and us this will be the first chemical substance registered as having Russian status. Actually, in this process, you can see both Aspectus Pharma's succession as a company in the organizational structure of Euroservis GC, and the import substitution policy.

It is already obvious that besides manufacturing your own products you will also be part of the now mainstream "contract manufacturing"?

Yes, our production program envisages the use of contract manufacturing, i.e. to produce finished medicines based on bulk products received from our partners (tablets or capsules, pre-filled syringes). To date, a number of agreements have been reached with foreign manufacturers on this matter.

During the "Contract Manufacturing" round table held at the Pharmtech & Ingredients exhibition, Natalia Chadova, Head of the Pharmaceutical Production Inspection Department of FBU GILS and NP, said that today the demand for contract sites from foreign partners exceeds what the Russian pharmaceutical plants can offer. Do you feel this excessive demand?

Yes, I would agree with this opinion. An increasing number of foreign pharmaceutical companies planning to operate in Russia on a long-term basis are considering the option of setting up their production as per their development policy. We are aware of this because Aspectus Pharma, being a part of the Euroservice group of companies, has been a reliable partner of leading European, American, and Indian pharmaceutical companies for many years. It is by responding to proposals that started to come quite often from partners, the founders of the company decided to develop the manufacturing capabilities, and to build the production site here at home.

What are the key requirements of foreign companies for Aspectus Pharma as a contract site?

First and foremost, it is to ensure consistent quality of products in accordance with the levels of the most stringent European standards. That is, the production site must comply with the most stringent requirements of GMP (Federal Law No. 61-FZ "On the circulation of medicines", Order of the Ministry of Industry and Trade of the Russian Federation No. 916 "On Approval of Good Manufacturing Practice Rules", EAU Rules of Good Manufacturing Practices (GMP)). When designing and setting up the enterprise, the adhering to and scrupulously following these strict rules from the project to implementation were our top priorities. To date, several inspection groups from foreign partners visited our site, and they commended our efforts. Another important factor in selecting a contract site is its geographical location.

Today, the most production sites are located either in Moscow, or Kaluga regions, which are rather far from Moscow, or in very distant regions. Aspectus Pharma is conveniently located logistically, and it is in close proximity to the office and warehouses of the parent company EUROSERVICE Firm JSC. Although strictly speaking we are located in the Moscow region, we are essentially in Moscow. (Aspectus Pharma production complex is located in village Razvilka – Ed. remark). Our enterprise site consists of a raw materials warehouse, products quarantine warehouse, reference samples warehouse as well as a warehouse of our partner, which is already pharmaceutically licensed, and it's where we plan to store our finished products.

Without a doubt, product distribution also attracts partners. Aspectus Pharma is a manufacturing facility in a vertically integrated corporate holding: it is a production site but it is also among the TOP-10 National Pharmaceutical Distributors.

I cannot but note that the equipment installed at Aspectus influenced partners' decision. In order to produce

high-quality products, a quality control process must be established at the outset. Our QA laboratory is equipped with the newest analytical equipment from the leading companies. We opted for Agilent products for chromatographic research methods. For accelerated aging, computerized BINDER systems are installed: several climatic chambers are combined into one network to register all parameters, record and archive this data. The newest equipment is also installed in the microbiological laboratory. When purchasing the equipment, we preferred European manufacturers. For example, we have a blister cardboard line from MARCHESINI GROUP, a well-known Italian company that has been supplying this type of equipment for a long time.

We also have equipment from domestic manufacturers. As such, we opted for laboratory furniture from LaMO. We approached the selection of furniture fairly carefully; we also considered European manufacturers and even visited the sites where their furniture was installed. LaMO, a Saint Petersburg company, offered a solution similar to the one by the European companies in terms of design, but the delivery terms were significantly shorter whilst the price was significantly lower. In addition, we opted for the Russian manufacturer also because of the fact that we can never know with a 100% certainty the final specifications of the furniture when equipping laboratories and production facilities: there are always some changes (for example, when moving a laboratory or changing what the room is used for, furniture mobility is very important and that is why we, of course, opted for the furniture with an iron base and a plastic table top, which let us quickly transform it and never worry about the consequences).

The geographical location of the company also played its role: if we chose a foreign supplier, then the process of assembling, let alone laboratory furniture transfer, identifying any factory defects and replacing them would take much longer. In this regard, it is much more convenient to work with a Russian supplier.

What are the requirements that Aspectus Pharma has towards a potential partner?

On our end, we expect that we and our partners cooperate in a mutually beneficial manner.

As a contract site, we also have our own specific criteria, according to which the partners are selected: first of all, it is the past relationship with the group companies and the product portfolio, as we are interested in launching of innovative products demanded on the market. Then, certainly, the economic aspect also plays a role, that is, the medicines must be competitive, and must be of high demand among the hospitals and citizens in the Russian Federation. We will first work with those companies that have such drugs in their portfolio and want to market them in Russia. However, we are not waiting for them to come to us: we are always in negotiations and discussions with new companies and acting partners of EUROSERVICE GC. Of course, if some new companies initiate similar relationships and are interested in marketing their products, we are ready for negotiations. Aspectus Pharma is a fairly young company and we are only taking our first steps. If we compare the company's development with a child's growth, we are still in babyhood and therefore, it is still premature to talk about Aspectus Pharma's widespread popularity and a solid place in the information space. But we are working on it.

Could you name your company's partners who helped you implement the idea of creating a modern manufacturing facility like that?

As I have mentioned, Aspectus Pharma is a very young company, created from scratch in less than 2 years. It is thanks to our partners that we gained such a rapid pace and transformed the idea and project into an enterprise ready for audit in such a record-breaking short time. Among them, I specifically would like to mention Pharmcontract Group of Companies, whose employees delivered and launched the set of equipment for pharmaceutical substances synthesis and R&D/microbiology/QA laboratories on time.

For a newly organized manufacturing facility with a complete production cycle, among the important cooperation features were the prompt preparation and approval that were characteristic of URS. Representatives of this partner performed a detailed specifications study of the reactor equipment and organized SAT and FAT tests. Almost all our employees worked very closely with the service department of Pharmcontract GK, which not only installed, IQ/OQ validated and commissioned,

but also trained the staff, programmed the methods and algorithms required in our routine work.

In general, we were not only satisfied, but pleasantly surprised by this high level of service combined with professional competence. Naturally, our cooperation will continue and we will recommend this company to our partners if they need to perform similar tasks.

In your opinion, is Russia's regulatory system ready for contract manufacturing? What should be changed in the legislation?

Today, the Russian legislative framework regulating the national pharmaceutical production, Federal Law No. 61-FZ "On the circulation of medicines", Order of the Ministry of Industry and Trade of the Russian Federation No. 916 "On Approval of Good Manufacturing Practice Rules", EAU Rules of Good Manufacturing Practices (GMP), is sufficiently harmonized with the European regulations, and even more stringent in some aspects. Therefore, it is quite comfortable for us to work within this structured framework. We focus primarily on Russian laws, and, since they are almost identical to the European regulations, even our foreign partner companies have no questions. In other words, the basic legislative level is rather high today. Therefore, after passing the Russian GMP audit, we will be prepared to receive foreign inspectors, as obtaining the European GMP certificate will be a significant advantage for us, as a contract site.

In addition to the manufacturing facility, Aspectus Pharma has medical laboratories too. Are you planning to obtain GLP accreditation for the laboratories?

Today, as part of our enterprise we have 2 laboratories: the analytical control and microbiological laboratories of the quality control department. First we plan to receive a production license, for which the enterprise should have such laboratories as part of it; and in the future, the microbiological laboratory will most likely be accredited. The GLP certificate is not in the near future plans.

Perhaps the most discussed issue of 2017 and 2018 is the one of the marking. How do you plan to tackle it? Which Track & Trace systems do you use?

Immediately after Roszdravnadzor (The Federal Service of Surveillance in Healthcare of the Russian Federation) announced the launch of the labelling pilot project using means of identification of medicinal products for medical purposes, Aspectus Pharma joined its working group. We participate in all meetings of the working group on the automation of the system for monitoring of the circulation of medicines. For ourselves, we have set the goal to be the pioneers in this field and to implement, at the earliest time possible, all stages of the marking in our products: serialization of products based on two-dimensional matrix barcode Data Matrix and the subsequent aggregation. Aspectus Pharma follows all the items in the methodological recommendations, answering the following questions: what criteria should the marking process comply with, what equipment should be used, what should be the final result of the data exchange with the FTS being the aggregator of this system. Today, there are several marking equipment options available. We plan to install the Italian equipment from the Marchesini Group in the serialization/aggregation area, because, when selecting a specific system for the primary, secondary and group packing sector, we concluded that it is more convenient for us to have the entire line from one manufacturer. This way the blister cardboard line INTEGRA together with the serialization/aggregation line TRACKPACK constitute a single packing complex building a blister and a pack, applying control identification marks, serializing and then aggregating it in a corrugated box – the whole process from the beginning to the end.

The production and delivery time for such an equipment is 9 to 12 months, but we managed to place the order on time; especially since the European countries are now also switching to the new labelling rules and marking equipment manufacturers already have a queue of production orders. However, it is said now that such equipment can be ordered from domestic manufacturers too.

Despite the deadline being 2020, the pharmaceutical community is already switching to Pharma 2030. Export is one of the items of the new policy. How competitive are Russian medicines on the foreign markets, or can we only sell our developments to Big Pharma, which will then become international products registered in the US? Or, when speaking of export, do we mean the EAEU markets? What has Aspectus Pharma already presented or prepared to present to the world?

In order to export products to Europe, a European GMP certificate is required, and a few domestic enterprises have it now. If we are talking about the EAEU market, our company plans to move there after the Russian market. In the long term, we also consider the possibility to export to Latin American countries, where regulatory requirements are less stringent, and many domestic enterprises consider these markets as their first step onto the foreign markets. Perhaps, Aspectus Pharma will follow the same path. After we receive the European GMP certificate, we will consider the possibility to export to the EU countries, but this is not in the near future.

One last question. It's no secret that human resources are of key importance. What can you tell us about it at Aspectus Pharma?

The success of any company comes from several factors: a correctly defined policy, a modern production base and, of course, a team of professionals, because, as they say, "human resources are of key importance". At Aspectus Pharma, we are attempting to build a "dream team" by attracting employees with high motivation and qualifications, searching for competent and experienced specialists to appoint to the key positions. Our team has truly unique employees, like, for instance, technologist Valentina Fedorovna Okhotnikova who has worked in the pharmaceutical industry for more than 50 years. She shares her knowledge and experience with young employees. Our young employees are not recent graduates, but came to work for us from the best and the most progressive Russian enterprises. At this stage, we invite the experts who already have the experience in the areas we plan to develop. Nevertheless, we consider young people too.

Our production site is designed in a way that the R&D area is very clearly arranged: it is possible to follow the route of a birth of a medicine, if we are talking about a pill or capsule. Therefore, we do not exclude the possibility of offering training to students, postgraduates and young scientists as part of the agreement with the leading chemical and pharmaceutical university faculties. ■

Alexandr Spasskiy
Head of Representative Office
OOO "LaMO"

When building the pharmaceutical factory, our distributor Pharmcontract GK had to design two new laboratories complying with latest requirements: the analytical control laboratory and the microbiological laboratory. In the process of designing and building the laboratories, it was essential to select the suitable laboratory furniture manufacturer so that the project would succeed and "everything was in the right place". It was also important to establish communications and maintain them beforehand.

Furniture is of major importance in the laboratory. Important characteristics are safety, durability, ergonomics, quality, colour solutions, functionality, modularity, etc.

Today, there is a significant number of domestic and foreign laboratory furniture manufacturers presented on the market. Aspectus Pharma was very careful when selecting the supplier. They tried to take into account all the pros and cons of various manufacturers. Their main requirement was to have safe, pastel-coloured, light, comfortable, and reliable furniture in the laboratory.

All nonworking surfaces are made of steel. This material is durable, solid and fireproof. In addition, it may be cleaned with literally any disinfectant, and cannot be contaminated. We paid considerable attention to the design and color solutions of the products. Functionality and aesthetics should, of course, complement each other, so that employees of the future laboratory could feel comfortable at their workplaces.

Our specialists carefully prepared a project considering every detail, which were then implemented. Some products were customised. Meetings with contractors building and design the manufacturing facility allowed us to establish a mutual understanding. In fact, this approach allowed us to coordinate and promptly solve all emerging issues. We offered the best table tops, like the Italian monolithic seamless ceramics or the American Wilsonart monolithic plastic table tops.

Before commencing production, rooms were measured, requirements were adjusted accordingly, and necessary changes were introduced to the furniture structure and design.

Our highly professional customer service quickly and accurately assembled the furniture and supported the project.

As a result, we have built a truly splendid laboratory. And we hope that the employees of Aspectus Pharma will work there with great pleasure! ■

Success Formula of Pharmasyntez

23 March 2018

Pharmasyntez is the largest player in the pharmaceutical market that manufactures drugs and substances in great volumes, and has an extensive facilities network from Saint Petersburg to Ussuriysk. The history of the company begins in Irkutsk with an import substitution program. Twenty years later, Pharmasyntez has taken the lead in manufacturing domestic antituberculosis, anticancer, cytostatic drugs, and medicines for HIV0 treatment, and other major socially significant diseases. **Alexander V. Keiko**, Senior Vice-President of Pharmasyntez Group of Companies is sharing the recipe for successful company's growth.

Statistically, about one in two antituberculous tablets in Russia is manufactured by your company. How did you manage to get such a strong position?

We do our best to remain highly sensitive to all changes in the market and to supply and demand, in the first place. We've been keeping our finger on the pulse. Pharmasyntez looks for and finds viable solutions, we are ahead of the field here. We offer better, all-inclusive, user-friendly services to our customers. Given that our company has been present on the market for 20 years, we have already proved our credibility by what we do, not by what we say. Quality and accessibility are the policies that make us stand out as the best on the market. Beyond that, our company is the only one to manufacture drugs for multidrug-resistant tuberculosis. It is worth noticing that there are only two drugs for this kind of tuberculosis worldwide and one of them is manufactured by our company. Our fight against tuberculosis takes place together with the development of other important areas. We understand that we deal with socially significant disease that stands apart in this range. We produce pediatric doses, but the demand for them is low – thank goodness, children rarely have tuberculosis. However, we find it important to manufacture drugs, even if they are economically unprofitable, but can save the life of a child. We consider this social responsibility of our business.

What other drugs from Pharmasyntez are top-selling products at the moment?

Pharmasyntez holds almost a 50% share of the drugs for HIV market. Thanks to our efforts, health professionals will get an innovative drug for type 2 diabetes this year. Pharmasyntez is the only Russian company in the whole history of Russian pharmaceutical industry that brings innovative DDP-4 inhibitors to the market. Supplying drugs for type 2 diabetes with delivering all-inclusive services to healthcare system is our main goal for 2018. I am sure that this drug will hold a significant share of the market as soon as in 2019.

When speaking about manufacturing process, equipment for manufacturing modern drugs can hardly be named unique. Technology is the most delicate part of this process and is of great importance. Many intellectual resources are to be invested in its development. Our company has become well versed in it, and combines its experience with the transfer of new technologies.

What objectives does the company have on the domestic market today? What about its export development line?

Import substitution, becoming less depended on foreign supply in a wide range of drugs, and mastering complex technologies for manufacturing modern drugs, indeed, still remain our main goal. The other objective is mastering new

modern manufacturing technologies. As for export, there is already a dozen of countries we are working with. It takes time and effort. Registration of pharmaceutical products in different countries takes a lot of time. We are examining this issue closely, and we are planning to increase export.

Are you going to manufacture any other innovations besides the new drug for type 2 diabetes?

Pharmasyntez conducts its own research and development of original drugs almost since the day it was founded. For the moment, we have managed to bring only one original product to the market. Creating an innovation is complex and very time-consuming, however, we have learnt a lot by our first experience of bringing a new drug to market and we now know how to proceed. At this moment, there are several new drugs that are going to appear. Some of them will be a great surprise not only for the national, but also for the world markets as well.

We are looking forward to this news, but we respect the "Don't count your chickens before they are hatched" principle. Still, remaining in the topic, we would like to know what kind of technological innovations have already been implemented at your manufacturing sites?

We do our best to keep an eye on new manufacturing technologies in the pharmaceutical industry and to adopt the best of them at our sites. But manufacturing of drugs is not everything, auxiliary manufacturing (e.g. clean utilities manufacturing, etc.) plays a significant role. Our company motivates every employee to to keep up with novelties in his/her field of competence. We organize Innovations & Rationalization Awards annually. This event has already helped us to save dozens of millions of rubles thanks to technical solutions proposed by our employees. According to our estimation, this competition delivers 2,000% return.

I can't believe it! Employees bolster their company. And when talking about authorities and their support for the pharmaceutical sector, what kind of questions arise here?

We have no big questions for the authorities, we work according to the established rules. At the same time, there are some procedures that remain non-transparent for us and other market players. I am sure that it would be no wonder if we witness the reformation of this area soon, and we may even take part in it.

However, does Pharmasyntez have any state support?

We take part in all kinds of programs granting subsidies and preferences and we receive state support regularly in different forms. Thanks to that, our growth rate is high. On this occasion, I would like to express gratitude to the Government of the Russian Federation and to the Ministry of Industry and Trade for their active support and efficient "Pharma 2020" state program.

Pharmasyntez has several manufacturing sites and plans to build new facilities. How do you solve the employee issue?

It is an important issue and not only in the pharmaceutical industry. There is a prominent education quality degradation trend in Russia. It is obvious. We are confronted daily with half-educated and poorly motivated candidates to fulfill our vacant positions. The only way out that we can see is to create a feedback, to articulate quality requirements to higher education institutions that industry imposes on candidates. We cooperate with several leading higher education institutions today not only on training issues, but also on creation of specialization areas needed. Wishing to work in a creative and responsible manner is key for future members of our team, and if a candidate has it, the company will find a way to improve his or her professional development.

Let's speak about modernization of manufacturing sites and the adoption of GMP standards. How much is your company planning to invest into that?

Adopting the GMP standards took place officially in 2015 and became no milestone event for the company. The GMP's essential procedures had already been implemented in our company by that time. We followed those rules anyway, before they became compulsory in Russia. This is why it is difficult to identify our expenses related to creation of the GMP system at Pharmasyntez. Modernizing manufacturing is a non-stop process, the average age of our equipment does not exceed ten years and reduces progressively. As for investing in new sites, we suppose that we will manage to raise it to no less than 10 billion rubles during the following three to five years.

If we look at the whole picture, what direction, in your opinion, does the pharmaceutical industry follow at this moment in Russia?

Russian pharmaceutical industry is developing very quickly, much quicker than its competitors. Its development rate is very high today. Undoubtedly, we have to develop substances manufacturing. To become stronger, we need to give life to innovative molecules, to bring them to the market and to control prices of the manufactured goods. It is necessary to adopt pharmaceutical products support program. It will open new horizons for the sector. ■

The Fifth Element of Russian Pharma

13 March 2018

NovaMedica, a portfolio company of RUSNANO, has concluded the biggest SPIC for creation of a greenfield pharmaceutical manufacturing facility in the pharmaceutical industry

Russian pharmaceutical company NovaMedica (investment project of Rusnano), Ministry of Industry and Trade of the Russian Federation, and Government of the Kaluga Region have concluded Special Investment Contract (SPIC). Denis Manturov, Minister of the Ministry of Industry and Trade, Anatoly Artamonov, Governor of the Kaluga Region, and Alexander Kuzin, General Director of NovaMedica, signed the contract. Arkady Dvorkovich, Deputy Chairman of the Government of the Russian Federation, and Anatoly Chubais, Chairman of the Executive Board of Managing Company "RUSNANO", were present during the ceremony. SPIC envisages creation of a greenfield facility for manufacturing of sterile injectable dosage forms in the Kaluga region. During its implementation, NovaMedica will invest more than three billion rubles in the creation of the facility. Today, this SPIC is the biggest one in the Russian pharmaceutical industry in terms of the amount of investments.

State-of-the-art pharmaceutical complex of NovaMedica will be constructed in the Industrial park Vorsino in the Kaluga region. Large portfolio of EDL products of Pfizer, strategic partner of NovaMedica, will be localized there, and the facility will produce drug products developed within the own R&D program of NovaMedica as well. The facility will be created in full compliance with the strictest international and Russian standards of quality including GMP EU. In future, this will allow NovaMedica to export part of the manufactured products to international markets, which is one of the conditions of the SPIC. In the frameworks of the investment project implementation, the company will create about 300 high-tech jobs.

"It is the fifth SPIC in the Russian pharmaceutical industry – thus we are developing competences in a large number of therapeutic areas", noted **Denis Manturov, Minister of the Ministry of Industry and Trade of the Russian Federation**, *"It is planned to localize unique drug products, which do not have analogues, and this makes the Russian Federation actually the second world manufacturing site"*. According to the head of the MIT Russia, the facility will manufacture socially significant drug products demanded by the Russian hospitals. These are injectable drugs for treatment of oncological diseases including children, drug products for general anesthesia, blood stopping drugs, drugs for inflammatory diseases treatment as well as severe bacterial and fungal infections.

"Implementation of the investment project of NovaMedica will help to significantly increase for the Russian patients availability of contemporary, effective, and safe drug products the majority of which are included into the EDL list, and the price of which is controlled by the state", the Minister concluded.

"SPIC with NovaMedica is the second in the Kaluga pharmaceutical cluster. It is obvious for us that this instrument is an effective measure to support investors in implementation of promising projects, it confirms responsible attitude of the government of the region to business partners, and strengthens our mutually advantageous cooperation. It is important that eventually it will make a favorable impact on localization of innovations in our region, and will increase manufacturing volumes of products in demand, tax liabilities, and it will help to create new jobs, including high-tech", said **Anatoly Artamonov, Governor of the Kaluga region.**

"Our portfolio company NovaMedica not only distributes drug products of foreign manufacturers, but also invests into creation of innovations, having constructed and launched its own R&D Center in Moscow. The next logical step is to create a local state-of-the-art manufacturing facility which will manufacture products both developed in-house, and drugs from Pfizer's portfolio, who is the partner of NovaMedica. It is important that 20% of all the biotech products manufactured at the facility will be exported, as it is envisaged by the SPIC conditions", said **Anatoly Chubais, Chairman of the Executive Board of Managing Company "RUSNANO" and Chairman of the Board of Directors of NovaMedica**.

"The Government of Russia creates powerful instruments to enhance transfer of foreign pharmaceutical technologies to Russia. With the help based on large experience, knowledge, and investments of our investors and Pfizer, our strategic partner, as well as on the opportunities provided to us by the state, we are creating a plant which will set new high standards of localization of foreign pharmaceutical innovations in Russia", said **Alexander Kuzin, General Director of NovaMedica**.

As per the data of the MIT Russia, within implementation of the SPIC, more than 9.3 billion rubles of investments were attracted into the Russian pharmaceutical industry in total, taking into account the SPIC of NovaMedica. ■

Alexander Kuzin:

You Cannot Always Create Everlasting Greenhouse Conditions for Domestic Companies

Alexander Kuzin
General Director of the pharmaceutical company NovaMedica

What is the way of development of the Russian pharma until 2030? What priorities in the development and challenges will be topical for the industry today and tomorrow? These are the questions which occupy minds of all key players of the market, experts, and industry regulators. Sure thing! The stage where the Russian pharmaceutical industry is now can definitely be called transitional – review of results of the state program "Pharma 2020" and discussion of principals of the new state program "Pharma 2030".

RBK, one of the major media holdings of the country, is keeping a close eye on the development of this story. Representatives of the state and business discussed results of "Pharma 2020" and its further development during the conference set up by RBK this spring.

WHAT ABOUT THE PRICES?

Cutting the prices for drug products will take place not only due to the fact that the state is making attempts to regulate them, but also due to the increase of competition in Russia.

As you know, some companies in the USA are experiencing problems, and they try to either raise prices for their products, or to sell out OTC departments. The reason for it is high competition. They have such a system of procurement and tenders which leads to price drop without the Federal Anti-Monopoly System (FAS). I think that in Russia, prices are going to decrease as well, and not only due to regulatory activities of the FAS, but also thanks to the competition. This is certain to happen. In this situation, the right thing is to make the cake, i.e. the market, bigger. Is there any background for it? Today, drug utilization in Russia is heavily held back by the low purchasing power. So let prices be lower and let the consumption grow! Vladimir Putin, President of Russia, has recently said that 3.8% of the budget for health care can be turned to 5%, meaning there are capacities for it. The most clear step, from my prospective, is introduction of the medicines reimbursement program.

REGARDING EXPORT

On 7 March, we signed Special Investment Contract (SPIC) with the state to localize drug products from the portfolio of our partner – Pfizer. Our SPIC envisages an obligation to export not less than 20% of the manufactured biotech products.

Moreover, I meet with representatives of Big Pharma on a regular basis, who are interested in contract manufacturing at the Russian capacities. We see the interest in placing such orders in Russia, and this is not least because of the third-is-out rule. This is the way to increase export of the drug products manufactured in Russia as well.

REGARDING R&D

We launched our own R&D Center in Moscow a year ago. Considering prospects of its effectiveness, we follow the same logic: we shall not isolate ourselves in our world – Russia is only 1.7% of the world market. Developing new products, one shall focus on the global market. Only this approach can return investments into R&D. In general, I agree with the position of the Association of International Pharmaceuticals Manufacturers – you cannot always create everlasting greenhouse conditions for domestic companies – one day, seedlings shall be put into the open ground and grow further. Of course, we can create special mild climate for the manufacturers in the 1.7% of the world market, but then we shall not think about export – these manufacturers will not be competitive further on. This is why greenhouse conditions shall be created, but only for a while. ■

Vladimir Ilyushin
Rafarma CEO

Vladimir Ilyushin:

We are consistently working on building contract partnerships

In less than a year since Rafarma was merged into the manufacturing segment of the PROTEK Group of Companies, we have shown that we can tap the full potential of the Terbuny manufacturing facility in the next 2-3 years. To make it a reality, the management and the team are to consistently implement the entirety of the measures planned.

The strategic goal of Rafarma is to validate all the processes to ensure their compliance with the EU GMP standard. This is an essential step to building contract partnership both with Sotex, actively exporting its own products to a number of European countries, and with other pharmaceutical companies. In this regard, an undisputable competitive edge of Rafarma lies in its capacity to manufacture a wide range of oncology products in various dosage forms.

The resources allocated by the PROTEK Group contributed significantly to the development of Rafarma. We are upgrading the production facilities to meet new requirements, implementing a new quality management system, and auditing and improving procedures in the field of production, technology, and administration. To keep up with the latest developments in the Russian industry, we are also working on the implementation of the state drug circulation monitoring system. This is another project demanding significant investment of human and financial resources.

Currently, both in-house, and contract manufacturing operations are carried out on a scheduled basis. In 2017, we produced the first oncology product as a contract manufacturer for Sotex. A number of other Sotex products are to be transferred to Rafarma in 2018-2020. We also work consistently on attracting new partners for contract manufacturing, and keep building up the portfolio of Rafarma's own products. ■

RAFARMA

Rafarma – full cycle pharmaceutical enterprise was merged into PROTEK Group's manufacturing segment in 2017

- **Total 25 000 sq m, 5 self-contained sites** for the full cycle manufacture of antibiotics, oncology and other products
- **R&D**: research, development and testing laboratory, in-house experimental base at cleanroom
- Manufacture of preparations in **15 dosage forms**
- **Equipment**: GLATT, Kilian, Romaco Macofar, IMA, CAM, Fedegari, Tofflon
- **24 hectares** are available for construction of additional manufacturing facilities

sotex

Sotex Pharmaceutical Firm is the core facility of the manufacturing segment of the PROTEK Group of Companies

- **GMP EU** Certificate
- Contract manufacturing **partners**: Bayer, Sanofi, Novartis, Pierre Fabre, Takeda
- **Product portfolio** – 148 SKU, including 97 positions of own brands
- **Unique production** line for pre-filled syringes with automatic needle protection device
- **R&D platform** and competences to develop injectables and biotechnology products
- E**xport of products** to 13 countries

PARTNERSHIP ADVANTAGES

- AVAILABILITY OF PRODUCTION FACILITIES FOR CONTRACT MANUFACTURING AND AREA FOR ADDITIONAL CONSTRUCTION
- LOCAL PRODUCTION AND TECHNOLOGY TRANSFER EXPERIENCE
- ATTRACTIVE PRICE-OFFER
- INTEGRATED BUSINESS APPROACH: PRODUCTION, DISTRIBUTION AND PROMOTION OF MEDICINES
- GUARANTEED SALES VOLUMES
- MINIMIZED RISKS FOR INVESTMENTS RETURN

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PRODUCTION LINES OF RAFARMA

SITE NO.1 / NONSTERILE DOSAGE FORMS

TABLETS	Tablet press	S 250 SMART CLASSIC	Killian, IMA	100 000 tablets/hour
COATED TABLETS	Film coating machine	GMPC II	GLATT	45 kg
TUBES	Semiautomatic tube filling machine	C735	IMA, COMADIS	26 litres (35 tubes/min)
SUPPOSITORIES	Filling, sealing, coding and cutting machines for suppositories	BP-2 BP-3	Dott. BONAPACE	60 supp/hour
SACHET	Automatic machine for packaging heat-sealed sachets on 4 sides	OMAG C3/2	OMAG	120 packages/min

SITE NO.2 / CEPHALOSPORINS

INJECTABLE FORMULATIONS				
VIALS 10 ML	Aseptic powder filling automatic line		Romaco Macofar	9 000 vials/hour
NON-STERILE FORMULATIONS				
POWDERS AND SUSPENSIONS FOR CHILDREN	Automatic machine for packaging heat-sealed sachets on 4 sides		Romaco Macofar	3 000 vials/hour

SITE NO.3 / CYTOSTATICS

INJECTABLE FORMULATIONS				
VIALS 10 ML	Combined automatic line for aseptic powder & liquid filling		Romaco Macofar	9 000 vials/hour
LIOPHYLIZAT	Vacuum freeze drying machine	LYO - 5	Tofflon	11 400 vials (10 ml)
NON-STERILE FORMULATIONS				
TABLETS	Tablet press	S 250 SMART	Killian, IMA	100 000 tablets/hour
CAPSULES	Capsule filling machine	CD 40 12366	Romaco Macofar	40 000 capsules/hour
COATED TABLETS	Film coating machine	GC Smart 175 12053	GLATT	100 kg

SITE NO.4 / FINISHED DOSAGE FORMS

INJECTABLE FORMULATIONS				
VIALS 10 ML	Combined automatic line for aseptic powder & liquid filling		Romaco Macofar	3500 vials/hour
LIOPHYLIZAT	Vacuum freeze drying machine	LYO - 5	Tofflon	11 400 vials (10 R)
NON-STERILE FORMULATIONS				
TABLETS	Tablet press	S 250 SMART	Killian IMA	100 000 tablets/hour
CAPSULES	Capsule filling machine	CD 40 12366	Romaco Macofar	40 000 capsules/hour
COATED TABLETS	Film coating machine	GC Smart 175 12053	GLATT	100 kg

SITE NO.5 / CYTOSTATICS

VIALS 10 ML	Combined automatic line for aseptic powder & liquid filling		Romaco Macofar	3 500 vials/hour
LIOPHYLIZAT	Vacuum freeze drying machine	LYO - 1	Tofflon	1 800 vials (10 ml)

COMBINED PRODUCTION CAPACITY

Pre-filled syringes	**13** million	**Ampoules**	**143** million
Tablets	**1,330** billion	**Liophylizat**	**1,35** million
Gelatine capsules	**280** million	**Sachets**	**18** million
Vials for injections	**54** million	**Semi-solid formulations**	**7** million
Vials for suspensions	**10** million	**API**	**220** kg

PRODUCTION LINES OF SOTEX

AMPOULES 1, 2 ml	Line A	Est Edelstahlbau Tannroda GmbH Bausch+Ströbel Mashinenfabrik	18000 ampoules/hour	38 million ampoules/year
AMPOULES 2, 5, 10, 20 ml	Line B	Est Edelstahlbau Tannroda GmbH Bausch+Ströbel Mashinenfabrik	18000 ampoules/hour (2 ml) 15000 ampoules/hour (5 ml) 10000 ampoules/hour (10 ml) 9000 ampoules/hour (20 ml)	35 million ampoules/year
AMPOULES 1, 2, 5 ml	Line C	BRINOX Bausch+ Ströebel Mashinenfabrik	24000 ampoules/hour (1, 2 ml) 18000 ampoules/hour (5 ml)	70 million ampoules/year
PRE-FILLED SYRINGES		Glatt Optima	4 500 syringes/hour	13 million pcs/year

Contract Manufacturing:

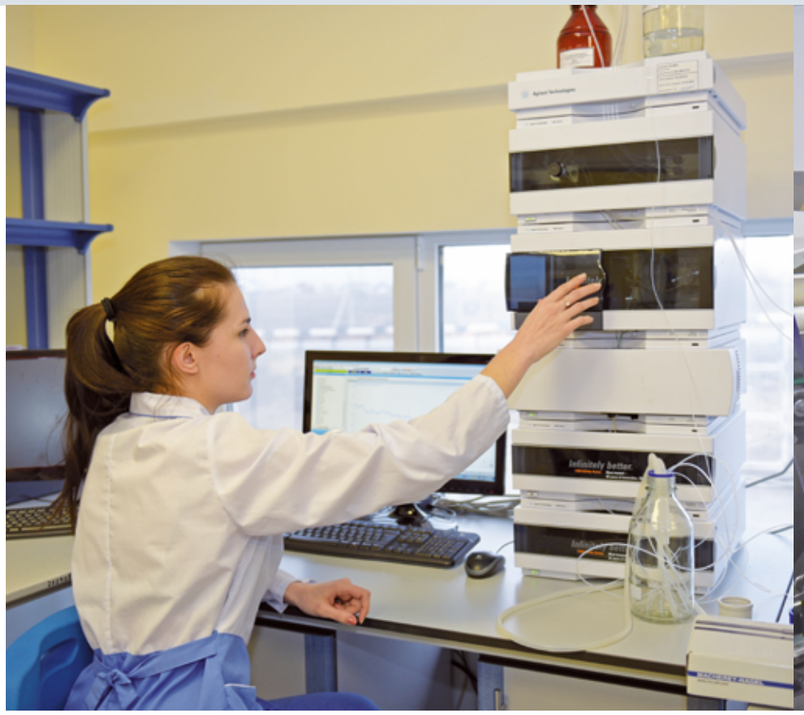
Experience of PIQ-PHARMA Group of Companies

16 March 2018
Press Service of PIQ-PHARMA

PIQ-PHARMA is one of the first innovative pharmaceutical companies on the Russian market, a group of companies responsible for various stages of development and distribution of pharmaceutical products (development and registration of drugs, production of pharmaceutical substances and drug products, and promotion and sale of drugs).

The company was founded in 1994 in Moscow, and has developed steadily and successfully ever since. In 2009-2011, the company launched its own manufacturing facilities. First in Leningrad Region to produce finished pharmaceutical products, and second in Belgorod to produce pharmaceutical substances. In 2015, PIQ-PHARMA LEK factory was put into operation to produce drug products. The factory obtained a GMP Certificate in 2016.

The automated engineering system of PIQ-PHARMA LEK provides all the necessary parameters of process and auxiliary rooms: range of purity, air circulation rate, climate conditions, and excess pressure. The factory uses modern equipment from leading western manufacturers: IMA (Italy), Kilian (Germany), Romaco (Germany). The factory employs highly skilled staff, and has developed and introduced a pharmaceutical quality system. The pharmaceutical quality system of PIQ-PHARMA



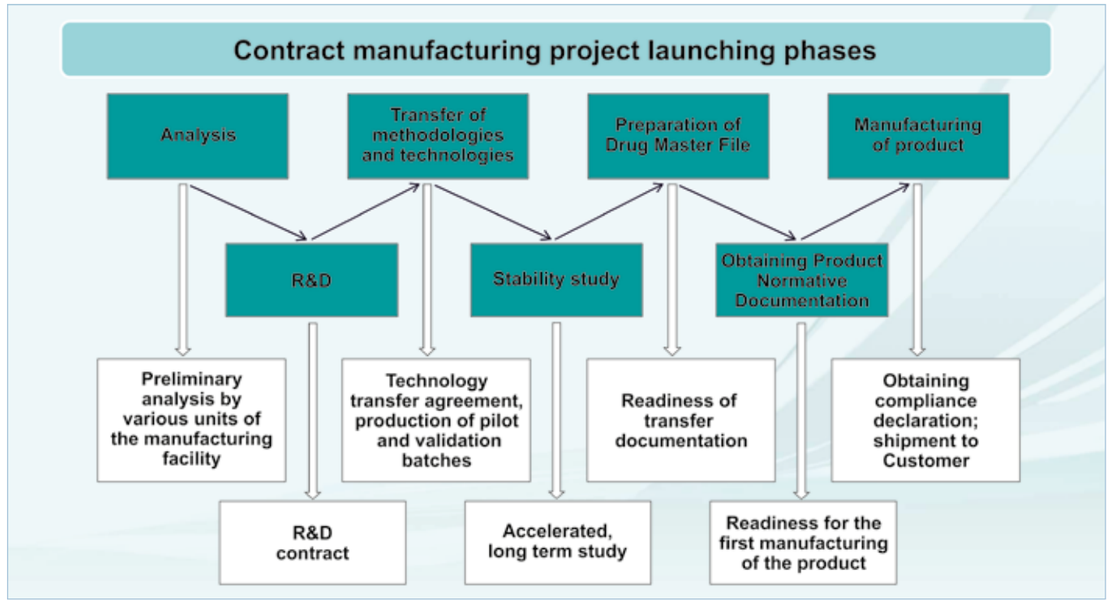
LEK provides monitoring at each stage of production, including quality control of raw and other materials and finished products, document management, and a staff training system. The laboratory of PIQ-PHARMA LEK has all the analytical equipment necessary and allows using nearly all analysis methods used in pharmaceutical industry – HPLC, GLC, atomic adsorption spectroscopy, Infrared Spectroscopy, and other basic methods of analysis.

The factory's design capacities for production of solid dosage forms are 500 million tablets and 100 million capsules per year. The manufacturing capacities of PIQ-PHARMA LEK were initially designed for the manufacturing of the company's own products as well as for completion of contract orders; therefore at present, PIQ-PHARMA LEK can use its capacities to make third party products at the rate of up to 350 million tablets and up to 70 million capsules per year.

In addition to the solid dosage forms workshop, an automated oral liquid dosage forms production section (solutions, syrups, suspensions, and emulsions) is to be launched by 2019, with the design capacity of up to 10 million vials per year.

In the area of contract manufacturing, PIQ-PHARMA group of Companies is providing full-cycle manufacturing services as well as individual operations from development of new dosage forms and products to assistance in organizing pre-clinical and clinical trials.

Having gained some experience in working for customers under contracts, including foreign customers, PIQ-PHARMA developed a clear **algorithm for communication with potential partners**, which could be illustrated as follows:



Once the parties have signed the confidentiality agreement and the company has received initial information from the customer, various production related units of the company perform a preliminary analysis of the product the manufacturing process of which is to be transferred. Production and engineering units, quality control, and purchase departments have a month to determine if it is technically and technologically feasible to manufacture and provide quality control of the relevant drug on the production site.

Where all the relevant units confirm the possibility of the technology transfer and the customer expresses willingness to perform the transfer, the Parties enter into a technology transfer agreement, which normally includes the following activities: validation of analysis methodologies, production of pilot scale batches (where necessary), production of validation batches with preparation of manufacturing process validation protocols and report, testing the stability of the batches produced, and additional services as requested by the customer (e.g. a dissolution profile test or preparation of the drug master file.) Depending on the complexity of the technology being transferred, the contract performance period can be two to four months.

Where the current technology cannot be transferred to the existing manufacturing facilities, and with the customer's consent, an R&D phase is proposed including development and adjustment of a new manufacturing method on the facility. Upon completion of said phase, the processes are scaled to match the

capacity of equipment and the customer's requirement. With no unexpected difficulties and a good understanding of the goal, this work can be finished within two months.

One of the longest phases when a contract manufacturing project is launched is waiting for results of the drug stability study. If preparation of the dossier to add another manufacturing site only requires six-months' worth of data, a shelf-life confirmation requires stability monitoring throughout the expected shelf life.

The file for including another manufacturing site can be prepared by the customer's, or the contractor's Regulatory Affairs department, as previously agreed. On average, the execution of the documentation necessary (provided it is prepared properly) takes 1 to 2 months, including the time for the parties to agree upon and approve all the information provided. Article 30 of Federal Law No. 61-FZ of 12.04.2010 "On drug circulation" provides a time frame for the processing of application for amendments to documents within the master file for a registered drug, which is 90 working days maximum. However, one should remember that this period excludes the time required for a quality assessment of a drug from a new manufacturing platform, as well as the time it takes to prepare answers to comments from the Regulatory Authorities, if any, which can make the assessment period much longer.

The tentative timeframe for launching an "ideal project", i.e. one that is not complex in terms of manufacturing technology, can be about 1.5 years (excluding the ongoing stability study).

The transactions between the contractual customer and contractor are governed by the Contract for Manufacturing and Supply of Commercial Batches as well as other related agreements (quality agreement, pharmacovigilance agreement, trademark use agreement, etc.).

Despite the seeming transparency of all those phases, there are difficulties that may arise in the course of every particular project, including technological, technical, economic and procurement difficulties, registration, legal and other problems that require a case-by-case approach. Let us look at some of those more carefully.

- The most significant problems are those arising at the technology level, e.g. when the manufacturing technology of a product that is to be produced on the facility cannot be implemented for various reasons.
- The technical issues are those arising from insufficient equipment on the production facility for particular products, e.g. extra format parts for the packaging line or specific tablet tooling may be required. Such issues are resolved by providing the equipment necessary, which normally requires extra investment from the customer.
- Another important issue is negotiating the price for the service of manufacturing a drug on the contracted facility since the customer's target price does not always match the contractor's offer. Various communication options are assessed in order to resolve such issues, one example being a progressive price scale depending on the volume of orders.
- Prior to starting the production of commercial batches, all units of the manufacturing facility have to confirm that they have enough necessery consumables and reserves, including standard samples, chromatographic columns, packaging materials, etc. since delivery of such materials may take a significant amount of time.
- Registration-related issues are common with customers and contractors alike. While the main difficulty for marketing authorization holders is the toughening of legal requirements regarding the documentation for registration, contractors have to deal with the restriction on the International Non-Proprietary Names of their products. The current legislation does not allow state registration of one drug produced by one manufacturer under different commercial names and presented for state registration as two or more drugs. That means that the contractor has to choose one, or the other customer if both are interested in placing the production of drugs with the same International Non-Proprietary Name. However, the State Duma is considering a bill that would eliminate that restriction for manufacturers of contracted drugs.

PIQ-PHARMA group of Companies invites pharmaceutical companies that do not have their own manufacturing capacities, or that are interested in localizing in the Russian Federation to contract the manufacturing of their drugs – solid and liquid dosage forms – to PIQ-PHARMA manufacturing facilities. We are prepared for long term and open cooperation and we are willing to provide comprehensive support to our partners. ■

For more information on PIQ-PHARMA group of Companies, please go to ***pikfarma.ru*** *(in Russian) and* ***piqpharma.com*** *(in English). Should you have any questions regarding contract manufacturing, please contact us at* ***contract@pikfarma.ru****.*

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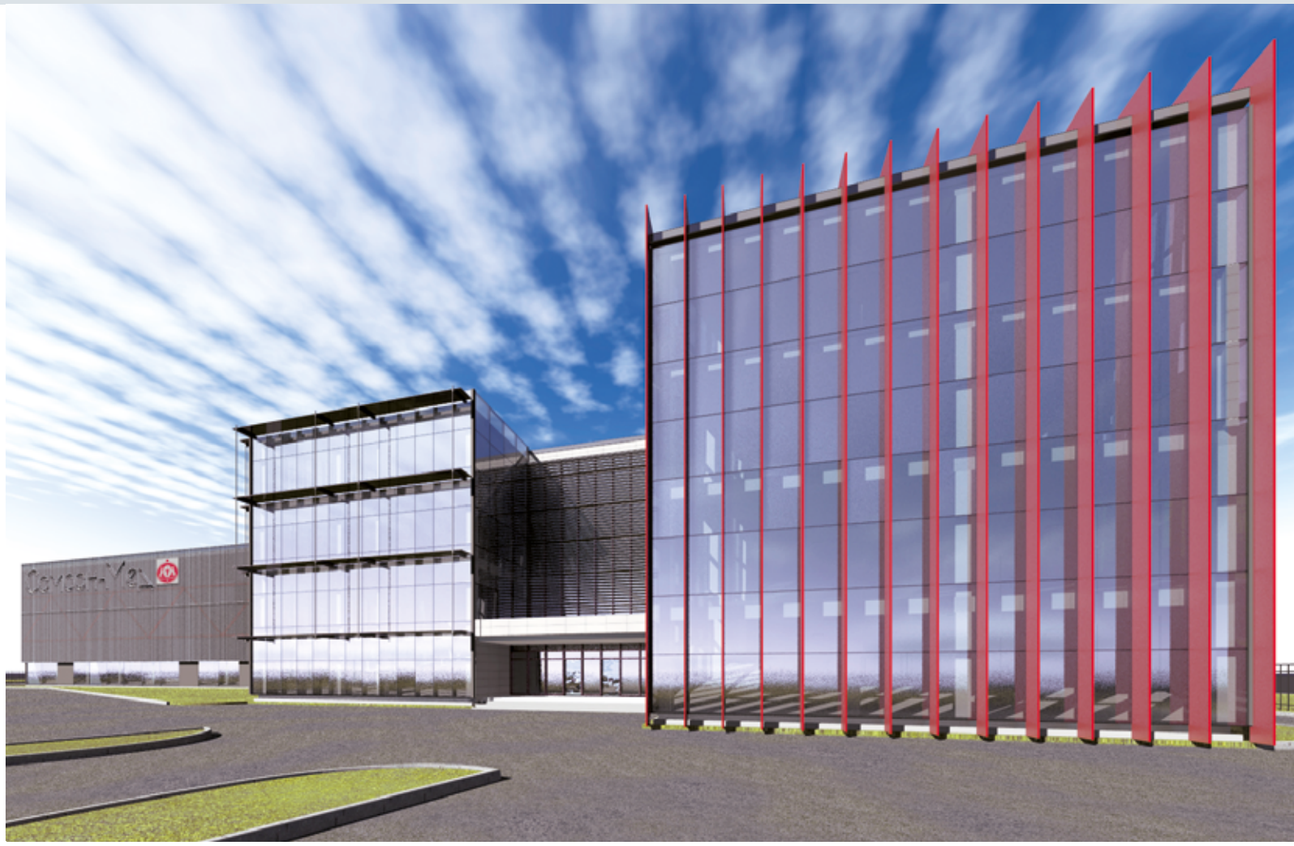
Samson-Med – an Innovative Full-Cycle Production Site



4 April 2018

"Samson-Med" is an innovative pharmaceutical company with full cycle production. It actively realizes the localization strategy, national pharmaceutical segment development, and provides affordable and effective vital medicinal products.

Pharmaceutical company "Samson-Med" is an innovative full cycle production manufacturer. The company realizes full variety of associated activities – from research and development of medicinal products to mass production and marketing thereof. **Since its foundation in 1937**, the company developed and implemented a number of unique production technologies of active pharmaceutical ingredients (API) and original endocrinal and enzymatic preparations.

Besides own medicine production, the company **performs contract manufacturing of API and finished dosage forms**. "Samson-Med" maintains stable and effective partnership with Russian and International companies such as Stada (Germany), Petrovax Pharm (Russia), Geropharm (Russia) for more than 15 years.

Nevertheless, the company is continuously looking for new strategic partnerships. Thus, on 16 June 2016, the Governor of Saint-Petersburg Georgy Poltavchenko, and the CEO of "Samson-Med", Adlan Elikhanov, signed an agreement of building a manufacturing plant for API and finished dosage form production in Pushkin District near Saint-Petersburg as cooperative strategic investment project. Also, Deputy Minister of Healthcare Sergey Krayevoy was present on the ceremony. Georgy Poltavchenko made a point that "Samson-Med" has proved itself as a trustworthy partner of the City of Saint-Petersburg with long-established good reputation. *"The city actively supports this project. I am sure it will serve to the benefit*

of Saint-Petersburg and Russia", – concluded **Georgy Poltavchenko**. The company is a resident of the Import Substitution and Localization Center from 2016.

The prospective of the project is recognized not only at the regional, but also at the Federal level. In September 2017, the company Samson-Med LLC received the approval of the Expert Council of the Industrial Development Fund for a soft loan of 500 million rubles. The company plans to spend borrowed funds on the technological equipment of the new plant.

The new production plant for the pharmaceutical manufacturing is designed and is being built in Pushkin on the area of 27,000 m^2. The lot is allocated for the deployment of two production units for API and finished form manufacturing, laboratory building of 2,800 m^2, warehouse, and engineering units, sewage facility, boiler-house etc.

State-of-the-art lyophilized injection form production line with packing ability, with the capacity of 18,000 vials/hour from "OPTIMA" company meets the designed manufacturing criteria. The major vial types are 2R, 4R with an option to use vials of types 10R, 20R, 50R, and 100R. The implemented dosage system allows to fill vials with high precision. There is a 100% in-process control that doesn't impair production efficiency. The designed vial loading for lyophilization is automatic and implemented in line by line order. The filling line and loading system will be isolated under automatic environment monitoring system. Vial drying will be performed by lyophilization on shelves having 25 m^2 area. Filling solution preparation will be done on automatic preparation systems made by leading international manufacturers. Water preparation is performed by "Stilmas" systems ensuring the quality of the obtained filling solutions. Unloading of the dried vials will be performed automatically line after line, followed by transportation to the RABS packaging machine using "flip-off" caps with the possibility of additional marking on the cap. The company negotiates with such contractors as Dividella, Uhlmann, Seidenader about the purchase of the marking, inspection, and packaging equipment.

The new enterprise already attracts potential customers. In January 2018, a series of frame meetings between Samson-Med LLC and OAO NPK High Technologies was held. The outcome of the negotiations was the adoption of decisions on cooperation in the development of new dosage forms and further contract production of the drug "Fermenkol" at modern facilities of Samson-Med LLC, which meet the requirements of GMP and FDA.

Today, "Samson-Med" actively cooperates with the most reputable and competent organizations in various areas. The company established partnerships with the following leading Russian scientific organizations: Mechnikov North-Western State Medical University, St. Petersburg Medical Academy of Postgraduate Studies, Saint-Petersburg I. I. Dzhanelidze Research Institute, Institute of Toxicology of Federal Medico-Biological Agency, A.N. Bakoulev Scientific Center for Cardiovascular Surgery, Saint-Petersburg State Chemical Pharmaceutical Academy, S. M. Kirov Military-Medical Academy, Pavlov First Saint-Petersburg State Medical University.

CONCLUSION

Today, the pharmaceutical company "Samson-Med" is one of the most dynamically developing pharmaceutical productions in Russia. Positive feedback given by the Federal Government to the project makes it very appealing to investors. With the collected knowledge and the pharmaceutical market experience, long-term strategic partnership, governmental support, and customer credibility the company's future view is filled with confidence allowing it to effectively overcome negative external economic factors. ■

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GMP Aspects of Contract Manufacturing

2 March 2018

1. INTRODUCTION

Contract manufacturing is used in situations when one company, the "contract giver" (CG), mandates another company the "contract acceptor" or "contract manufacturer" (CM), in the same country or another country to manufacture its products. This is also known as subcontracting or outsourcing.

In the frame of contract manufacturing, the contract giver provides the contract acceptor with all specifications and, if applicable, also with the materials required for the production process. A contract sets out the requirement concerning the quality of the product, certification, quantities, conditions and dates of delivery, which the contract acceptor must meet. It also establishes the guidelines for the inspection and testing of the products sets forth by the contract giver which contracts out the contract acceptor.

Since the process is essentially outsourcing production in foreign markets to a partner that privately brands the finished product, there are many different companies and industries that can make use of this type of contract.

This article presents the general aspects, advantages and risks that are related to the contract manufacturing between entities having to respect the Good Manufacturing Practices (GMP). The key elements that need to be taken in consideration in the frame of contract manufacturing are discussed in detail. A special attention is drawn to one aspect of that is rarely treated in the multiple articles that can be found in the published literature on this subject. This point of interest refers to the change control of any manufacturing procedure, test controls, and general management done by both parts in contract manufacturing.

2. PARTICULARITY OF THE CONTRACT MANUFACTURING

2.1 Description of the Business Model

In a contract manufacturing business model, the contract giver approaches the contract acceptor with a design or formula. The contract acceptor will quote the parts based on processes, production areas and processes, laboratory, tooling, and materials.

Typically, a contract giver will request quotes from multiple CMs. After the bidding process is completed, the contract giver will select a source, and then, for the agreed-upon price, the contract manufacture acts similarly and under the behalf of the contract giver, for producing, testing, releasing and shipping materials.

In addition, several activities can be considered: regulatory affairs, validation, in particular re-validation and current project development. A wide and relation between contract giver and contract acceptor is to be set in place. The picture 1 shows the complexity of the relationship between the 2 parts.

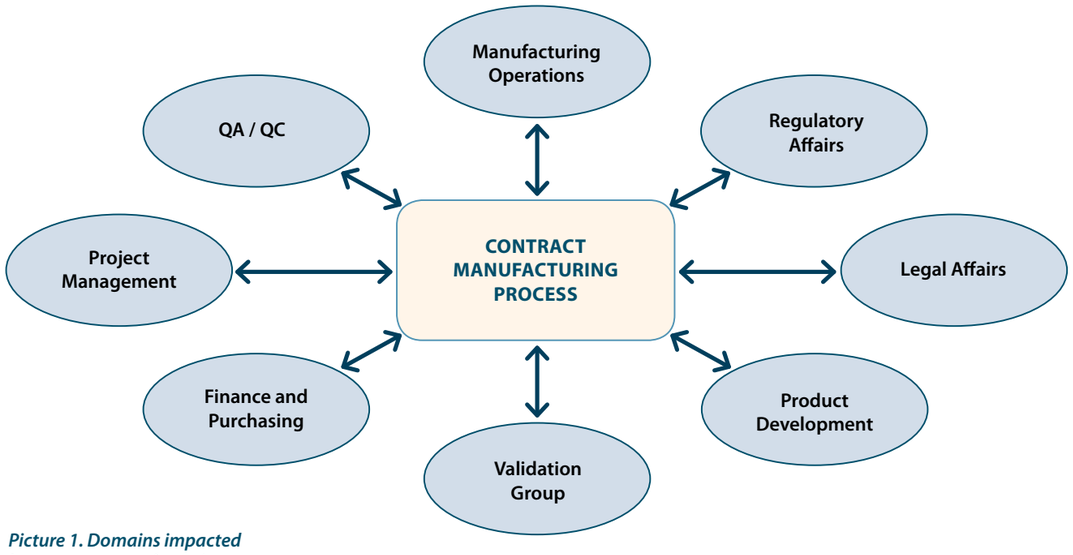
2.2 Job production

Job production is, in essence, manufacturing on a contract basis, and thus it forms a subset of the larger field of contract manufacturing. But the latter field also includes, in addition to jobbing, a higher level of outsourcing in which a client company entrusts its entire production to a contract acceptor, rather than just outsourcing parts of it.

2.3 Industries using Contract Manufacturing

Many industries use the Contract Manufacturing, for example aerospace, computer industry, energy, and pharmaceutical industries.

In particular, the pharmaceutical industry must be extremely strict with the requirements referring to the contract acceptor to ensure the accurate respect of GMPs. Any activity covered by the GMP Guide that is outsourced should be appropriately defined, agreed and controlled in order to avoid misunderstandings which could result in a product or operation of unsatisfactory quality. The chapter 7 "Outsourced activities" of the



Picture 1. Domains impacted by contract manufacturing.

EU GMP deals with the responsibilities of contract giver and contract acceptor in order to guarantee the quality.

In general, the contract acceptor will be inspected by the contract giver and by the regulatory authorities from any country where their products or materials will be distributed under the trade mark of the contract giver.

2.4 Benefits and Risks

There are many benefits as well as risks to contract manufacturing. Companies are finding many reasons why they should outsource their production to other companies. However, production outside of the contract giver has many risks attached. Companies must first identify their core competencies before deciding about contract acceptors. The company's competencies are what make them competitive in the marketplace. If a company allows another company to take control of them, it may lose that advantage. Therefore, when deciding about contract manufacture, the CG should weigh the benefits and the associated risks. The sections 2.5 & 2.6 describe some risks and benefits related to the contract manufacturing.

2.5 Benefit

- Cost savings – Contract giver save on their cost of capital because they do not have to pay for a facility and the equipment needed for production. They can also save on laboratory costs such as wages, training and benefits. Some contract giver may look to contractors in low-cost countries, such as India, to benefit from the lower costs.
- Mutual benefit to contract sites – A contract between the CM and the CG may last several years. The CM will know that it will have a steady flow of business during this time.
- Advanced skills – Companies, either the CG or the CM, can take advantage of skills that they may not possess. The CM is likely to have relationships formed with raw material suppliers or methods of efficiency within their production.
- Focus – Both companies can focus on their core competencies better if they can hand off base production to an outside company.
- Economies of scale – CG have multiple partners that they produce for. Because they are servicing multiple customers, they can offer reduced costs in acquiring raw materials by benefiting from economies of scale. The more units there are in one shipment, the less expensive the price per unit will be.
- Protectionism – In an international context, establishing a foreign subsidiary as a CM can have favourable tax benefits for the client company, allowing them to reduce overall tax liabilities and increase profits, depending upon the activities of the contractor.

2.6 Risks

- Lack of Control – When a CG signs the contract allowing a contractor to produce their product, they lose a significant amount of control over that product. They can only suggest strategies to the CM; they can force them to implement their suggestions.
- Relationships – It is imperative that the CG forms a good relationship with its CM. The client must keep in mind that the CM may have other customers.
- Quality concerns – When entering into a contract, CG must make sure that the CM's standards are congruent with their own. They should evaluate the methods in which they test the products to make sure they are of good quality. The CG has to rely on the CM for having good suppliers that also meet these standards.
- Intellectual property loss – When entering into a contract, a company is divulging their formulas or technologies. This is why it is important that a company doesn't give out any of its core competencies to the CM. It is very easy for an employee to download such information from a computer and steal it.
- Outsourcing risks – Although outsourcing to low-cost countries has become very popular, it does bring along risks such as language barriers, cultural differences, and long lead times. This could make the management of the CM more difficult, expensive, and time-consuming.
- Capacity constraints – If a CG does not make up a large portion of the contractor's business, the CM may find that they are de-prioritized over other companies during high production periods. Thus, the CG may encounter difficulties and delays to obtain the product they need when they need it.
- Loss of flexibility and responsiveness – Without direct control over the manufacturing facility, the CM will lose some of its ability to respond to disruptions in the supply chain. It may also hurt their ability to respond to demand fluctuations, risking their customer service levels.
- Pricing – This addition of a second company, the CM and second profit margin to be achieved, adds in cost to the product. The impact is seen either in a higher selling price to the customer, or in a reduced profit margin for the CG.

3. CONTRACT MANUFACTURING AGREEMENT

To mitigate the business risks related to the contract manufacturing, it is recommended to put in place a Contract Manufacturing Agreement. This contract is a country dependent document that considered the local laws governing standard contract manufacturing agreements.

Under the Contract Manufacturing Agreement, the CM is compensated on the basis of recovery of the fully-loaded costs of manufacture, plus a margin (user defined). The agreement assumes, that as between the parties, the principal owns all intellectual property rights relating to the products and the manufacturing process.

The document includes, as standard, an allocation of risks between the parties that is consistent with that found in a typical contract manufacturing relationship, as well as an obligation on the client to indemnify the contractor for any loss or damage arising out of the performance of the manufacturing activities.

3.1 Content of Contract Manufacturing Agreement

The following items are to be established and have to be part of the Contract Manufacturing Agreement:

- Purpose and background;
- Terms an termination;
- Products to be manufactured and specific requirements applicable to the manufacturing process;
- Budgeting, payment and reconciliation mechanisms;
- Territory;
- Purchase of production materials;
- Termination assistance;
- Sub-contracting and assignment rights;
- Provisions relating to notices;
- Dispute resolution, jurisdiction and arbitration;
- Other provisions (e.g. confidentiality, force majeure).

4. THE KEY ELEMENTS IN GMP CONTRACT MANUFACTURING

In addition to the business, general requirements to be considered between the CG and the CM presented in the previous chapter, the compliance to cGMP is an additional necessary condition to pharmaceutical contract manufacturing practice, as prescribed by chapter 7 "Outsourced activities" of the EU GMP. To ensure marketing authorisation, the CG and the CM must adhere to cGMP regulation to ensure their products to be commercialized.

Choosing a CM that adheres to cGMP rules may be the solution to avoid unfavourable outcomes presented in chapter 3.

Among other things, the following aspects have to be considered as key elements regarding the contract manufacturing:

- Quality Agreement;
- Adherence to manufacturing process;
- Supplier Audit;
- Release of manufactured product;
- Documentation and archive;
- Cleaning Validation;
- Change control.

These key elements must be clearly defined, agreed on, and controlled in order to avoid misunderstanding which could result in a product of unsatisfactory quality. The next sections describe these key elements in more details.

4.1 Quality Agreement

The Quality Agreement specifies the minimum requirements that will apply to the contractual partner's quality management system and defines rights and obligations with respect to the quality assurance of any products to be supplied.

The Quality Agreement should describe clearly who undertakes each step of the outsourced activity, e.g. knowledge management, technology transfer, supply chain, subcontracting, quality and purchasing of materials, testing and releasing materials, undertaking production and quality controls (including in-process controls, sampling and analysis).

Furthermore, the Quality Agreement should permit the CG to audit outsourced activities, performed by the CM or his mutually agreed subcontractors.

4.2 Adherence to manufacturing process

The basic principle is to assure the quality, potency, identity, and safety of products to protect both the consumer and the manufacturer. Therefore, adherence to manufacturing process is extremely important to guarantee the above-mentioned characteristics and to ensure the CM to enable its production to supply in time its consumers. Adherence to manufacturing process includes:

- Manufacturing time;
- Amount of material produced;
- Capacity of utilization;
- Overall equipment effectiveness;
- Schedule of production;
- Availability of the system.

4.3 Supplier Audit

As subcontractor, the CM will be audited by the CG. The goal of this supplier audit is to check, if the CM perform the manufacturing activity according to the quality standard defined in the Quality agreement.

One common way to carry out an audit is to check the adequacy of any procedures following to a checklist submitted by the CG.

- Review past audits, note indications of possible problem areas and items, if any, that were identified for corrective action in a previous audit.
- A checklist is to be used with a notebook into which detailed entries can be made during the audit.
- At least three production batches should be selected for thorough analysis to include: (a) traceability of all components or materials used in the subject batches, (b) documentation of raw material or component, in-process, and finished goods testing for the subject product batches, (c) warehousing and distribution records as they would relate to a possible recall.

4.4 Release manufactured product

Batch release of manufactured products is a necessary requirement to ensure high quality for use, sale, supply or export. Batch release testing expertise includes chemical, physical, and biological testing.

The batch release for commercial use has to be performed by the CG. The Quality Management System of the CG must clearly state the way that the Qualified Person certifying each batch of product for release exercises his full responsibility.

4.5 Documentation and archives

Documentation is the key to GMP compliance and ensures traceability of all development, manufacturing, and testing activities. Documentation provides the route for auditors to assess the overall quality of operations within a company and the final product.

All records related to the outsourced activities, e.g. manufacturing, analytical and distribution records, and reference samples, should be kept by, or be available to, the Contract Giver. Any records relevant to assessing the quality of a product in the event of complaints or a suspected defect or to investigating in the case of a suspected falsified product must be accessible and specified in the relevant procedures of the Contract Giver.

4.6 Cleaning validation

Due to the fact that CMs use usually multipurpose facility and equipment, the cleaning is a critical aspect in the frame of contract manufacturing activities. Cleaning validation may be a burning point, difficult to satisfy both CG and CM partners. In any case, the efficacy of the cleaning has to be demonstrated by the CM and a plan for cleaning validation has to be discussed and agreed on. This document should contain the following elements:

- Assess equipment and products;
- Evaluate the impacts of the other manufacturing processes on the contracted process. If the contracted process is covered and already validated under bracketing then no further validation is required;
- Determine an appropriate cleaning agent and method;
- Decide what residue(s) (including cleaning agents), are to be tested for based on solubility, toxicity, etc. and document rational behind the decision;
- Determine acceptance criteria for the residue(s) (including cleaning agents);
- Develop sampling methods, e.g. swab or/and rince methods to remove the residues;

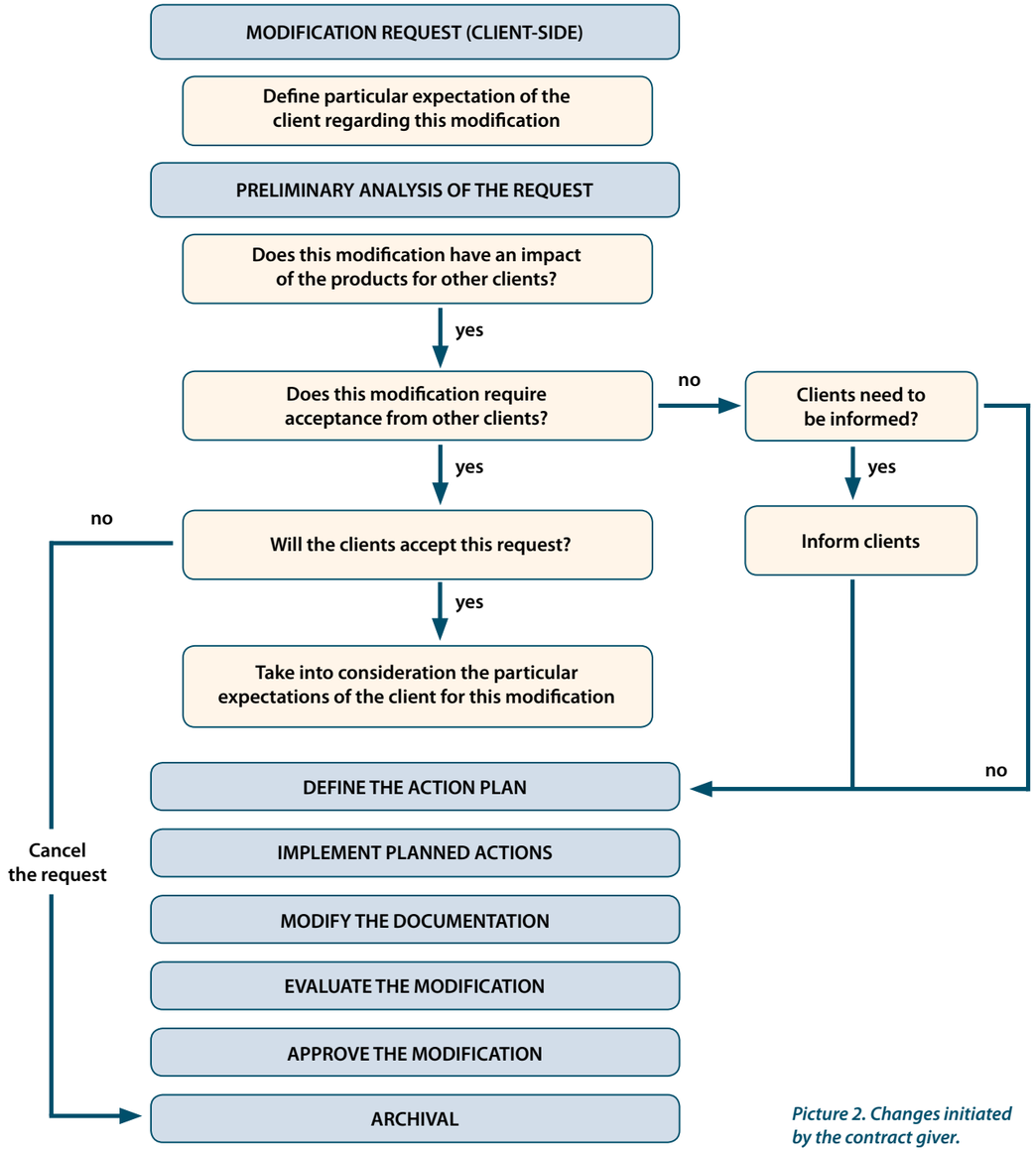
- Develop analytical methods for detection of the nature of the residues from swab or / and rince methods, e.g. visual residues, carbon organic total, HPLC methods;
- Compile and approve validation protocol;
- Perform validation studies in accordance with protocol;
- Compile and approve a validation report documenting studies, conclusions and recommendations.

4.7 Changes control process

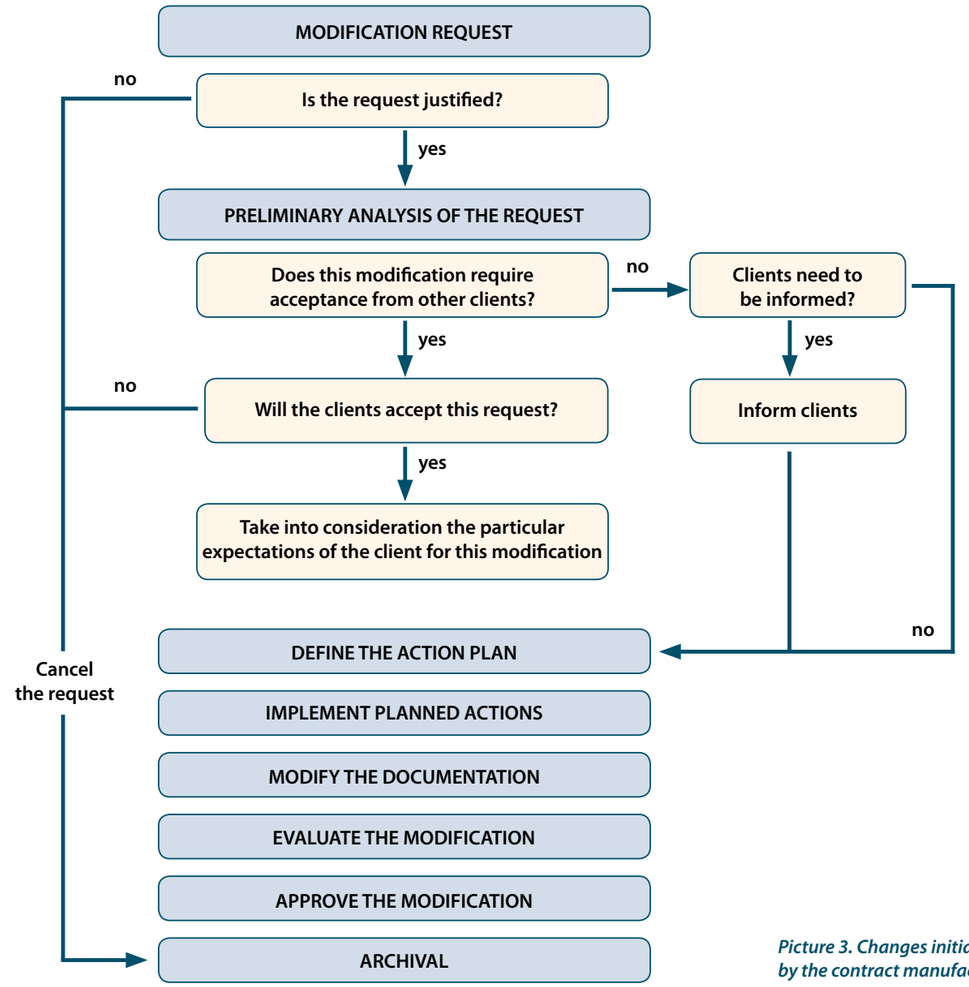
Many critical areas are generally satisfactorily fully covered by the client company and the contractor manufacturers.

When choosing a contractor, the client company is focused on and has resolved the different important items, as outlined in the previous chapters. After being established, the contract between the client company and the contractor might last months and years. A risk that is sparsely mentioned in the several articles on the contract manufacturing arises through the changes.

It makes sense to classify the changes either as minor, or as major and to establish a strategy to implement the changes in a right way. For example, the minor changes can be implemented on a customer notification basis, but the major changes have to be previously preapproved by the CG, before implementation.



Picture 2. Changes initiated by the contract giver.



Picture 3. Changes initiated by the contract manufacturer.

The pictures 2 and 3 present the different situations and change controls at CG. Presented as decisional trees, the two pictures help to understand the complexity of any change proposed either by CG, or by CM.

5. CONCLUSION

Selecting a cGMP certified contractor help to send a message of positivity and truth; it represents an overall goodwill to the target market and to the customers. For the consumer, a product manufactured by cGMP certified contractor is a guarantee of confidence. In this article, change control management relationship between client company and contractor was pointed out as an additional point of excellence to ensure high quality, safe and effective products to be available on the shelves of stores and homes. ■

PMS Process Management System (PMS) *is a Swiss independent enterprise, with Russian culture, located in Fribourg, Switzerland, and providing GMP consulting services for (bio-) pharmaceutical companies. To contact us, address your email to Dr. Andrei Issakov, Senior Consultant and Business Development Manager* ***(andrei.issakov@pmsystem.ch)****.*

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ISPE Opens
an Independent Eurasian Affiliate

13 March 2018
Source: *https://гилсинп.рф*

The presentation results of ISPE EAEU Affiliate Opening Ceremony in the framework of Educational Conference: "Effective pharmaceutical production. Regulatory aspects, latest technologies"

The presentation of ISPE EAEU Affiliate Opening Ceremony has been held in Moscow, within the framework of which a Memorandum of Intent was signed between the global ISPE and the founders of the independent Eurasian Affiliate, including: "R-Pharm", "Nizhpharm" (STADA Group), FAVEA Group, PHARMA GROUP BALTIC. The initiative was supported by the Ministry of Industry and Trade of the Russian Federation and Federal State Institution "State Institute of Drugs and Good Practices" of Minpromtorg of Russia. The General Partner of the Conference has been LLC "MSD Pharmaceuticals".

"ISPE EAEU Affiliate opening provides great opportunities to the pharmaceutical community of the Union countries in the field of pharmaceutical engineering. First of all, it is the access to the latest technologies and professional knowledge. Thus, advanced countries have gone far ahead in their scientific research and engineering projects. For example, today we are on the threshold of personalized medicine, in which individual patient differences will be considered for the most effective use of drugs. Such expertise and the best world experience in the sphere of pharmaceutical engineering are being developed particularly in the ISPE association, which unites more than 20,000 members from more than 90 countries of the world", – commented **Alexander Sharonov**, Director of the independent Eurasian ISPE Affiliate.

Sergei Tsyb, Deputy Minister of Industry and Trade of the Russian Federation, made a welcoming speech in the framework of ISPE EAEU Affiliate opening, and in his speech noted that the development of Russian pharmaceutical production is impossible in isolation from international practice. *"We want the professionals working in Russia be aware and enjoy the same opportunities as foreign colleagues. ISPE is a non-profit organization that conducts many educational programs, issues manuals and scientific materials on the design, construction and operation of pharmaceutical production. Thus, we help our specialists to be at the same educational and professional level with foreign colleagues. That is why the Minpromtorg of Russia actively supports the initiative to open ISPE Affiliate on the Eurasian territory"*, – underscored **Sergei Tsyb**.

Following the official opening presentation, a panel discussion between top managers of pharmaceutical companies on effective instruments for managing pharmaceutical production strategic vision took place. The invited guests of the discussion were Dmitriy Efimov, General Manager of Nizhpharm (STADA group of companies); Marwan Akar, General Manager of LLC "MSD Pharmaceuticals"; Vadim Vlasov, President of the Novartis group of companies; Alexander Kuzin, General Manager of "Novomedica"; Dmitriy Voloshin, CEO of "PHARMA GROUP BALTIC"; Andrey Chernogorov, Director of the Teva plant in Yaroslavl.

"Each pharmaceutical company follows its own strategy, but the industry has common goals – to meet the needs of a Russian patient and strengthen Russia's position in the world pharmaceutical arena. We can reach this goal by combining efforts, including assistance of professional association", – commented **Dmitriy Efimov**, General Manager of JSC "Nizhpharm", senior Vice President of STADA AG. – *That is why "Nizhpharm" was among the first to support the creation of the ISPE EAEU Affiliate. We see the great potential in interaction on key issues with the global industry community"*.

In general, the guests and participants of the presentation of independent ISPE EAEU Affiliate opening noted the high importance of the event. *"Today is a significant day for all of us. We are at the beginning of ISPE EAEU Affiliate establishment. Right now, the very moment has come when our market is fully ripe and ready for this step. Today it is obvious that further development of Russian pharmacy is simply impossible in isolation from the global market. We all understand that growing competition, both on the domestic and foreign markets, reinforces the requirements for the professionalism of employees, their competencies and the ability to quickly learn the latest technologies and knowledge"*, – commented **Vladislav Shestakov**, Deputy Head of the Russian GMP Inspectorate, Director of FSI "SID and GP". ■

Mikhail Morozov
Head of the International Cooperation Office,
Federal State Institution "State Institute of Drugs and Good Practices"

Establishing of ISPE EAEU Affiliate was approved on the European ISPE Conference in Barcelona in 2017 by the ISPE President – John Bournas and Vice – President for European Operations – Thomas Zimmer. The Director of ISPE EAEU, four companies-founders of the Affiliate and Thomas Zimmer were participating in the Ceremony of the Memorandum's Signing in October 2017 in Moscow. As per April 2018 there are about 90 ISPE members on the Russian Federation territory, and about 20 future members of the ISPE EAEU Affiliate. During the ISPE European Conference 2018 in Rome the Affiliate's representatives met with the management board of ISPE and had a discussion on organizing issues and future steps of the ISPE EAEU Affiliate. The Affiliate's plans for this year are intensive: participation in big conferences in Russia (III All-Russian GMP Conference, Pharmtech, etc.), publishing jointly written articles in the Pharmaceutical Engineering magazine and in other sector-specific publications. The main goal of the Affiliate's activities is to promote the best technical approaches in the industry and advanced practices within the framework of harmonization and enrichment of the pharmaceutical industry.

Scientific Research

and Development of Innovative Medicines in Russia

11 April 2018

The Scientific Centre of Innovative Drug Development by VolgSMU

Photo: *Nikolai Kotelnikov, Victor Morozkin*

The effectiveness and quality of novel pharmaceutical products undoubtedly define the landscape of modern medicine. The strategic program PHARMA-2020 initiated by the Russian authorities in the year 2010, aims to build a competitive pharma industry in Russia and provide new perspectives for drug developers from private companies as well as the academic sector.

The pharmaceutical industry is an ever-changing field that currently faces many challenges, which can be surmounted only by the means of the most advanced biomedical techniques, coupled with properly organised regulatory-based collaboration between the main stakeholders.

We would like to address our questions on these topical aspects of drug discovery and development in Russia to professor ***Vladimir Petrov*** *– a full member of the Russian Academy of Sciences, chancellor of Volgograd State Medical University, which now serves as a base for a recently launched Scientific Centre of Innovative Drug Development in Volgograd.*

Vladimir Petrov
Chancellor of the VolgSMU, Chief non-staff specialist - clinical pharmacologist of the Ministry of Health of the Russian Federation, Doctor of Medical Sciences (DMSc), Professor, Full Member of the Russian Academy for Sciences

What are the latest trends in the field of pharmacological research in Russia?

Many new drugs used to be a result of the chemical modification of already known pharmacologically active molecules. A relatively novel trend in pharmacology is to focus on target-based screening, which involves a variety of biotechnological methods. So modern drug development projects cannot be fully performed by small scientific groups: even the big pharmaceutical companies are forced to collaborate with each other to develop an innovative molecule. One of the most crucial points is the growing role of fundamental research projects aimed to explore unknown molecular mechanisms, which are involved in disease progression and could be used as pharmacological targets. Although the generally accepted path of drug development, including *in silico*, *in vitro* and *in vivo* studies, is quite common nowadays, further improvement in regulatory documents and their harmonisation with international standards are still needed.

What types of innovative drugs are supposed to be introduced in the near future?

It depends on how one would define "the near future" because drug research and development is a highly time-consuming process. Even the most efficacious molecules could fail clinical trials because of unpredictable risks, such as adverse drug reactions. Sometimes the drug's destiny depends on marketing. The most valuable trend in R&D is an increasing portion of biotherapeutic drugs, such as monoclonal antibodies, which are highly promising in the treatment for oncological, autoimmune and neurodegenerative diseases.

What is the main topic of scientific work in VolgSMU? Who are your collaborators?

Our main research projects are focused on the following therapeutic areas: diabetes mellitus, HIV and chronic pain syndrome. Several molecules are at the late stages of nonclinical trials and the results, which have been already obtained, are quite promising.

We collaborate with academic centers located in other cities in Russia such as Kazan, Saint-Petersburg, Rostov-on-Don and Ekaterinburg. Cooperation with industrial partners in regard to clinical research and advanced promotion of the most perspective molecules are our main priorities. We clearly realize that without these efforts, new perspective molecules will not reach patients, so the resources invested during long-stage development will just be expended for nothing.

What do you think about the scientific research on the development of innovative medicines in Russia as the chief clinical pharmacologist of the Ministry of Health?

There is an interesting concept named "conflict of interest". It coexists with all innovative inventions, however, it has become the most critical problem of contemporary medicine. Drugs are being created for saving lives or improving their quality. This is doubtlessly a noble pursuit but even the most promising molecule needs to be produced,

VolgSMU scientists work on the development of new drugs at the Scientific Centre of Innovative Drug Development

packed, advertised and sold to recoup the research and development of it and its associated research costs. It is often the case that it is more profitable to sell pills treating headaches or diarrhea than life-saving drugs, so a lot of pharmaceutical companies choose the former, developing "benefit" molecules. In Russia, we can see the aforementioned situation, as companies focus on producing drugs which are already well-developed, rather than taking an innovative approach. In the medium-term, we hope that there will be increased interaction between the research centers opened as a result of the PHARMA-2020 program. We need to understand that future innovative developments could become reality only due to the hard and coordinated interdisciplinary work of many research teams from different cities across our country. The result of the cooperation is not only the creation of novel pharmaceutical products but moreover the appearance of reasonable competition between research institutes. This will lead to a higher methodological level of applied and fundamental research. Obviously the process of establishing cooperation will be not instantaneous, it will be the result of long-term work. However, it is necessary to develop a regulatory framework to decrease the aforementioned risk of "conflict of interest" and to increase not only the productivity of the local pharmaceutical industry, but also the confidence of patients.

What obstacles arise during the commercialization of novel drug molecules? What needs to be done to solve these problems?

One of the key difficulties that hampers the final stages of drug development and marketing promotion, is the absence of clearly defined regulatory mechanisms of collaboration between potential investors and academic centres specialized in preclinical drug development.

It is well known that at the early stage of drug development, the risk of a negative result is at its highest. In addition, the search for new industrial partners in this regard used to be quite challenging, which made the whole process of innovative drug development even slower. However, nowadays it is getting better due to increased financial support gained through partnership of private companies and the state. For sure, this practice will bring us benefits in the nearest future, but unfortunately there is a lack of these projects. The next factor of similar importance is the regulation of the intellectual property of drug developers. The solution is to involve qualified experts in the field of law or even to develop them. Sometimes the biased analysis of new medicines could become a barrier for clinical trials as well as for further commercialization or marketing. The proper planning of clinical trials could reduce costs and increase their quality. Occasionally, clinical pharmacologists are faced with cases when promising drugs have no benefits because of misconceptions that took place with regards to their positioning or biased designs of non-clinical and clinical trials.

Could you please tell us about the Scientific Centre of Innovative Drugs Development by VolgSMU?

The opening of SCIDD is the moment of truth for us because it's the culmination of our previous efforts. It is a new start for us. By us, I mean not only VolgSMU, but also the whole region. We understand that our work will be based on the 3 decades of experience of our Research institute for Pharmacology. However, the need to introduce new technologies, standards and protocols, including such state-of-the-art techniques as highly throughput screening or genomic and proteomic exploration of the mechanisms of action, brings a new stream to our future flow.

The structure and the equipping of SCIDD are designed to meet the most advanced industry requirements and are aimed at achieving ambitious goals. I mean the foundation of a truly modern Scientific Centre, which should play a crucial role in the Volgograd pharmaceutical cluster and become the strongest research site for experimental nonclinical pharmacology with a strong commitment to the internationally recognised standards of good laboratory practice.

How can you describe the current state of pharmaceutical education in Russia?

Several aspects could be mentioned in this regard. The main problem is the lack of qualified specialists in particular fields related to drug discovery. There are many reasons for this and not many of them are particularly obvious.

Historically, pharmacists were primarily seen as merely shop-assistants at drug stores or sales representatives employed by pharmaceutical companies. Unfortunately, that opinion is also widespread among the graduate students and could be the reason that they do not to stay in this scientific area but move into the commercial sector. One can allege that currently approved standards related to pharmaceutical education do not meet real-life industry demands.

For the last few decades we have been teaching specialists who graduated from our various faculties, in order to prepare them to solve the problems which could occur during their further work for SCIDD. Firstly, we took a lot of talented youth scientists from the faculty of biomedicine. Many of them had a long-term practice at leading scientific centers in Germany, Austria, France and Finland. Their professionalism, enthusiasm and ambitions in regard to their scientific career will become the basis for the further growth and success of SCIDD. ■

The head of the VolgSMU Member of the RAS Vladimir Petrov (on the right) and the director of the PMFI Vsevolod Adzhienko

The Development of New Innovative Medicines

Focused on a Personalized Approach to the Treatment of the Patient

Last November, **the III International Scientific and Practical Conference "Actual aspects of experimental and clinical pharmacology: from molecule to drug"** was held at Pyatigorsk Medical and Pharmaceutical Institute (PMFI), a branch of the Volgograd State Medical University, with the support of the Ministry of Health (Stavropol region).

The conference was attended by leading pharmacologists of Russia, among whom there were the founders of the well-known Russian pharmacological scientific schools, practical health workers from various regions of Russia, and other countries, scientists from Russian universities and research institutes, as well as from Ukraine, Kazakhstan, Lebanon, and Algeria.

Subjects of the reports were devoted to various aspects of experimental and clinical pharmacology. Considerable attention was given to reducing side effects and increasing the effectiveness of several drugs from different pharmacotherapeutic groups.

The head of the Volgograd State Medical University (VolgSMU) of the Ministry of Health of the Russian Federation, the chief non-staff specialist (clinical pharmacologist of the Ministry of Health of the Russian Federation), Doctor of Medical Sciences, Professor, Member of the Russian Academy of Sciences **Vladimir Petrov** noted: *"Clinical pharmacology is the most rapidly developing branch of medical and biological sciences in the world. The decoding of the human genome and the development of new branches of science such as pharmacogenomics, metabolomics, and others made it possible to discover new ways and approaches in the creation of new drugs. This is important from the point of view of import substitution"*.

He also explained to journalists that the concept of creating new medicines has changed. This process began with the study of synthesized chemical molecules, and then it was searched for their correspondence to the receptor of a cell afflicted by some disease. Then came the stage of an in-depth study of the harmlessness and safety of the drug until the research was completed to the clinical stage.

Developers of new drugs are already on the path of personalization of therapy, which gives a real opportunity to "treat a patient, not a disease". The search for medicines is already conducted on the basis of genomic and proteomic technologies.

"The disease always develops individually", the academician said. There is the term "targeted therapy". There must be a drug that works specifically for this patient and specifically with this kind of pathology. "It is extremely difficult, we need new technologies. And we have them".

The academician spoke about the prospects for the development of the Volgograd Chemical and Pharmaceutical Cluster, the first phase of which was launched in December 2017. It is a unique Scientific Center of Innovative Medicines with pilot production of VolgSMU (one of the largest pharmacological research centers in the country).

Especially important is the further cooperation of the two scientific teams of VolgSMU and its branch – the Pyatigorsk Medical and Pharmaceutical Institute (PMFI) in the field of creation and development of new innovative medicines. ■

Information about new medicines attracts a lot of interest both for regional and for specialized media at the federal level

Cooperation

of the Pyatigorsk Medical and Pharmaceutical Institute for the Development of New Medicines

Interview with the director of the Pyatigorsk Medical and Pharmaceutical Institute, a branch of the Volgograd State Medical University, Doctor of Medical Sciences Vsevolod Adzhienko.

Prepared by Svetlana Bogdanova
Photos: *Valery Litvinov*
Translated by Natalia Andrienko

5 April 2018

Vsevolod Leonidovich, your institute celebrates its 75th anniversary this year. Please tell us a little about the history of the institute.

2018 is a special year for the Pyatigorsk Medical and Pharmaceutical Institute (PMFI), now a branch of the Volgograd State Medical University.

Created during of the World War II years as a pharmaceutical institute on the basis of evacuated scientific institutions, our Pyatigorsk pharmaceutical institute has turned into one of the largest universities of the country in this field with its scientific school. Since 2012, the institute has been attached as a branch to the Volgograd State Medical University; this allowed opening of another medical specialty in higher education in addition to the Faculty of Pharmacy. In subsequent years, the medical college and residency training were opened on the basis of the Institute. Annually more than 700 students enter the institute for various specialties.

How is the scientific cooperation with the head university established?

I would like to emphasize that the cooperation of our universities has developed for a long time before the formal unification. Nowadays, we carry out a number of state contracts in the developing of innovative domestic medicines, co-executors of which are the Volgograd University and Pyatigorsk Institute. The Volgograd State Medical University (VolgSMU) traditionally has a strong school of pharmacology: the university is headed by Member of the Russian Academy of Sciences Vladimir Ivanovich Petrov, chief non-staff specialist – clinical pharmacologist of the Ministry of Health of Russian Federation. In Volgograd there are also two key pharmacologists of Russia: Member of the RAS Alexander Alekseevich Spasov and Corresponding Member of the RAS Ivan Nikolaevich Tyurenkov.

Pharmacologist is a specialist who studies the effectiveness and safety of the use of medicines, the achievement of a clinically significant result.

Pharmaceutical science, well developed in Pyatigorsk, deals with a slightly different range of problems - these are the technologies for obtaining active substances and converting these substances into an easy-to-use dosage form.

The unification of the scientific potential of our largest scientific schools is to the benefit of scientific research and significantly reduces the development time for new drugs. Usually this takes many years.

Does PMFI have its own independent developments?

Yes. It is very important that in 2017, in Pyatigorsk, for the first time, scientists independently received the task to develop a new anti-ulcer drug, and complete the full cycle of its development, including the pharmacological part.

It is already proved that the future medicine exceeds the registered antiulcer remedy in regard of its effectiveness and safety.

Who are you going to cooperate with and in what directions?

Scientific researchers of PMFI are developing a new complex drug for the treatment of tuberculosis and leprosy; drugs for the treatment of AIDS, oncological and cardiovascular diseases, migraines and many other pathologies.

One of the important directions is actoprotectors, which are extremely in demand, including in the sport of high achievements. We have identified a number of plant and natural objects, which showed themselves very well in this capacity.

Together with the Research Institute for the Study of Leprosy (Astrakhan), we are working to create an anti-leprosy and anti-tuberculosis drug. An effective tuberculosis program is an important state task. "The issues of creating a whole series of new revolutionary medicines are still relevant," the chief non-staff phthisiatrician of the Ministry of Health of Russia Irina Vasilyeva reported.

It should be noted that successful cooperation in the development of fragments of the Federal Target Program "Development of the pharmaceutical and medical industry of the Russian Federation for the period until 2020 and beyond". Together with the Southern Federal University (Rostov-on-Don) and the Department for Pharmacology of the Volgograd State Medical University we create optimal tableted dosage forms for original domestic medicines intended for improvement of cerebral blood flow and possessing antithrombotic activity.

The combination of the scientific potential of leading pharmacological schools in Russia will reduce the time of the appearance of new drugs.

Alexander Terekhov
The Head of the Center for preclinical research of PMFI

The Center for Preclinical Studies of PMFI annually carries out studies of 20-25 generic medicines and several original medicines. These are medicines of various pharmacological groups. Antibiotics, non-steroidal anti-inflammatory drugs, neurotropic drugs (tranquilizers, neuroleptics), drugs for the treatment of gastrointestinal diseases, antiallergic drugs prevail among them.

Generic drugs are released to the market usually within a year after the end of preclinical research; it means that almost all preparations of our Center can already be found on the shelves of pharmacies. The research clients are mainly large Russian pharmaceutical manufacturers. Over the last five years, more than 100 medicines appeared on the pharmaceutical market of the Russian Federation, which were investigated by specialists of the preclinical research center of PMFI.

Andrei Voronkov
The Deputy Director for studies and educational work of PMFI

Specialists of the Pyatigorsk Medical and Pharmaceutical Institute in cooperation with FSBU "Research Institute for the Study of Leprosy" (Astrakhan) are developing a new domestic antimycobacterial drug for the treatment of tuberculosis and leprosy. This preparation has no structural analogues among existing antimycobacterial agents and it is also characterized by low toxicity and high effectiveness in the use (including against multidrug resistant strains of mycobacteria). The unique structure of the developed drug will help in overcoming the existing bacterial resistance and increasing the effectiveness of the pharmacotherapy of tuberculosis and leprosy.

Relevance of the work is obvious. The prevalence of mycobacterial infection becomes rampant. Significant side effects and development of drug resistance reduce the effectiveness of pharmacotherapy and dictate the need to develop new domestic effective and safe drugs.

Directions of development of the North Caucasus and Caucasian Mineral Waters – integration of resort medicine, pharmacology, and biopharmaceuticals

Currently, the computer-based simulation methods of new molecules are being actively introduced worldwide. On what hardware and software platforms do the scientists of PMFI conduct calculations?

Scientists of the Institute have long mastered the methods of molecular engineering and targeted synthesis for the development of new drugs. Several years ago, a supercomputer with a capacity of more than 50 trillion operations per second was designed and manufactured in the Laboratory of Computational Methods in Medicine and Pharmacy of the Pyatigorsk Medical and Pharmaceutical Institute. The basis of applied software for computer-based simulation is the program of self-engineered products of "Bioevrica". This program allows you to make an accurate prediction of the biological activity of new chemicals.

Thanks to such digitalization, molecules have been created in PMFI. In the future, these molecules can become medicines for peptic ulcer, cancer, and AIDS.

PMFI is located in the center of the North Caucasus – a region of medicinal plants. What are the prospects for their use in the development of new drugs and substances and in cosmeceuticals?

Ecologically pure natural products and herbal remedies are traditionally popular among the population of Russia. Under the program "HealthNet" of the National Technology Initiative of the Russian Federation provided for the creation an industry of medicinal plant growing and production of traditional herbal medicines with the use of the technology of evaluation and development of multicomponent natural medicines, as well as the production and targeted delivery of personalized therapeutic (functional) products and natural bioregulators.

The scientists of our institute actively cooperate in this direction with the scientific teams of the Nikitsky Botanical Garden – the National Scientific Center of the Russian Academy of Sciences (Yalta, Crimea), the Russian pharmaceutical company Vitaut and Polish pharmaceutical company Greenwit in developing and improving technologies for growing traditional medicinal plants and raw materials, as well as in the production of extracts and traditional medicinal herbs.

Employees of the Department for Pharmacognosy and Botany under the leadership of Doctor of Pharmaceutical Sciences, Professor **Dmitry Konovalov** in conjunction with scientists from the Nikitsky Botanical Garden are conducting studies on a number of valuable plant sources of medicinal raw materials (bay laurel, rosmarin officinalis, sweet wormwood, redstem wormwood). It is planned to develop pharmacopoeial monographs for this raw material and substances.

The staff of the Department for Pharmacology with the course of Clinical Pharmacology under the direction of the Deputy Director for studies and educational work of PMFI, Doctor of Medical Sciences **Andrei Voronkov** actively cooperates with scientists of the South Kazakhstan State Pharmaceutical Academy in the research of safety and effectiveness of extracts from some medicinal plants in Kazakhstan. These extracts are also part of some well-known medicines of oriental medicine.

In addition, a domestic preparation (based on pyrimidine derivatives) with endothelioprotective activity is currently being developed. This domestic preparation has an inhibitory effect on the activity of protein kinase C in cardiovascular pathologies of various genesis.

The new medicine has no analogues in the world according to the proposed mechanism, effect, and chemical structure. This medicine can be used in the therapy of the most socially significant cardiovascular and endocrine diseases.

And what about the use of medicinal resources of the ecological and resort region of the Caucasian Mineral Waters? It is known that Pyatigorsk is also a famous medical resort with more than 200-year history.

The Department for Pharmaceutical Technology with the course of Medical Biotechnology successfully works with a number of pharmaceutical companies. For several years, the Department has been cooperating with the firm Biviteks (Nalchik), which develops and sells pharmaceutical and cosmetology products obtained on the basis of Tambukan peloids.

The practical testing of scientific researches at the enterprise with respect to the development of an optimal technology for obtaining suppositories containing extract from Tambukan mud with a pharmacological effect against prostatitis was carried out.

The combination of pharmacology, biopharmaceuticals and resort medicine will undoubtedly fully reveal the opportunities of the Caucasian Mineral Waters region. It is necessary to create new products and brands. It would be great if they become known both in Russia and abroad.

This year in Pyatigorsk, it is planned to create, for the practical implementation of plans, a biopharmaceutical technopark for the development and production of new medicines. ■

Dmitry Konovalov
The Deputy Director of PMFI for Science

The Department for Pharmaceutical Technology with the course of Medical Biotechnology of PMFI continues research started in cooperation with the Smolensk State Medical Academy. The team of scientists-pharmacologists is working on an innovative medicine form – a transdermal plaster with Mexidol – a domestic medicinal method with an antioxidant, nootropic, anxiolytic effect, and with the ability to stabilize the cerebral circulation.

Researches of the staff of the Department in the field of transdermal medicinal forms of Mexidol were awarded with the First Prize of the 12th National Congress of Therapists held last year in Moscow.

Maksim Chernikov
The Dean of the Faculty of Higher Professional Education (PMFI)

At the end of last year, the Ministry of Education and Science of Russia concluded with our institute a three-year state contract for performing applied research and experimental development for state needs. The project provides for preclinical studies of an anti-secretory anti-ulcer agent. This drug is based on the original chemical substance synthesized by chemists from the Institute of Physical and Organic Chemistry (Southern Federal University) and it should be effective, among other things, when Helicobacter pylori occurs. Preclinical studies will be conducted by the researchers of the Departments for Biology and Physiology with courses of Biochemistry and Microbiology, Department for Pharmacology with the course of Clinical Pharmacology, Department for Pathology and Morphology of our institute, and by the researchers from VolgSMU.

The project aims to create a domestic anti-secretory anti-ulcer drug that surpasses a number of known drugs in terms of strength and duration of action, and also without the typical side effects.

AstraZeneca and Skolkovo

Launch Goint Accelerator Programme for Biomed Startups

The two sides signed the agreement at a forum in central Moscow devoted to Russian healthcare

17 April 2018
Skolkovo Press Office
Source: *sk.ru*

The Skolkovo Foundation signed a landmark agreement with the global pharmaceutical company AstraZeneca on Tuesday on the setting up of a corporate accelerator programme for biomed startups working on treatments and diagnosis systems for cancer, cardiovascular disease, kidney disease, respiratory and metabolic illnesses, and autoimmune diseases.

Six innovative biomed companies will be selected via a competition to take part in the six-month Startup Challenge 2018 accelerator programme at the Skolkovo innovation centre: three companies working on the development of drugs and medicines, and three working in the field of diagnosis tests, systems and devices.

"The companies chosen during the competition will get mentor support from experts at AstraZeneca, and can get access to the Sk BioLab: a fully equipped laboratory," said Kirill Kaem, senior vice president for innovations of the Skolkovo Foundation, who signed the agreement on behalf of Skolkovo.

The competition to find startups was launched Tuesday, and is open to all biomed companies and projects across Russia, not only to resident companies of the Skolkovo Foundation. Thirty projects – 15 in each category – will be selected by a jury as finalists in July, before six projects are chosen from those finalists to take part in the accelerator and become Skolkovo residents. Early-stage startups will get a place in the Sk BioLab sponsored by AstraZeneca, while more developed companies will win a place on the 100 Days of Growth for Biomed Startups accelerator programme devoted to developing business skills that is accredited by the Skolkovo Foundation.

At the end of the Skolkovo-AstraZeneca accelerator programme in December, the companies will demonstrate their research results to venture investors and industrial partners at a demo day. All six participating companies will be eligible for mini-grants of 5 million rubles ($80,000) from the Skolkovo Foundation.

"This is an important milestone for the biomed cluster," said Kamila Zarubina, acceleration director within the biomed cluster.

"We hope to find some interesting startups for AstraZeneca," she said.

The world's biomedical market – and, to a large extent, that in Russia – is dominated by several large international biopharmaceutical companies, said Kaem.

"One of these is AstraZeneca, which is without doubt a strong partner, a leading innovative company, which actively looks for promising developments around the world and supports projects with good potential, even early-stage projects. It's great that Russia, which global pharma companies previously often tended to overlook, is becoming a place where those companies can find interesting projects," he said.

"Acceleration in biomedicine is somewhat different to in IT, for example, so this kind of collaboration with AstraZeneca will enable companies taking part in the accelerator to access infrastructure both inside Skolkovo and outside of it," added Kaem, who was previously head of Skolkovo's biomed cluster.

"The value of this joint approach lies both in the synergy of skills in technology, investment, business and mentorship possessed by the developer companies, the Skolkovo Foundation and AstraZeneca, and in the selection of projects, assessment of their risks, and the assistance the winning projects will get," he said.

AstraZeneca's cooperation with Skolkovo began two years ago when the U.K.-headquartered company's CEO visited Moscow and four Skolkovo start-ups presented their projects.

"When AstraZeneca's CEO Pascal Soriot visited Moscow, we demonstrated the discoveries of four Skolkovo residents to him: Gero, National Pharmaceutical Technologies, Real Target and TheraMAB," said Zarubina. Since then, Skolkovo has organised demo days for the pharmaceutical giant, and Skolkovo also has a resident company, M&S Decisions, which provides exclusive mathematical modelling services for new drug development for AstraZeneca, she added.

In May 2017 Skolkovo and AstraZeneca signed a strategic partnership agreement to carry out joint research and educational work across Russia. AstraZeneca opened a $224 million drug manufacturing and packaging factory in Russia's Kaluga region back in October 2015.

Four Skolkovo biomed startups recently won sponsored places in the Sk BioLab from the U.S. healthcare giant Johnson & Johnson.

Applications to take part in the accelerator should be submitted before June 18. The competition rules and more information about applying can be found here: *http://sk.ru/foundation/events/april2018/astrazeneca/* ■

Ilya Naroditskiy
International Business Development Director at Navicon

“Smart” Pharmaceutical Production:

How Is It Being Implemented Right Now?

NAVICON
IT-CONSULTING

12 April 2018

Every pharmaceutical company that operates in today’s highly competitive market has to take on the task of maximum reduction of the production cost and increase the profit while maintaining the quality of products at a consistently high level. To achieve that, the business executives more and more often choose the way of creating a “smart” production cycle. **Ilya Naroditskiy**, International Business Development Director at Navicon, explains how pharmaceutical companies realize this concept in practice with minimal resources costs.

The pharmaceutical market is one of the fastest growing sectors of the world economy: according to the analytical agency Mordor Intelligence, in 2017 the global pharmaceutical market was estimated at 92.144 billion US dollars, and its growth was projected at more than 8% annually in a five-year time frame. At the same time, like any sector of the economy with high investment potential and high business margins, pharma industry is one of the first to react to the emergence of new technologies in the market. The resources allow the “big pharma” to test innovative solutions and determine their potential for business optimization.

McKinsey believes that innovative technologies such as big data processing tools and machine learning will completely change the pharmaceutical business in the near future. According to the forecasts of the research agency, innovations can annually generate up to 100 Bn US dollars in pharmaceuticals and medicine, primarily by optimizing the process of making managerial decisions, increasing the speed and effectiveness of research and clinical trials of new products (for example, today the development of a single drug may cost to a global company up to $ 2.6 billion, and may take up to 14 years), and creating new tools for the work of pharmaceutical companies with consumers and regulators.

The global market is on the way to create a new type of enterprise – “smart” pharmaceuticals.

WHAT DOES A “SMART” PHARMACEUTICAL ENTERPRISE LOOK LIKE?

Of course, the requirements for pharmaceuticals-oriented technologies vary greatly depending on the country in which the pharmaceutical company operates. But in general, the common trend is the use of digital technologies to optimize production and business processes. Innovations that can optimize the costly processes of production, promotion and sales of goods, almost instantly emerge on the pharmaceutical market.

In fact, the first and foremost task of “smart” production is to find ways to efficiently collect and use a large number of different types of data on research and development (R&D), production and business, partners and customers. In other words, the market is being conquered by intellectual algorithms, technologies for business processes automation (RPA), and artificial intelligence.

The first element to fit under the optimization program is the actual production – for the costs associated with it account for 20-25% of the budgets of pharmaceutical companies as they calculated it in the Moscow Exchange’s Innovation and Investment Market, and in the Industrial Development Fund. When applied to the pharmaceutical production, IT systems usually solve three main production tasks:

TASK #1: OPTIMIZING PRODUCTION PROCESSES

To increase the marginality of an enterprise, it is necessary to determine exactly how to harmonize the output of finished medicines, taking into account a lot of factors: the availability of raw materials and warehouses stocks, the dynamics of demand for medicines, the number and volume of orders, shipments by distributors and returns, competetive tender supplies, and other conditions.

Imagine the situation: the company won the competitive tender for medicine supply for an unplanned epidemic. How to reschedule the rest of the working month in order to fulfill the planned shipments as much as possible, and have time to ensure the release of a new FPP batch?

To rely only on the practical experience of specialists will not be enough, especially when a managerial decision has to be made in several hours time span and you don't have several days to make it. After all, a large order which seems profitable in a short-term perspective (a month or two), may not yield the desired profit due to back charges, overhauls and downtime of equipment, poor calculation of the actual need for the necessary raw materials or logistics resources. To get precise calculations of how exactly the potential economic effect of each order will be achieved, it's better to use the optimization (target) planning systems.

In the shortest possible time these IT systems form various forecast scenarios "what will happen if ..." based on a variety of input data, from physical limitations of production lines to the competitive and macroeconomic environment of the enterprise. At the end of this process the system will show which orders should be performed first and how to best distribute them on production sites and lines, taking into account the delivery time of materials, the need to use unique equipment, as well as the time for washing and disinfection of equipment between the batches release. Moreover, the production plans can be quickly revised which allows business leaders not to be attached to one scenario, but to consider the possibility of changing it, for example, in the case of an unexpected competitive tender win.

TASK #2: HARMONIZING THE WORK OF DIFFERENT UNITS

"Smart" pharmaceutical production among other things means using the approach related to integrated planning of the enterprise's activities, which allows to synchronize the work of all its divisions: sales, production, equipment repair and maintenance, procurement. IT systems create a unique ecosystem within the organization through which all documents and communications pass.

Usually, each department has its own tasks to perform which may not be correlated with the goals of other departments. For example, production units are focused on a uniform, harmonious planned release of agreed batches of the product and do not like to change the production plan due to new contracts. On the other hand, getting the maximum number of orders is the task of the sales department. Also, in the pharmaceutical industry, there is a number of special standards in the field of certification and production execution (GMP): the amount of time for equipment disinfection has been increased, the availability of staff of certain qualifications "in the workplace" at the time of product release is regulated more rigidly than in other industries. If the sales department does not take these factors into account when formulating extensive production plans in terms of the output volume, then there is a risk that the detailed plan will not completely cover the sales needs.

Worth noting separately is the process of rescheduling in the event of a hazardous situation. For example, if the production line has stopped, how do you determine if it is worth resuming the release of the consignment immediately after it has been repaired? How long will it take to repair? And what losses will the organization incur? Any deviation from the planned targets will be optimized by the system in such a way as to achieve the final goal of the company with the least losses.

TASK #3: SAVING ON MECHANICAL OPERATIONS

Finally, the last task that "smart production" solves is the creation of an integrated innovation infrastructure at the pharmaceutical enterprise.

It should be understood that any successful business today is built on data – competition in business is moving from characteristics of goods to the field of automatic information management. In just 5-10 years, a large number of management decisions will be made on the basis of the data analyzed by the algorithm and the recommendations issued by it. And in order to not to lose their competitive position and win new markets and regions, pharmaceutical companies master such technologies and various IT tools – predictive analytics, optimization planning and scenario modeling, as well as cognitive ("smart") big data processing technologies that detect hidden patterns in terabytes of data almost instantly.

Pharmaceutical business has two ways of saving on routine activities. First, pharmaceutical companies introduce elements of artificial intelligence: for example, AI is already being used to monitor clinical trials, formulate optimal marketing and price strategies. Such industry's giants as Johnson & Johnson or Sanofi use IBM Watson in their research work.

Secondly, pharmaceutical companies "hire" the bots. Robotizing business processes using RPA technology makes it possible to delegate boring, repetitive tasks that do not require making complex decisions to robots in order to free personel from doing them. As a result, the company's costs of processing the documents in standardized forms, gathering the data from multiple sources, searching and aggregation of information on various research and development tasks as well as registration of clinical trial results are substantially optimized.

RUNNING TO STAY STILL

Optimization and predictive modeling technologies, tools based on machine learning, artificial intelligence and robotics already help big pharma to make operational activities completely manageable and transparent at all stages, from research to marketing and product promotion. Nevertheless, the pharmaceutical business still has to solve a number of problems that arise when implementing the "smart" production.

First, it is necessary to provide a completely secure IT infrastructure for working with large data sets. Fortunately, in this direction, many developments are under way, from advanced antivirus programs to unique quantum encryption technologies that allow data to be transmitted over short distances through secure channels.

Secondly, the leadership of the pharmaceutical enterprises will have to accept the fact that a number of innovations are aimed at returning investments in the long term. Historically, pharmaceutical companies were not ready to innovate if this did not entail an immediate increase in profits. Pharma enterprises must learn to see value in innovative solutions that will allow them to optimally control business processes in enterprises, but will not increase substantially the revenue in the first months after implementation.

Once these problems are solved, the pharmaceutical manufacturers will be able to create a single information space at enterprises, where high-tech equipment, analytical and managerial IT systems exchange data in a non-stop mode. This will be the last step towards the intellectualization of business. ■

International Conference on Drug Development

28 November 2018, RUDN University, Moscow

RUDN university

Peoples' Friendship University of Russia (RUDN University) is a unique higher educational institution, a large internationally oriented educational and scientific center.

RUDN University is known in the world for its achievements in the organization of the educational process, innovative research in the field of fundamental and applied sciences, broad international connections.

RUDN University takes high places in international and Russian scientific ratings due to the active scientific work of the University's scientists.

Slogan of the University is "Uniting people of different cultures by knowledge RUDN University creates leaders to make the World better"

In 2015, RUDN University was among the competition winners to receive the state support within the 5-100 Project framework. The goal of Project 5-100 is to maximize competitive position of a group of leading Russian universities in the global research and education market.

Over 150 science events are held annually in RUDN University. More than 14 thousand people take part in these activities, including 15% of foreign participants.

The RUDN University's scientific events are authoritative platforms for business communication among scientists, postgraduate and international students, thereby ensuring a possibility of testing scientific research results, setting new goals and objectives in the new knowledge development and promotion.

Maintaining the tradition of international cooperation, on 28 November 2018, RUDN University is holding an international conference with the participation of leading scientists in the field of pharmaceutical development of Russia, Great Britain, Germany, Switzerland, Finland, and with the participation of relevant federal ministries and departments. The main aims of the Conference are the exchange of scientific theories, concepts, hypotheses, innovative ideas, innovative approaches, and modern practices; creation of international research teams.

Scientific and technological progress in the pharmaceutical industry is accompanied by the search, development, and continuous improvement of technologies for the production of active pharmaceutical substances and pharmaceuticals. A modern trend in the development of the pharmaceutical industry is the building of a system of cooperation between industry and higher education. Within the framework of the conference the following topical issues will be discussed:

- Current trends in effective cooperation with Russian and foreign partners in the field of pharmaceutical development
- Modern methods of research in pharmacognosy, homeopathy, and metabolomics.
- International experience in the development of innovative medicines. Expert's view.
- Actual directions in modern biotechnology
- International experience in the development of innovative medicines.
- Search for innovations through partnerships.
- Development of professional competencies and skills in the field of the full production cycle of medicines.

Participation in the international conference is free of charge.

We invite scientists, like-minded people, creative speakers, employees of Russian and foreign pharmaceutical companies to participate in the conference.

Additional information is available at ***pharmdevelopment.rudn.ru***.

RUDN university

5100

International Scientific Conference "Harmonization of approaches to pharmaceutical development"

Moscow, Russia, November 28, 2018

Центр коллективного пользования (Научно-образовательный центр)

The conference is held with the participation of leading scientists in the field of pharmaceutical development of Russia, Great Britain, Germany, Switzerland, Finland, as well as with the participation of relevant federal ministries and departments of the Russian Federation.

Key topics:

- Development of professional competencies and skills in the field of the full cycle production of medicines
- Innovations in the methodology of pharmaceutical development
- Development of mutually beneficial relations between R&D teams and technology transfer centers
- Standardization of medicines is the basis of their proper quality
- Preclinical and clinical studies in accordance with the requirements of EurAsEC
- Pharmacognosy and plant metabolomics in the development of herbal medicines
- Possibility of additive technologies applying in pharmacy

We invite you to participate in the conference!

Participation is free!

Additional information is available at:

pharmdevelopment.rudn.ru

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New Biopharma

Event Launches Alongside CPhI WW 2018

10 April 2018

UBM's pharma portfolio announces the launch of a new bespoke and independently branded biopharma event, **BioLIVE**, next year in Madrid (**October 9-11, 2018 at IFEMA, Feria de Madrid**) – specifically for **bioprocessing** and **manufacturing**

The new event has been created after independent research identified a gap in the market for a new global exhibition and content platform that could establish premium-class, global leadership across the entire bio manufacturing value chain.

BioLIVE will serve as a global hub for both upstream and downstream processing and manufacturing, connecting biotechs, big pharma and service providers including CDMOs and CROs from early stage development to commercial manufacturing and regulatory services. It will also feature biogeneric and bioinnovator audiences through to manufacturing and laboratory specialists.

Analyst research indicated that running the new event in parallel to its enormous contract services (ICSE) and small molecule (CPhI Worldwide) exhibitions – both currently the world's largest in their respective areas – would create natural synergies and establish the first truly global hub covering the entire biopharma and pharma supply chains.

"It's a hugely exciting time for the bio industry globally and we expect rapid growth in what is now a maturing supply chain. Independent research showed a dissatisfaction amongst existing options, and we have identified that we can provide broader depth in bio manufacturing and processing, whilst capitalising on our collective portfolio strength to bring additional value by combining the small and large molecule worlds together with contract services", commented **Rutger Oudejans**, Brand Director at UBM. He added, *"It is firstly to provide an ecosystem to bring together the bio development and manufacturing sectors. But it also enables companies and professionals involved across the full pharma value chain of both small and large molecule to learn from each other and evolve new strategies to overcome the challenges in bio processing and manufacturing"*.

Attendees at BioLIVE will benefit from a mixture of science and technology content – including presentations and conferences on the latest bio innovations and techniques – alongside specialised business development and partnering programmes to help them directly match with the most appropriate partners.

BioLIVE will help big pharma's bio divisions and biopharma giants to assess the specific niche services they need, such as analytics and testing. Conversely, the event will empower the small and medium sized bio innovators who want to feed new therapies into the development pipelines of larger companies. Bio innovators will also be able to look for the external partners they need to push forward their drug development and commercialization programmes.

Additionally, BioLIVE will include the producers of specialized bio lab equipment – such as high-performance liquid chromatography – needed for biopharmaceutical research, QC and regulatory submissions. Alongside the plethora of adjacent industries from reagent suppliers, CROs to equipment, consultancy and service providers from across the whole bio value chain.

There is great potential in bringing the bio community together under the auspices of one new global event – running at the same time as CPhI Worldwide. The launch of BioLIVE will help accelerate the development of the bio supply chain, improve knowledge exchange, and create a more collaborative bio/pharma environment.

Eric Langer, President and Managing Partner, BioPlan Associates added his support to events that facilitate collaboration, commenting: *"This event has been developed to provide an opportunity for both bio and pharma executives to meet and exchange ideas, and to address key challenges the industry faces, including how to overcome supply chain, processing and manufacturing challenges. The industry needs an effective forum where it can centralize both bio and pharma partners who can now meet different parts of the global bio/pharma industry, especially as the bio manufacturing segment matures. Industry data suggests that biopharma can still learn much from small molecule pharma, and that is why this new event could provide unique perspectives that can advance the bio industry"*.

GLOBAL BIOPHARMA COUNTRY RANKING

To build on the success of last year's global small molecule country rankings we are introducing a biologics manufacturing and processing league table. The results of which will rank the perception of the world's largest biologics markets for "overall quality", "growth potential" (for exports and domestic market), "innovation" and "ability to meet future capacity constraints".

"Biologics capacity is growing quickly and will increase by nearly 40% over the next four years. Asia and European countries are building more facilities, which is reducing the USA's overall market share of capacity. What no one has yet evaluated is the relative perceived strengths of each region. The perception of each country will undoubtedly be a factor in realizing its growth potential", added Rutger Oudejans, Brand Director at UBM for BioLIVE.

The study will evaluate the consequences for the supply chain, as with an increasing number of bio facilities globally, the perception of the ability to meet future demand could well be a decisive factor in major investment decisions. What will also become clearer is which markets are seen to have the best potential growth both domestically and for exports.

Last year's small molecule ranking demonstrated that the traditional economies of the USA, Germany, and Japan were still perceived as the strongest, but with the rapid emergence of newer bio regions – we could see countries like Korea, China, and Singapore ranking much higher for large molecule manufacturing. Additionally, the research will also evaluate what the potentially geopolitical and supply chain risk is in newer regions, as well as the knowledge of bio professionals. Thus, we might see a picture emerging of certain countries being seen as exceptional for capacity and production, and others for knowledge and innovation.

One of key considerations behind launching BioLIVE was the potential benefits of integration of the small and large molecule industries. But also, with an increasingly globalized supply chain, it's important that the industry can centralize and share learning. For example, information on which countries are the leaders in the associated types of services needed to help meet changing commercial requirements and bring bio products to market. These include activities as diverse as recruitment services to regulatory submission support, cell line development (e.g. CHO, mouse myeloma and human cell lines), analytical testing, and custom assays.

A central feature of BioLIVE will be access to the best available bio content, and later this year, the company will also add a new biologics section to its annual expert report. Global bio industry experts such as Eric Langer are being called upon to forecast the industry's' direction over the next few years.

"One of the great successes of the small molecules space has been the internationalization of the supply chain, and we want to bring this experience and couple it with industry analysis from prominent experts, and new original research, so that we can better inform the bio community on the opportunities available. To sustain the next wave of growth, the industry will need to meet new partners, but also, access insights and content to know how best to work with new customers. With this in mind, BioLIVE will be a mixture of biotechs, big pharma and service providers, coupled with an extensive learning programme for bio processing and manufacturing professionals", added Oudejans. ■

About GMP news

In autumn of 2010, the first edition of the "GMP news" industry magazine was published. The print edition was created to spread the information about international standards for manufacturing medicinal products in Russia and CIS countries. Thanks to "GMP news", professionals and specialists are up to date with everything regarding the pharmaceutical market. Among the main topics is modernization of pharmaceutical productions in accordance with GMP, development and launch of new medicinal products into production, changes in regulatory rules and standards introduced not only to pharmaceutical market of CIS, but international markets as well.

"CIS GMP news" – an English language publication – was created to show readers the modernization and the development of pharmaceutical industry of Russia, EAEU, and CIS countries in general. Special attention is given to localization of pharmaceutical industry, technology transfer, contract manufacturing in order to give the professional community from different parts of the world a chance to cooperate in scientific research, and business.

To learn more about "GMP news" project, go to ***gmpnews.net/about***

Media Partnership

Media partnership is one of the ways you can cooperate with "CIS GMP news". We offer media partnership to everybody interested – organizations, learning centers, conferences, exhibitions, magazines, newspapers, internet portals, and other mass media.

We also extend our partnership to pharmaceutical industry specialists and experts, who are going to be able to publish topical articles on manufacturing of medicinal products on the pages of our publication. Companies are invited to share the details about their work as well.

Today, our project is comprised of internet news portals GMPnews.Net (in English) and GMPnews.Ru (in Russian), and print publication – magazines «Новости GMP» in Russian, and "CIS GMP news" in English. This allows us to spread the information of our partners quickly and efficiently! In addition, an every day newsletter with fresh publications is sent out to our subscribers, is broadcasted in news aggregators and social networks.

We are always happy to work with you on mutually agreeable terms!

Contact email: ***editor@gmpnews.net***

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