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Cooperation in the field of clinical trials

Analytical Report

September 2012





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Glossary of acronyms

АСТО	Association of Clinical Trial Organisations
BE (studies)	Bioequivalence (studies)
САРА	Corrective and preventive actions
СНМР	Committee for Medicinal Products for Human Use
DRA	Drug Regulatory Authority
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration of the United States of America
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Products
IMCTs	International Multicentre Clinical Trials
IRB	Institutional Review Board
MAA	Marketing Authorisation Application
MHSD	Ministry of Health and Social Development
QA	Quality Assurance (system)
QMS	Quality Management System
RF	Russian Federation
RZN	Federal Service of Surveillance in Health Care and Social Development of the Russian Federation, Roszdravnadzor
SOP	Standard Operation Procedure
ToR	Terms of Reference



General Administrative remarks to the project

The Consultants team would like to stress the fact that the following Analytical Report reflects the situation as **until July 2012**. Due to a limited timeframe of the project, further changes in EU and RF pharmaceutical legislation that will occur after July 2012, will not be considered by this document.

Translations

The laws, governmental Decrees, and Executive Orders listed in Annex 1 were received in Russian language from the Ministry of Health and Social Development (MHSD; Ms. Beda) or were retrieved from the Ministry's and/or Governmental websites.

The Legal Department of the MHSD has no English translations of the relevant legislative documents available, nor does it certify/approve translations. Consequently, the experts retrieved English translations from the Internet, in particular from the website of the Association of Clinical Trial Organisations (ACTO). The English versions of the documents were sent to the ROID Translation Agency (www.roid.ru) in order to assess correctness and accuracy of the translations and to certify this. This Agency is a certified translator of Russian-English texts. All relevant EU texts are now available in Russian.

Planned revision of Directive 2001/20/EC

A revision of the "Clinical trials Directive" 2001/20/EC is underway. A "Concept Paper for Public Consultation" has been published on 09/02/2011 (SANCO/C8/PB/SF D(2011) 143488. Section 3 presents an appraisal on "Ensuring compliance with Good Clinical Practice in clinical trials performed in third countries". Key issues are (1) to ensure GCP-compliant conduct of trials in third countries when the data is submitted in the EU in the framework of the marketing authorisation process, and (2) entry of clinical studies into a public register (EudraCT). It is expected that a revision will not be effective within the next years.

Amending the "On Circulation of medicines" Law

The "Expert Council for Developing Competition in the Social Sphere and Healthcare" of the "Federal Antimonopoly Service of the Russian Federation" announced in its meeting on 05 March 2012 that a Draft Federal Law "On Introducing Amendments to the Federal Law "On Circulation of medicines" has been submitted to the Ministry of Health and Social Development for consultations. These amendments include changes in the accreditation system of clinical sites (i.e. to abolish the system), and to change the 5 years' time of experience for investigators to 2 years. In addition, the experts have been informed [lit.9] that in particular the requirement to conduct so-called confirmatory clinical trials (see Chapter 4.2.1) in the marketing authorisation application process is under reconsideration.

Approval/Registration of legal documents

Russian legal documents like Executive Orders (issued by Ministries and other State bodies), must be registered/approved by the Ministry of Justice in order to get in power.

Acknowledgement

The project team thanks Ms. Svetlana Zavidova from the Association of Clinical Trial Organisations (ACTO) [lit.9] for permission to use ACTO documents and many informative discussions.



Executive Summary

General

Most of the data from pivotal clinical trials submitted for marketing authorization applications to the EMA are from third countries and the Russian Federation (RF) is one of the key players in this respect. In fact about 60 per cent of all clinical trial data included in MA applications to the EMA has been generated outside the EU and this underscores the importance of aligning foreign GCP systems such as that of the RF with the EU

The described findings are based on a survey of the relevant regulatory/legislative documents and were substantiated during three co-inspections in RF which took place during the course of the project in May and June 2012

In general, it can be stated that for the conduct and supervision of clinical trials in the EU and the RF equivalence of the respective regulatory/legislative framework provisions is given:

- Executive Order no. 266 [10] "Rules for Clinical Practice in the Russian Federation" stipulates that "these rules for clinical practice are binding for all participants of clinical drug trials on the territory of the Russian Federation". However, this order is from 2003 and has legal force only in those parts, which do not contradict those in the current legislation
- GOSTP52379-2005 [24], a direct translation of the ICH-GCP guideline, has like in EU-the legal status of a guideline. In addition to the provisions given in [10], sponsors of International multicentre clinical trials (IMCTs) also follow ICH-GCP rules in order to ensure acceptance of the clinical trial data by the EU Drug Regulatory Authorities
- Local clinical trials, which can be conducted only within a registration process in RF, need to comply with the rules for clinical practice [10]. However, RZN GCP inspectors check GCP compliance against [10] and [24]. Similar situations exist concerning the "Rules on Laboratory practice" and the "Rules on Manufacturing practice".

However, a number of differences exist, which have been identified and classified in the following four (4) categories:

- (1) Differences that might affect the trial participant's rights, safety and welfare, credibility of study data and thus acceptance of the clinical study results by the DRAs in EU:
 - Despite clinical trials must be conducted in compliance with "Rules on Clinical practice", this is not an obligatory requirement within the registration/marketing authorization process in the RF [D2]
 - Definitions given in the "On Circulation of Medicines" Law are not always identical with the ones provided in Directives 2001/83/EC and 2001/20/EC [D3]
 - There are no specific, separate inspections performed concerning Clinical laboratories, Computer systems, Sponsor and CRO Phase I units, Record keeping and archiving of documents, Bioanalytical part, Pharmacokinetic and Statistical Analyses of bioequivalence trials [D15]
 - No consistent classification of Adverse events/Adverse Drug reactions in the Law
 [1, Article 64] and [18] [D17]



(2) Differences, which restrict the nature and extent of trials that can be carried out in RF, in a manner more restrictive than those in EU:

- Except of so-called international multicentre clinical trials (IMCTs) and post registration studies, applications for conducting a clinical trial in RF can only be submitted in the course of a registration process [D1]
- Clinical studies can be conducted only for pre-defined purposes [D7]
- Clinical trials involving healthy volunteers, i.e. in phase I studies, with "medicinal products manufactured outside the RF" are prohibited, but for local sponsors are permitted. Also phase I studies with foreign drugs involving patients are possible [D8]

(3) Country specific requirements that go beyond those applied in EU:

- Only defined applicants/organisations are entitled to organise clinical trials[D9]
- Clinical sites for conducting clinical trials need to be accredited by the MHSD
 [D10]
- (Principal) investigators must have a 5-year experience in the conduct of clinical trials in order to be eligible as investigator in a clinical trial [D12]
- The law provides very strict rules concerning the conduct of clinical trials on defined vulnerable persons, exceeding those in EU [D13]
- "Local registration studies" on safety and efficacy (except for IMCTs) trials need to be repeated (so-called confirmatory trials) in the marketing authorisation process [D14]

(4) Other, country-related, differences:

- Article 3 (5) of the On circulation of medicines Law states that the results of clinical trials conducted outside of RF shall be acknowledged based on "International treaties" and/or the principle of reciprocity [D4]
- Direct contacts of an applicant with the Ethics Council or the Expert Organisation are not allowed [D5]
- In RF GCP inspections are free-of-charge [D6]
- Drug manufacturing licenses are issued by the Ministry of Industry and Trade, not by the Drug regulatory authorities (or the RZN) [D11]
- The RZN doesn't conduct inspections outside the country [D16]

When the new "On Circulation of Medicines" law went into force in 2010 in RF, substantial changes in the regulatory/legislative framework and in the structures, and organisations relative to the conducting of clinical trials were made. In the clinical trials area, except for the "Control" and "Drug Safety and Pharmacovigilance" functions, which were given to the Roszdravnadzor (RZN), all other regulatory functions were awarded to the Ministry of Health and Social Development (MHSD)

Many stakeholders share a common positive view of the changes triggered by the implementation of the new On Circulation of Medicines Law: clinical trial application, the registration process etc. are now more transparent, fast and need to follow stringent timelines.

Problems and delays in implementing the new provisions, such as the procedure for importing IMPs and registered medicinal products (e.g. as comparators), the rules concerning insuring



study participants in clinical trials, and keeping the timelines set by the MHSD for re-accrediting clinical sites to conduct clinical trials, have been resolved or are under revision.

Two-thirds of all clinical trial approvals in 2011 in RF were for so-called International multicentre clinical trials (IMCTs), *i.e.* phase III studies. As already described above, these trials are conducted by adhering to ICH-GCP rules in order to ensure acceptance of the clinical trial data by the EU DRAs. This is in addition to the "Rules for clinical practice" laid down in Executive Order no. 266 [10], which are "binding for all participants of clinical drug trials on the territory of the Russian Federation". However, according to ICH-GCP, 5.2.1, the "ultimate responsibility for the quality and integrity of the trial data always resides with the sponsor": therefore, sponsors make sure (in their own interest) that ICH-GCP rules are strictly followed.

In addition it needs to be mentioned that both the EU Clinical Trials Directive as well as the "On Circulation of Medicines Law" are under revision. In RF, some amendments, *i.e.* addressing biosimilars and orphan drugs, are in preparation and the requirement for conducting so-called local registration trials will be reconsidered.

Topical actual addendum: After the new Government in RF went into force on 21 May 2012, a Presidential Decree no. 636 "On the Structure of Federal Executive Bodies" was issued, which splits the "Ministry of Health and Social Development" into a "Ministry of Health" and a "Ministry of Labour and Social Protection". In parallel, changes in the staff took place

The "Federal Service on Surveillance in Healthcare and Social Development" has been renamed to "Federal Service on Surveillance in Healthcare".

Key points

(1) In general, it can be stated that for the conduct and supervision of clinical trials in the EU and the RF equivalence of the respective regulatory/legislative framework provisions is given

Clinical trials in RF must be conducted according to the "Rules for Clinical Practice in the Russian Federation" (Executive Order no. 266 [10]). However, this order is from 2003 and has legal force only in those parts, which do not contradict those in the current legislation

GOSTP52379-2005 [24], a direct translation of the ICH-GCP guideline, has – like in EU-the legal status of a guideline. In addition to the provisions given in [10], sponsors of International multicentre clinical trials (IMCTs) also follow ICH-GCP rules in order to ensure acceptance of the clinical trial data by the EU Drug Regulatory Authorities

Local clinical trials, which can be conducted only within a registration process in RF, need to comply with the rules for clinical practice [10]. However, this is not an obligatory requirement within the registration/MAA process in the RF

RZN GCP inspectors check GCP compliance against [10] and [24]. Similar situations exist concerning the "Rules on Laboratory practice" and the "Rules on Manufacturing practice"



(2) A number of differences exist, which have been identified and classified in four (4) categories

These differences have been described before and are summarized in Chapter 6, Lessons learned, Summary and Conclusions:

There are 4 differences that might affect the trial participant's rights, safety and welfare, credibility of study data and thus acceptance of the clinical study results by the DRAs in EU (D2, D3, D15, D17). However, these differences- like the other identified differences- are not principal, system immanent ones, but might be resolved within the planned revision of the "On circulation of medicines" Law

Differences, which restrict the nature and extent of trials that can be carried out in RF, in a manner more restrictive than those in EU (3 differences, D1, D7, D8), and the Country specific requirements that go beyond those applied in EU (5 differences, D9, D10, D12, D13, D14), reflect the in general more strict provisions for conducting clinical trials in RF, in particular this applies to the nature and extend of clinical trials. Examples are the requirement that clinical sites need to be accredited by the MHSD, that only defined applicants/organisations are entitled to organise clinical trials, that investigators must have a 5-year experience in the conduct of clinical trials, and that (except of so-called international multicentre clinical trials (IMCTs) and post-registration studies), applications for conducting a clinical trial in RF can only be submitted in the course of a registration process. In particular, the requirement to repeat safety and efficacy clinical trials (so-called local registration studies) whose results have already been assessed in the "original" registration process, which put study participants on unnecessary risk(s), generate additional costs for the applicant, and postpone access of the population to modern drugs, should be re-assessed

Other, country-related, differences (5 differences, *D4*, *D5*, *D6*, *D11*, *D16*) refer mainly to administrative, organisational issues with no influence on a possible mutual acceptance of clinical trial results.

(3) The legislative/regulatory framework should be rounded off (recommendations)

The following provisions should be addressed and might be added to the regulations (they are not necessarily problems for the mutual acceptance of clinical trials results per se and some of them have already been selected to be included into the next version of the Law [1]), *e.g.*:

- -It should be possible to file clinical trial applications independently of a registration process
- -Definitions, like for adverse events/reactions, should be harmonised with International provisions
- -The Ethics Council should be empowered to issue, besides an approval or rejection, conditional approvals to conduct a clinical study (to avoid restarting of the entire application process in cases of rejection)
- -votes from other Independent Ethics Committees should be recognised
- -Provisions on biosimilars, paediatrics and orphan drugs should be provided
- -Inspections addressing specific aspects of GCP, like Computer systems, pharmacovigilance, should be made possible



1. Project organisation and synopsis

1.1. Project objectives

According to the Terms of Reference [lit.1], the (1) System of implementation, (2) Control, and (3) Enforcement of compliance of good clinical practice (GCP) rules in the Russian Federation (RF) and the European Union (EU) were assessed. The key question to be answered by this assessment was whether the implementation, control, and enforcement of GCP (in clinical trials with medicinal products for humans) in RF are equivalent in particular to the corresponding provisions of Directives 2001/20/EC and 2005/28/EC.

1.2. Activities and timescales

The experts' work started on 12 December 2011 and finished in July 2012. As laid down in the service contract, the experts conducted three in-country missions. In addition, a project briefing meeting was held at the SANCO offices in Brussels on 13 March 2012, as well as a videoconference on 19 June 2012. The missions to Moscow took place in February, April, May and June 2012. In total the consultants participated in 3 inspections which were conducted by the GCP inspectors from the Roszdravnadzor.

The results from the missions have been documented by reports (Annex 5).

This report first discusses the **details of the findings and results** of the various missions and analyses. Then **conclusions are drawn with concomitant recommendations**. The recommendations include proposals for closing possible gaps between the regulatory/legislative systems in order to come to a mutual agreement.



2. Part I - Legislation

2.1. Legislation overview

The Parliament is the supreme legislative body on healthcare issues. The "On Circulation of Medicines" Law [1] is a Framework Act, underpinned by a number of Governmental Decrees, Executive Orders (by the Ministry), and further regulations, guidelines, etc. to bring its policies into practice.

In Chapter 2, *Articles 5 and 6*, respectively, of this law ("Enabling Act") the powers of the Federal Executive bodies and of the Constituent Entities (*i.e.* the member states of the Russian Federation) of the Russian Federation (RF) in the area of "circulation of medicines" are stipulated. The term "circulation" includes not only the manufacturing, distribution, storage, and dispensing of medicinal products, but also the areas of drug development, import, prices for medicinal products, up to the approval of professional training programs. In *Article 5*, *point 8* <u>inspections for compliance with the "rules on manufacturing practice" [25] compliance</u> are explicitly mentioned, but there are no provisions concerning "clinical practice" [24], and "laboratory practice" [26]; these are mentioned in Article 9, Point 4.

The powers of the executive bodies of a constituent entity of the RF (*Article 6*) are limited to price control, mark-ups in wholesale and retail, and the establishing of regional programs for supply of medicinal products to the population.

Article 9 empowers the national and regional Drug regulatory authorities to control medicines. Point 4 lays down that State control of compliance with e.g. the rules on laboratory practice, clinical practice and manufacturing practice is accomplished by inspections; also mentioned are medicinal products for veterinary use. Point 17 of Article 5 empowers the Federal executive bodies to impose sanctions in cases of violations of the legislation; i.e. enforcement of the law is within the responsibility of the Ministry of Health and Social Development (MHSD) and the Federal Service of Surveillance in Health Care and Social Development of the Russian Federation (Roszdravnadzor; RZN).

In general, the provisions in this law on defined issues, like Ethical aspects of a clinical trial, are scattered over the entire text: the same issue is stipulated in several articles, concerning Ethics *e.g.* over 4 Articles. In addition, the rights of study participants and their insurance when participating in a clinical trial, are regulated in different articles (Articles 43, 44), but are genuine issues for Ethics Committees.

Directly related to individual Articles in the "On circulation of medicines" Law are the **Governmental Decrees** (issued by the Government of the Russian Federation) and **(Executive) Orders** of the MHSD, which regulate defined issues in detail, *i.e.* how regulatory functions should be executed (a list of these Laws, Decrees and Orders is attached [Annex1].

The fourth layer of regulatory/legislative provisions is **guidelines**, which give advice of how to interpret, understand, and to comply with the applicable regulations. They are "straightforward recommendations" and therefore not legally binding (they get legally binding only when incorporated into the law(s) and/or regulation(s). In RF for example, the ICH-GCP guideline has been directly translated into GOST P 52379-2005 ("National standard of GCP in RF") and has thus the



legal status of a guideline [24]. Order no. 266 from 2003 "Rules for clinical practice" [10] has legal force only in those parts, which do not contradict those in the current legislation. This order states that "these rules for clinical practice are binding for all participants of clinical drug trials on the territory of the Russian Federation".

Applications for conducting a clinical trial in RF (except of so-called international multicentre clinical trials (IMCTs) and post-registration studies) can only be submitted in the course of a registration process (1, Articles 14, 21)[**D1**]. In EU a clinical trial application is independent of an MAA.

Except of so-called international multicentre clinical trials (IMCTs) and post-registration studies, applications for conducting a clinical trial in RF can only be submitted in the course of a registration process [**D1**]

Despite clinical trials should be conducted in compliance with the rules on clinical practice, this is not an obligatory requirement within the registration/marketing authorization process in the RF [1; Article 18][**D1**]. In EU acceptance of clinical trial results within the MAA process is granted only if the clinical trial has been conducted under GCP rules

Despite clinical trials should be conducted in compliance with the "Rules on clinical practice", this is not an obligatory requirement within the registration/marketing authorization process in the RF [1; Article 18][**D2**]

In essence the regulatory/legislative framework ruling clinical trials comprises the:

- (1) Law "On Circulation of Medicines" and it's amendments [1]
- (2) Order no. 266 from 19 June 2003 on "Rules for clinical practice in RF" (defined parts only) [10], and the list of Governmental Decrees and Executive Orders in [Annex1]
- (3) GOSTP52379-2005 ("National standard of GCP in RF"), equivalent to the ICH-GCP guide-line [24]

Concerning the area of <u>controlling</u> adherence to the rules on clinical practice by inspections through the competent authorities, the recently (26 January 2012) implemented Executive Order 1091n applies [23]. The basis for inspections in general is laid down in Federal law no. 294-FZ [4]. However, this law provides only general rules for all kinds of inspections, but addresses no specific issues concerning clinical trials:

- (4) Order no. 1091n "On approval of Administrative Regulation for the Governmental Function of Control over Preclinical Studies and Clinical Trials of the Pharmaceuticals meant for Medical application as Developed by the Federal Services on Surveillance in Healthcare and Social development" [23]
- (5) Federal Law no. 294-FZ "On the protection of legal entities and individual entrepreneurs' rights in the course of state control (supervision) and municipal control" [4]

Like in most non-EU countries it is often difficult to cross refer to EU legislation and it is usually necessary for all provisions to be written in detail into the Law or the details need to be covered by separate Regulations, Normative Acts, etc.



The Law "On Circulation of Medicines" deals only with medicinal products for human and/or veterinary use; provisions for clinical studies with biosimilars, paediatrics, orphan drugs are not covered. The experts were told [lit.12] that these areas will be addressed in a future amendment to the Law. Clinical studies including active medical devices are not within the scope of this report.

Definitions given in the "On Circulation of Medicines" Law are not always identical with the ones provided in Directives 2001/83/EC [36] and 2001/20/EC [33]. This might be misleading in some cases like:

"Preclinical testing" Article 4, point 40: much broader definition including physical, chemical trials(?), whereas in Western countries it is restricted to pharmacological / toxicological / pharmacokinetic evaluations in animals.

Article 3, point 5 states that the results of clinical trials conducted outside of RF shall be acknowledged based on "International treaties" and/or the principle of reciprocity. Such provision is not in place in EU: clinical trials conducted outside EU are recognized on the basis of principles, "which are equivalent to the provisions of Directive 2001/20/EC." Mutual recognition Agreements exist only in the GMP area. In place is a "Statement of Intent on Collaboration between the Food and Drug Administration of the United States of America and Federal Service on Surveillance in Health Care and Social Development of the Russian Federation", FDA-Roszdravnadzor, 27 May 2010 [lit.3].

Definitions given in the "On Circulation of Medicines" Law are not always identical with the ones provided in Directives 2001/83/EC [36] and 2001/20/EC [33] [**D3**]

Article 3 (5) of [1] states that the results of clinical trials conducted outside of RF shall be acknowledged based on "International treaties" and/or the principle of reciprocity. Such agreements are not in place in EU [**D4**]

2.2. Regulatory scope (Cross-reference)

Under this heading a comparative table is drawn between relevant EU and RF legal stipulations in the field of clinical trials. In particular, it is assessed whether, and to which extent, the most important issues in the field of clinical trials are regulated in the RF and the EU (list is adopted from Directive 2001/20/EC) [32]. The following comparative table can be shown:

Item	EU	RF*
Protection of clinical trial	[33]: Article 3	[1]: Article 43
subjects	[34]: Article 2	[10]
Clinical trials on minors	[33]: Article 4	[1]: Article 43
		[10]
Clinical trials on incapaci-	[33]: Article 5	[1]: Article 43
tated adults not able to give		
informed legal consent	[34]: (10)	[10]
Ethics Committee	[33]: Article 6	[1]: Article 14, 17, 19, 20
	[34]: Article 6	[10] [16], [19]
Commencement of a	[33]: Article 9	[1]: Article 14-17, 19-26, 35, 36,
clinical trial		38-44



T					
	[10], [13]				
[33]: Article 10	[1]: Article 30,31				
	[10], [20]				
[33]: Article 11	[1]: Article 64, 66				
	[17]				
[33]: Article 12	[1]: Article 40, 65				
	[10], [11]				
[33]: Article 13	[1]: Article 8, 23, 24, 45				
[34]: Article 9-15	[9]				
[33]: Article 14	[1]: Article 46				
	[10]				
[33]: Article 15	[1]: Article 45				
[34]: Article 11					
[33]: Article 16	[1]: Article 64, 66				
	[10], [17] [23]				
[33]: Article 17	[1]: Article 64, 66				
	[10], [18] [23]				
[33]: Article 18	[1]: Article 40(11)				
	[10]				
Additional provisions in RF:					
Accreditation of sites authorized to perform clinical trials [7], [15]					
List of Principal investigators [14]					
	[33]: Article 11 [33]: Article 12 [33]: Article 13 [34]: Article 9-15 [33]: Article 14 [33]: Article 15 [34]: Article 15 [34]: Article 17 [33]: Article 17 [33]: Article 18				

^{*}The non-legally binding guidelines on (ICH-) GCP [24], GMP [25], GLP [26], and ICH guideline 2EA (Expedited reporting of adverse events) [37] are followed in IMCT studies



3. Part II – Structure, Status, Organisation and Working procedures of the competent bodies in RF

Submissions for marketing authorization applications to the EMA in the years 2005-2009 revealed that more than 60% of the patients in pivotal clinical trials were from third countries, *i.e.* countries outside the EU [lit.2]. The Russian Federation (RF) is one of the few countries which contributed more than 100 pivotal clinical trials in this time period, this underlines the important role Russia plays in the area of clinical research [lit.2; 9-11].

According to the Terms of Reference [lit.1], the

- System of implementation
- Control, and
- Enforcement of compliance

of good clinical practice (GCP) rules in the Russian Federation (RF) and the European Union (EU) were assessed.

The key question to be answered by this assessment was whether the implementation, control, and enforcement of the "Rules on Clinical Practice" (in clinical trials with medicinal products for humans) in RF are equivalent to the corresponding provisions in particular Directives 2001/20/EC [33], 2003/63/EC and 2005/28/EC [34].

General

This analysis has been carried out on the assumption that the RF wishes to align its legislation in the field of clinical trials as closely as possible with EU Clinical trials legislation.

The legal basis for the actual assessment is laid down in Annex I, point 8, Introduction and general principles, to Directive 2003/63/EC amending Directive 2001/83/EC [36], where it says that "...clinical trials, conducted outside the European Community, which relate to medicinal products intended to be used in the European community, shall be designed, implemented and reported on what good clinical practice and ethical principles are concerned, on the basis of principles, which are equivalent to the provisions of Directive 2001/20/EC [33]. They shall be carried out in accordance with the ethical principles that are reflected, for example, in the Declaration of Helsinki".

Directive 2005/28 [34] stipulates that the <u>ICH</u>-GCP rules should "be taken into account" [34, point 8], the Declaration of Helsinki on Ethical Principles for Medical Research Involving Human Subjects in its form of 1996 be followed [34, Article 3], and it defines the requirements for authorisation of the manufacturing or importation of Investigational Medicinal Products (IMP) [34, Article 9]. Directives need to be transponded into national law and thus, there are slight differences in the respective legal texts in each EU member state: nevertheless, said Directive (and its amendments) is the basis of the evaluations reported here.

Concerning the corresponding regulatory/legislative framework in RF, Law 61-FZ "On Circulation of Medicines" and its amendments [1], Governmental Decrees, Executive Orders, and guidelines apply. Lists of the relevant Laws, Orders, Decrees and other regulatory documents ruling the clinical trials area in RF and EU can be found in [Annex 1 and 2], respectively. Other supportive literature, reports, publications in the sector is compiled in [Annex 3]. In Annex 4 on overview of the structure of the "On Circulation of Medicines" Law [1] is given.



3.1. Evaluating the implementation of equivalent provisions ruling clinical trials in the Russian Federation

In RF there are two key regulators concerning clinical trials:

The Ministry of Health and Social Development (MHSD) (in May 2012 split into "Ministry of Health" and "Ministry of Labour and Social Protection") is charged with the implementation of the policy and defined executive responsibilities laid down by the law "On Circulation of Medicines, whereas the "Drug Agency", Roszdravnadzor (RZN) (in May 2012 renamed into Federal Service on Surveillance in Healthcare), as the Surveillance and Inspection Agency, generally comparable with the EMA, FDA, is responsible for the control and enforcement of the regulation of medicines for humans and medical devices [5].

Registration, control and enforcement of the regulations concerning veterinary medicinal products are within the responsibility of the Federal Service for Veterinary and Phytosanitary Surveillance, Rosselkhoznadzor.

Thus the MHSD is held responsible for ensuring quality, safety and efficacy of medicines marketed in the RF, whereas the RZN is charged with responsibilities in the areas of Control and Pharmacovigilance. It is a competent body, which has been established within the organisational structure of the MHSD and to which it reports. Both key regulators in the clinical trial area are charged with numerous responsibilities/obligations in the social sphere (see Chapter 3.2.1 and 3.2.2), however, since May 2012, when the "Social development" part was removed from the titles of both the MHSD and RZN by Presidential Decree no. 636 (see page 8), responsibilities in this area will be charged to other governmental bodies.

3.2. Structure, Status, Organisation and Working procedures of the competent bodies ruling the clinical trials sector in RF

The implementation of the new "On Circulation of medicines" Law in 2010 had a huge impact on the entire pharmaceutical sector, including the area of ruling clinical trials. In particular, the new distribution of regulatory functions between the two key competent bodies regulating the sector, the Ministry of Health and Social Development of the Russian Federation (MHSD) and the Federal Service of Surveillance in Health Care and Social Development of the Russian Federation, Roszdravnadzor (RZN), required an almost complete re-distribution of functions, powers, responsibilities and obligations. In addition to the pharmaceutical (incl. clinical trials) area, both organisations were charged (until May 2012) with numerous responsibilities in the field of Social Development.

3.2.1 The Ministry of Health and Social Development (MHSD): Functions and Organisation

(in May 2012 split into "Ministry of Health" and "Ministry of Labour and Social Protection")

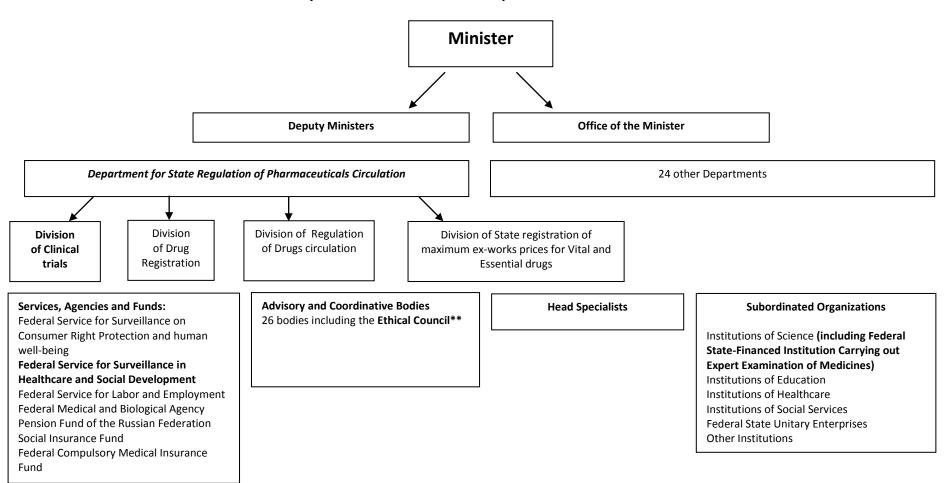
According to (governmental) Decrees no.321 and 423 [5], the MHSD is a "Federal executive body in charge of working out a state policy as well as normative and legal regulations in the sphere of healthcare, social development, labour and protection of consumer rights..." Aside its functions in the areas of *e.g.* occupational medicine and prevention, health resorts, social protection, labour compensation, pension benefits, rehabilitation, provision of medical



aid, etc., the MHSD is charged with the responsibility to ensure "quality, efficacy, and safety of pharmaceutical products". The MHSD's structure and scope of work (responsibilities/obligations) are summarised below (taken with permission from lit.9).



The Ministry of Health and Social Development of the Russian Federation*



- * In May 2012 split into "Ministry of Health" and "Ministry of Labour and Social Protection"
- ** The Ethical Council is a subordinated organization of the MHSD



Powers of the Ministry of Health and Social Development with respect to clinical trials:

The MHSD approves statutory acts

On Ethical Council, composition and regulations on the council, requirements to qualification and experience of ethical council experts in expert assessment of scientific, medical and ethical aspects of clinical trials of medicinal products for medical use, procedures for arrangement and performance of ethical expert examination and a form of ethical council conclusion

On issuance of approvals for the conduct of clinical trials of medicinal products for medical use

On Rules of Clinical Practice

On maintenance of the register of issued approvals for the conduct of clinical trials of medicinal products for medical use

On publishing and placing of the list institutions entitled to conduct clinical trials of medicinal products for medical use on the official web-site of the Ministry of Health and Social Development

On maintenance of the register of investigators who are conducting or conducted clinical trials of medicinal products for medical use and its placing on the official web-site of the Ministry of Health and Social Development

On maintenance of the register of permits to export/import of biological materials of clinical trials

On notice on completion, suspension or termination of the clinical trial of the medicinal product for medical use, and publishing and placing it on the official web-site of the Ministry of Health and Social Development

On report on the findings of clinical trial of a medicinal product for medical use

On examination of amendments to the protocol of clinical trials of medicinal products for medical use

The MHSD exercises:

Foundation of Councils responsible for issues related to circulation of medicines

Approving of Ethical Council composition

Carrying out of assignments to conduct ethical examination of medicinal products for medical use

Issuance of approvals for the conduct of clinical trials of medicinal products for medical use



Accreditation of medical organizations for the right to conduct clinical trials of medicinal products for medical use

Maintenance of the register of issued approvals for the conduct of clinical trials of medicinal products for medical use

Maintenance of the register of investigators who are conducting or conducted clinical trials of medicinal products for medical use

Issuance of permits to import into the Russian Federation a specific consignment of registered and (or) unregistered medicines to be used in clinical trials of medicinal products, a specific consignment of unregistered medicines for state expert examination of medicines for the purpose of state registration of medicinal products, or for delivery of health care in accordance with individual vital indications for the patient

Issuing permits to export/import biological materials of clinical trials

Implementation of the new law "On Circulation of Medicines" led to three new organizational structures within the MHSD in the area of clinical trials:

- (1) Department of State Regulation of Drug Circulation
- (2) Ethics Council
- (3) State Federal Budget Organisation for evaluation of medicinal products ("Expert Organisation", "Expertise Centre"; FGU)

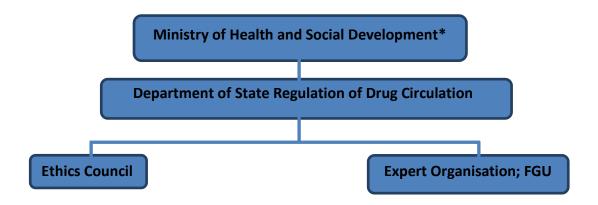
The key functions of the **Department of State Regulation of Drug Circulation** are:

- Granting marketing authorisations
- Regulating clinical trials, like approvals, amendments of study protocols [12,20]
- Regulating the import of investigational medicinal products (IMPs) and export of biological samples (from clinical trials, like blood, urine) [6,9,21,22]
- Accrediting clinical sites, hospitals, etc. for conducting clinical trials and to maintain a list (on the website) of these institutions [7,15]
- Maintain a register of investigators fulfilling the conditions to conduct/participate in clinical trials and to keep this register updated on the Ministry's website [14]
- Placing and maintaining a register of approved clinical trials [17]

Directly reporting to the MHSD are the Ethics Council and the Expert Organisation.

A flowchart describing the roles of the three organizational bodies involved in the clinical trial application, conduct and after-trial activities, as well as in the marketing authorization application process is below and described in detail in Part III of this report:





*In May 2012 split into "Ministry of Health" and "Ministry of Labour and Social Protection"

The <u>Ethics Council</u> is charged with the responsibility to provide expertise on the ethical considerations in clinical trial applications: in 2009 it received more than 3.000 applications, mainly for phase III studies [lit.10]. The Ethics Council works on the legal basis of Articles 14, 20, 25, mainly 17 "Ethical Expert Examination" of the "On Circulation of Medicines" Law [1]. Article 17(5) defines that provisions concerning the Ethical Council's composition, regulations on the council, qualifications and experience of its experts, working procedures, etc. are to be established by the "authorized Federal executive body", *i.e.* the MHSD. The following Point (6) stipulates that the composition of the Ethical Council, its plan of operation and current activities shall be placed on the official Internet site of the MHSD. An expert benefit/risk evaluation -as well as the examinations of the quality of a medicine- is carried out during the marketing authorisation application process after a clinical trial has been conducted: this process will be described in more detail in Chapter 4.1.

Executive Orders no. 753n "Approval of procedure to organize and conduct ethical expert examination of possibility of clinical trial of medicinal products for medical use, and the form for Ethical Council conclusion" [16] and no. 774n "On Ethical Council" [19] provide more detailed information. Order no. 753n lays down the general operational issues of the Ethics Council and provides a form for documenting the Ethics Council decision on a clinical trial application. Order no. 774n presents a list with the 18 members of the Ethics Council (name, profession, working area) as well as general provisions concerning the statutes of the Ethics Council, its composition, the required qualifications for Council members, and the working procedures of the Council.

The experts have been told [lit.12] that the Councils working procedures are documented in a respective SOP-system, and that "Notes for Guidance/Notice to applicants", which allow applicants to comply with the requirements and defining the conditions, content and format of marketing authorization applications, have been published on the website of the MHSD. Until now (June 2012) five SOPs have been produced by the Ethics Council:

- SOP No.1 on the "Legal basis of the Ethics Committee activities" [27],
- SOP No.2 on the "Procedure of carrying out of ethical review of Patient Information Sheet" [28],



- SOP No.3 on "Clinical trials on children. Requirements for the provision of information to a child and their parents/adopters" [29],
- SOP No.4 "On order of review of the documents containing revisions to protocol of approved clinical trials of medicinal product" [30], and
- SOP No.5 "Clinical trials of mental patients. Requirements for provision of information for patients" [31].

ICH-GCP 3.2.2 demands that "The IRB/IEC should perform its functions according to written operating procedures" [24]: a comprehensive, full-flexed system of written operating procedures, i.e. SOPs, is in the process of preparation. This should include also a formal procedure for the selection/appointing of Council members: at present the chairwoman/man of the Ethics Council is appointed by the Minister. Guidance can be retrieved from the "Guide for Research Ethics Committee Members" (of the Council of Europe) [lit.7] "The crucial requirement for RECs is to work independently from the researchers and their sponsors, as well as of their establishing institution or authority. The mechanism designed to achieve this independence should be reflected in their appointment and membership renewal process, as well as in their working methods and decision making", the "The Good Regulatory Practice (GRP)" described in the "Blue Book" of the WHO [lit.4], and from the proceedings of an International Scientific Conference on Ethics Review of Clinical Research in Pharmaceuticals [lit.6].

NB. All of the three IRBs, which were visited during the three inspections, had a well prepared, comprehensive set of operating procedures on file.

Council members do not work fulltime for the Council, but stay in their usual daily work; they are invited to participate in the Council meetings depending on their availability and special knowledge in the therapeutic area the clinical trial is planned to commence: for *e.g.* a clinical trial with cardiologic patients a cardiologist will be invited for the meeting. It is not clear to the experts how the Ethics Council can manage more than 3.000 submissions per year.

In order to fight corruption, direct contacts between applicant and the Ethics Council and the State Federal Budget Organisation for evaluation of medicinal products are forbidden: Applicants can contact only the Department of State Regulation of Drug Circulation, *e.g.* in order to clarify questions from the Ethics Council concerning *e.g.* study-related procedures, like inclusion/exclusion criteria of study participants [15]. This is different to common practice in EU, where a dialogue between applicant and drug regulatory authorities and Ethics Committees is considered to be beneficial.

Direct contacts between applicant and the Ethics Council and the State Federal Budget Organisation for evaluation of medicinal products are explicitly forbidden [**D5**]

The Ethics Council is fully integrated ("subordinated") into the MHSD, the main regulator and its members are paid from the Federal budget. The Ethics Council is independent in its decisions from the MHSD, the term "subordinated" refers only to the administrative/legislative supervision of the Ethics Council by the MHSD. The MHSD legalises the Ethics Councils' decisions (like approvals) by publishing them. This is not different to some EU member states, like Cyprus, Estonia, Hungary, Malta, Slovenia, were such central Ethics Committees exist.



Despite that only the MHSD's Ethics Council decisions are legally binding in RF, a number of other Ethics Committees exist, like the "Independent Interdisciplinary Ethics Committee on Ethical Review for Clinical Studies" [lit.13], which was founded in the year 2000. One of its founders is the Russian Academy of Medical Sciences. According to the information on its website it works strictly according to ICH-GCP. Thus, sponsors, who need to comply with ICH-GCP (IMCTs) apply —in parallel to the MHSD's Ethics Council- to such Independent Ethics Committees.

The <u>State Federal Budget Organisation for evaluation of medicinal products (FGU)</u> conducts —exclusively on the request of the Department of State Regulation of Drug Circulation- a review of the clinical trial study documents, like study protocol, Investigator's brochure, analytics, etc. The legal basis is Articles 14 - 23, 25, 26 of the "On Circulation of Medicines" Law [1] in conjunction with Decrees no. 748n [12] and 750n [13]

In **Article 14** of [1] the 2-stage process of registration is described: *Step 1*: Examination of documents for the <u>clinical trial approval</u>, *Step 2*: benefit/risk analysis and examination of the quality of a medicine <u>for the registration process</u>

Article 15 charges "a Federal State-financed institution", *i.e.* the "Expert Organisation" (FDGU) and the "Ethics Council" with the responsibility of clinical trial approvals and the granting of marketing authorisation.

Article 16 lays down detailed rules and procedures for the proper and adequate examination of the "Expert Organisation", whereas

Article 17 outlines the general provisions of the "Ethics Council"

Article 18 provides applicants for marketing authorisation with details of the documents, which are needed for a submission, including the documents for a "registration" clinical trial **Article 19** sets a 5-days' time limit for the initial check of completeness and reliability of documents submitted for expert examination

Article 20 sets a 30-days' time limit for the examination of submitted documents for Ethics Committee approval and examinations by the Expert Organisation

Article 21 describes the two-stage approach to get clinical trial approval (for registration purposes)(see Article 14). More details will be presented in Chapter 3.3 The clinical trial application process.

Article 22 specifies the documents in addition to those, which have already been submitted in the first step (see Article 18), which need to be submitted in the course of a "registration" clinical trial application (for IMCTs Article 39 applies!)

As already mentioned, in **Article 23**, examinations of the quality of a medicinal product and a benefit/risk evaluation must be conducted -after the clinical trial has been conducted- within 110 days after receipt of the documents from the Department of State Regulation of Circulation of Medicines

Article 25 stipulates the process if both examinations (Ethics Council, Expert Organisation, FGU) need to be repeated, and **Article 26** provides rules for a so-called "Accelerated procedure", which applies for the registration of generics.

Executive Order no. 748n [11] regulates the procedure for granting a clinical trial approval and sets a 5-days' time limit for the approval (excluding the time for producing the expertise).

Executive Order no. 750n [12] gives a detailed description (incl. the applicable forms) of the procedures to be followed by the Expert Organisation for its examinations.



The latter two organisations forward the results of their assessments directly to the Department of State Regulation of Drug Circulation, which is the only competent body regulating clinical trial issues, except of the two key regulatory functions "Control" and "Pharmacovigilance" (Drug safety) which rest with the RZN.

The Expert Centre has a staff of over 900 and embraces a number of organisations charged with various responsibilities mainly in the area of Quality Control of medicinal products.

The <u>Clinical trials Department</u> has the basic tools/legal basis to handle the aspects concerning clinical trials, like assessing trial applications, grant applications, amendments, withdraw/suspend an application, ask for changes in the study protocol, etc. [lit.4]. However, it has only limited human resources.

3.2.2 The Federal Service on Surveillance in Healthcare and Social Development, Roszdravnadzor (RZN)*: Functions and Organisation

The second key Drug regulatory authority (DRA) in RF is the Roszdravnadzor (RZN). It has been established as a "subordinated organisation" of the MHSD and reports directly to the MHSD. Like the Ethics Council it is part of the MHSD organisation, but independent in its decision making. However, like the Ethics Council, the RZN cannot take legal actions on its own responsibility, but needs to ask MHSD to do so: *e.g.* both organisations cannot suspend or prematurely terminate a clinical trial by their <u>own</u> decision. Only the MHSD has the legal power to do so (in general by issuing an Order).

As mentioned earlier, in the past the RZN has been charged with many responsibilities in the area of "Social development", like the control over the proper medical support to the population. According to Presidential Decree no. 636 (see p. 7 "Topical actual addendum") most of this responsibility will be removed from the RZN. In the <u>area of Clinical trials</u> it has two main functions: **Control and Pharmacovigilance (Drug safety).**

Neither the MHSD, nor the RZN received an internationally recognised accreditation, like ISO 17020 ("General criteria for the Operation of various types of bodies performing Inspection"), an internationally recognised standard for the competence of bodies charged with Inspections.

The key regulatory/legislative documents concerning the scope of work in the "Control" area are the

- Federal Law no. 61-FZ [1], in particular Article 9, and its amendments, in particular Law no. 93 FZ (from 25 June 2012)
- Federal law no. 294-FZ [4], and
- the just (26 January 2012) enacted Executive Order no. 1091n [23].

The scope on controls ([23], Point 5) is focussed on "preclinical studies" and "clinical trials", i.e. compliance with "laboratory practice principles", regulations on the use of animals,



^{*} In May 2012 renamed into "Federal Service on Surveillance in Healthcare"

"clinical practice principles", and "control over organizing and holding of preclinical studies and clinical trials" (*i.e.* control that administrative requirements are met).

Concerning **clinical trials**, Decree no. 266 [10] requires adhering to the "Rules on clinical practice" in the conduct of clinical trials (despite that this order is from 2003 and has legal force only in those parts, which do not contradict those in the current legislation).

GOSTP52379-2005 [24], a direct translation of the ICH-GCP guideline, has — like in EU-the legal status of a guideline. In addition to the provisions given in [10], sponsors of International multicentre clinical trials (IMCTs) also follow ICH-GCP rules in order to ensure acceptance of the clinical trial data by the EU Drug Regulatory Authorities.

Despite local clinical trials need to comply "only" with the rules for clinical practice [10], RZN GCP inspectors check GCP compliance against [10] **and** [24]. Similar situations exist concerning the "Rules on Laboratory practice" and the "Rules on Manufacturing practice". The "On Circulation of medicines" Law [1] stipulates in Chapter 4, Article 9 and Chapter 5 "Development, Preclinical testing of Medicines and Clinical Trials of Medicinal Products for Veterinary Use, Article 11 Preclinical testing of a Medicine for Medical use", that the "Rules on Laboratory practice" must be applied.

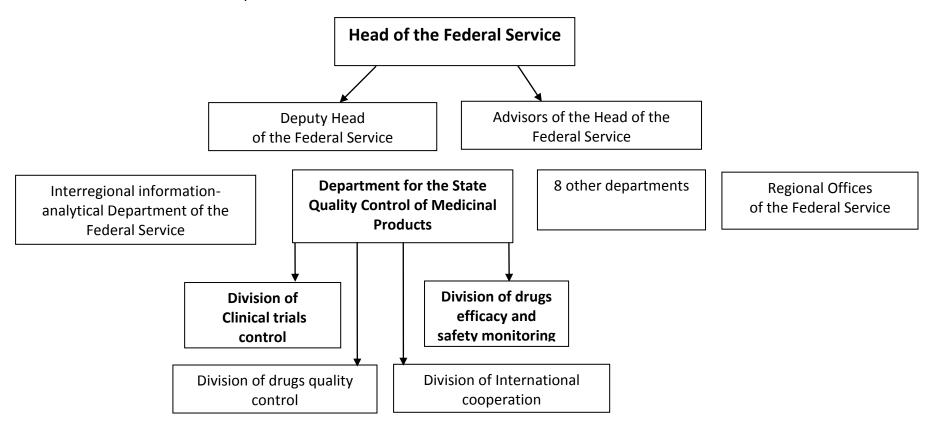
In RF, all inspections are free-of-charge [D6]

The structure and main functions of the RZN is described below:



Federal Service on Surveillance in Healthcare and Social Development*

*In May 2012 renamed into "Federal Service on Surveillance in Healthcare"



Subordinated organisations:

Federal State-Financed Institution 'Consultative and Methodical Center',

Federal State-Financed Institution 'Information and Methodological Center for examination, registration and analysis of medicines'

Federal State-Financed Institution 'Russian Scientific Research and Experimental Institute of Medical Technology'

Federal State-Financed Institution 'Center of Expertise and quality control of medicinal products'



Powers of the Federal Service on Surveillance in Healthcare and Social Development with respect to clinical trials

The Federal Service on Surveillance in Healthcare and Social Development exercises <u>control</u> over:

Preclinical trials of medicinal products, clinical trials of medicinal products as well as quality, production, manufacture, compounding, storage, transportation, import into the Russian Federation, advertising, dispensation, distribution, destruction, use of medicinal products, and

Exercises:

Safety monitoring of registered drugs in circulation in the Russian Federation

The following business areas of the RZN were assessed:

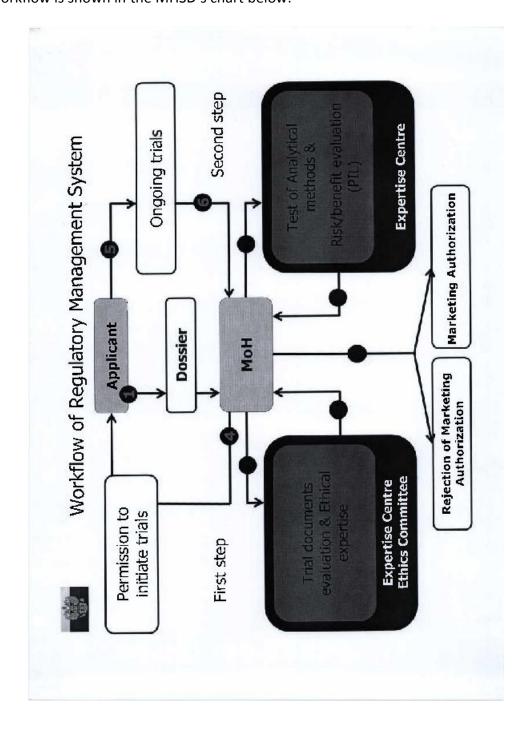
- Regulatory functions
- Mission, vision, Policies
- Organisation and Operations
- Documentation of policies and standards
- Quality Management System ensuring that all operations are performed by following defined, uniform standards and are identified and documented
- Quality manual
- SOP System
- Code of conduct
- Impartiality, transparency (Rules and decisions need to be transparent and applicable)
- Guidelines on conflicts of interest
- Guidelines on confidentiality
- Maintenance of records
- Accountability aside to the public, to the Minister of Health, Parliament
- Appeals and Complaints procedures
- Expert advisory board
- Funding
- List of fees payable for the various approvals, permissions necessary for the conduct of a clinical trial
- Payment for inspections
- Staff/Personnel
- Human resource Management system
- Job descriptions
- Responsibilities/obligations
- Training records
- Qualifications
- Risk Management



4. Part III - Practices in the Clinical Trials Sector in RF

4.1. The clinical trial application process

In the following, the clinical trial application process is described, applicable regulatory/legislative sources identified, and relevant specific issues in the process in the RF addressed in detail. In 2011 the MHSD granted approvals for 567 clinical trials, mainly IMCTs (370) [lit.9]. The workflow is shown in the MHSD's chart below:





Step 1: Submitting the required study documentation

Article 38 of the "On Circulation of Medicines" Law [1] defines

- for which <u>purposes</u> clinical trials may be conducted to:
- "(1) establish safety and/or tolerance of medicinal products for healthy volunteers, except for the trials of medicinal products manufactured outside the Russian Federation
- (2) select optimal dosages of medicinal product and course of treatment for patients with specific disease, optimal dosages and vaccination schemes of immune-biological medicinal products for healthy volunteers
- (3) establish safety and efficacy of a medicinal product for patients with specific disease, prophylactic efficacy for immune-biological medicinal products for healthy volunteers
- (4) study the possibility to widen the indication for medical use and identify earlier unknown side effects of registered medicinal products".

Such restrictions (concerning the <u>purpose</u> of a trial) are not reflected in the applicable EU regulations: clinical studies need to involve "research" and must be "scientifically sound" [**D7**]

In addition, the provisions that clinical trials involving *healthy* volunteers, *i.e.* in phase I studies, with "medicinal products manufactured outside the RF" are <u>prohibited</u>, but for local sponsors are <u>permitted</u>, and phase I studies with foreign drugs involving *patients* are possible, is inconsistent and different to EU regulations [**D8**]

- that only defined organisations are entitled to organize clinical studies:
- (1) "developer of the medicinal product", *i.e.* a drug developing entity; private persons intending to develop a drug need to be authorized by a developer, *i.e.* a Company/firm
- (2) defined "educational institutions"
- (3) Research Centers

Such restrictions are not reflected in the applicable EU regulations: Article 2(e) of [33] defines that the Sponsor can be an individual, a company, an institution or an organisation [**D9**]

• that clinical trials can be conducted only at clinical sites, which have been accredited by the MHSD according to Decree no.752n [14]

A list of accredited clinical sites (at present more than 800) is placed on the website of MHSD. Accreditations are issued for a 5-years period and can be renewed (Governmental Decree no. 683 [7]).

The latter Decree charges the MHSD with the accreditation of clinical sites to perform clinical trials. The MHSD has the right to do field inspections at the applicant to assess compliance with the accreditation requirements (Article 10). This is done by following the provisions in the Federal Law [4] "On the protection of legal entities' and individual entrepreneurs' rights in the course of State control (supervision) and Municipal Control" (Article 24)

Clinical sites for conducting clinical trials need to be approved by the MHSD. Such an accreditation requirement is not reflected in the applicable EU regulations, as there is no such accreditation process for clinical sites in place [**D10**]



that clinical trials must be conducted by following the <u>"Rules on clinical practice"</u>. "Failure to follow the "Rules on clinical practice ...shall entitle liability", *i.e.* will be subjected to legal actions (Article 40(12)).

As described already earlier, Executive Order no. 266 [10] states that "The rules for <u>clinical practice</u> are binding for all participants of clinical drug trials on the territory of the Russian Federation". On the other hand the guideline GOSTP52379-2005 ("National standard of GCP in RF") [24] is identical to the text of the ICH-GCP guideline, but —as a guideline- is not legally binding.

Competent Drug Regulatory Authorities in the EU will recognize during the MAA process only those clinical trial conducted outside the EU, which are "designed, implemented and reported on what good clinical practice and ethical principles are concerned, on the basis of principles, which are equivalent to the provisions of Directive 2001/20/EC [33]. They shall be carried out in accordance with the ethical principles that are reflected, for example, in the Declaration of Helsinki" [36]. Directive 2005/28 [34] stipulates that the ICH-GCP rules should "be taken into account" [34, point 8], the Declaration of Helsinki on Ethical Principles for Medical Research Involving Human Subjects in its form of 1996 be followed [34, Article 3], and it defines the requirements for authorisation of the manufacturing or importation of Investigational Medicinal Products (IMP) [34, Article 9].

Thus, clinical trials conducted in the RF need to adhere to <u>ICH</u>-GCP rules, if the sponsor intends to present these studies within an MAA process to the authorities in the EU. Due to the fact that this condition must <u>not</u> be fulfilled for studies to be presented to the national DRA in the RF, there is a kind of "split/ double-standard situation" in RF concerning the way clinical studies are conducted and presented in the registration process: ICH-GCP compliance in studies, which will be presented within an MAA process <u>outside</u> the RF (so-called "International Multicentre Clinical Trials", IMCTs), and those for <u>national</u> registrations. The provisions concerning the conduct of IMCTs in RF are regulated in a separate Article (Article 39) in the "On Circulation of Medicines" law [1]

Nevertheless, like in the provisions in Directive 2001/20/EC [33] in EU, **all** clinical studies conducted in the RF must be done by following the "Rules on clinical practice" [10]

In this context it needs to be mentioned that according to Directives 2003/94/EC [35] and 2001/20/EC [33], investigational medicinal products for human use (IMPs) must be manufactured under good manufacturing practice (GMP) conditions. In RF the "Rules on manufacturing practice" must be followed; the respective National standard GOSTP52249-2009 [25] is a non-legally binding recommendation

In RF, manufacturing licenses are issued by the Ministry of Industry and Trade (Decree no. 684), not by the Drug regulatory authorities or the RZN

In RF Drug manufacturing licenses are issued by the Ministry of Industry and Trade (Decree no. 684), not by the Drug regulatory authorities (or the RZN)[**D11**]



As already described earlier [**D1**], except of so-called International multicentre clinical trials (IMCTs) and post-registration studies, applications for conducting a clinical trial in RF can only be submitted in the course of a registration process. For both cases different procedures apply: in case of a clinical trial as part of the registration, a two-stage process (1, Articles 14, 21): in a **first step** the applicant submits a registration file, and the necessary documents for clinical trials approval are examined. After having received a positive vote, the registration is suspended and the applicant conducts the clinical trial (Article 21, point 2).

In **step 2** the registration is resumed and the results of the clinical trial are assessed; a decision is then made whether or not to issue a marketing authorization/registration (Art. 27). The results from efficacy and safety trials must be available in the course of the marketing authorization/registration process and such trials can be conducted only within a registration process. Such provisions are not reflected in the applicable EU regulations.

In case of an IMCT/post-registration trial such 2-step procedure is not mandatory.

Only those (Principal-) Investigators in clinical trials with a proven professional record (their CVs are checked accordingly), including 5-years of experience in the conduct of clinical trials, can be involved in clinical trials.

Such provision doesn't exist in the EU legislation, however, e.g. German regulations request a 2-years' experience in the conduct of clinical trials for investigators in Germany

(Principal) investigators must have an appropriate professional record, including 5-years of experience in the conduct of clinical trials, in order to be eligible as investigator in a clinical trial. Such provision doesn't exist in the EU legislation, but exist in the national legislation of member states like Germany, where a 2-years' experience in the conduct of clinical trials is mandatory for investigators [**D12**]

Concerning the **Insurance of study participants**, the provisions of the "On Circulation of Medicines" Law, Article 44 "Compulsory Insurance of Life and Health of the patient involved in clinical trials of medicinal product for medical use", and Decree no. 714 "On Approval of typical rules for compulsory insurance of the life and health of a patient involved in clinical trials of a medicinal product" [8], foresees only the insuring of individual persons, *i.e.* only a strictly study participant-related, insurance for study participants is possible. This causes huge administrative barriers, because each individual study participant must be notified to the Insurance Company by a 33-digit code and if the study participant fails *e.g.* to pass the screening procedures, the whole process must be reversed.

The provisions of the following rules laid down in Governmental Decree no. 714n [8] must be followed:

- (1) The procedure for establishment of the individual identification code of the patient by the Insurant
- (2) The procedure for informing the insurer by the insurant of the patients involved in clinical trials of a medicinal product
- (3) Insurance rates, the Procedure for the payment of the insurance premium
- (4) The procedure for payments of benefits and the list of documents to be provided by insured persons (beneficiaries) to obtain the benefits
- (5) Rights and obligation of the parties to the contract and insured persons (beneficiaries).



In practice, there are still some problems which need to be addressed, like the coverage of children born during participation of the mother in a clinical trial or whether companions through life are entitled for possible payments of benefits

The best practices in EU, to conclude compulsory liability insurance for **all study participants**, instead of insuring **each individual study participant** separately, would reduce administrative burdens and errors in the exhaustive data transfers of the Patient identification code during the study

Article 43 "Rights of patients involved in Clinical trial of medicinal product for medical use" of the "On Circulation of Medicines" Law [1] defines those cases when clinical trials are prohibited or permitted only if defined conditions are fulfilled (Point 6)

- Orphaned children/Children without parenteral care
- Law enforcement personnel

Clinical trials are not allowed at all with:

- Individuals serving sentences at places of confinement
- Individuals in custody at detention facilities

Clinical trials are allowed with:

- Pregnant and nursing women
- Military personnel, if defined conditions are fulfilled.

Such strict rules, like on "Persons deprived of liberty", are not in place in EU. The principle of respect of the autonomy [lit.7, p.41-42] needs also to be taken into account [**D13**]

In Point 4 it is laid-down that study participants may withdraw their participation in the trial at any stage of such trial". A provision is missing that the investigator "should make a reasonable effort to ascertain the reason(s) (for withdrawing prematurely from a trial), while fully respecting the subject's rights [24, 4.3.4]

Step 2: Checking the supplied documentation [Time limit = 5 working days]

The Department of State Regulation of Drug Circulation checks the submitted documents for completeness and issues a written acceptance notification to the applicant within 5 working days

Step 3: Review by the "Ethics Council" and the "Expert Organisation" [Time limit = 30 working days + 5 working days for issuing the preliminary notification letter]

Both subordinated organisations review the documents and the Ethics Council gives its favourable approval and the Expert organisation its expertise. Compared to the "old" procedure, the new procedure should accelerate the study approval procedure considerably: following the application for an expertise (step 1), the "Department of State Regulation of Drug Circulation" coordinates the interactions between the Ethics Council and the Expert organisation, so these may work in parallel on the same documents (step 2). After both expertises have been completed, the MHSD issues the final approval (step 3). Before this procedure came into force, an applicant had to submit the same documentation in parallel to both organisations (Ethics Council and FGU) (step 1), and then the (final) approval was issued by the Roszdravnadzor.



This step must be finished within 30 working days plus an additional 5 working days for sending a preliminary approval notification to the applicant. In practice these timelines are often not met [lit.9]; this is probably related to the fact that implementation of the new regulations is still underway.

The **Ethics Council's decision** is limited to a favourable opinion (approval) or rejection: a conditional approval is not foreseen. Rejected applications must be re-submitted, after having corrected the stated flaws, *i.e.* the entire process starts again. This holds true also for rejected applications from the Expert organisation.

Step 4: Final approval notification of the applicant [Time limit = 5 working days]

In total a time limit of 45 days is set by the lawmaker for an application to conduct a clinical trial. According to the "On circulation of Medicines "Law (1, Article 38) and Decree no. 754n [17], a list of approved clinical trials should be placed on the MHSD's website. Referring to [lit.9], this list contains not all of the information the law requires, and —due to a non-transparent numbering- it is difficult to calculate exact figures. The experts were informed [lit.9] that this inconsistency has been resolved

4.2. Clinical trials as part of the Marketing Authorisation Application (MAA) process in RF

In the present "On Circulation of Medicines" Law [1] there is always a tight connection between the approval/conduct of a clinical trial and the registration (*i.e.* MAA) process: the Law distinguishes strictly between clinical trials that may be conducted irrespectively of a subsequent registration in RF, *i.e.*:

- International multicentre clinical trials (IMCTs) and post-registration trials
 [1; Article 39], and
- Clinical trials which can be conducted <u>only</u> within a marketing authorisation process [1; Article 22].

The entire Chapter 6 "Performance of State Registration of Medicinal Products" encloses 24 Articles (Articles 13-37) covering all kind of information, from the Principles of expert examinations till decision on conducting clinical trials.

For marketing authorisation in RF, clinical trials are <u>not</u> required, if IMCTs have been conducted that included clinical sites in RF, nor for medicinal products in use in RF for more than 20 years (in the same indication) [1; Article 18(5)].

4.2.1. "Local registration studies"

During the market authorisation application process to register drugs in RF, it is mandatory to present data gained from local efficacy and safety trials (such trials can be conducted only within a registration process).

The legal basis is Article 14 of the "On Circulation of Medicines" Law [1], which establishes a two-stage registration process (IMCTs that include clinical sites in RF are excluded), which has been described already in Chapter 4.1: in a **first step** the applicant submits a registration file, and the necessary documents for clinical trials approval are examined. After having received a



positive vote, the registration is suspended and the applicant conducts the clinical trial [1; Article 21(2)]. In **step 2** the registration is resumed and the results of the clinical trial are assessed; a decision is then made whether or not to issue a marketing authorization/registration [1; Article 27]. The results from efficacy and safety trials must be available in the course of the marketing authorization/registration process and such trials can be conducted only within a registration process. In case of an IMCT/post-registration trial such 2-step procedure is not mandatory (also not for veterinary products).

By definition, marketed medicinal products are considered to be effective, safe and of good quality. Thus, the requirement to repeat clinical trials on safety and efficacy, whose results have already been assessed in the "original" registration process, puts study participants on unnecessary risk(s), generates additional costs for the applicant, and postpones access of the population to modern drugs. Therefore, the requirement to conduct "Local registration studies" should be restricted to defined, (country-specific) cases, like special national medical care system/population/ethnic groups/diet.

The proposal from the Russian side to overcome this problem by signing an agreement on mutual recognition of clinical trial results between RF and EU (and other countries), has been discussed earlier in this report [**D4**].

The issue of local registration trials came up on the 02 June 2011 Meeting of the "Commission for Modernisation and Technical Advancement of the Economy" [lit.9]. The last developments in this issue have been communicated to the experts as follows [lit.9]:

"At the end of last year the Federal Antimonopoly Service of Russian Federation (FAS) examined the process of drug registration. The reason for it was the Order of the Deputy Chairman of the Government Igor Sechin. Last week (=week 10 in 2012) FAS presented to the public the results of this examination and their proposals how to improve the situation. Furthermore they have prepared some suggestions on changing our law "On Circulation of Medicines" (on the basis of the next Order of I.Sechin). And on March, 5 they presented their proposals at the "Expert Council for developing competition in the social sphere and healthcare".

As a member of the Council I participated at this meeting. And I'd say that most of their proposals are quite reasonable. But the main one (from my point of view) is - to cancel the requirement to repeat clinical trials – they suggest recognizing the results of international clinical trials.

FAS asked all the participants to submit their additional proposals and was preparing to present officially the draft of the amendments to MHSD till March."

<u>Note:</u> We've got some publications from this event: http://en.fas.gov.ru/news/news_32072.html (website of FAS), and SCRIP Intelligence from 22 and 25 May 2012."

The requirement to repeat safety and efficacy clinical trials (so-called local registration studies) whose results have already been assessed in the "original" registration process, puts study participants on unnecessary risk(s), generates additional costs for the applicant, and postpones access of the population to modern drugs. Therefore, the requirement to conduct "Local registration studies" should be restricted to defined, (country-specific) cases, like special national medical care system/population/ethnic groups/diet [**D14**]



For **generics** (some exceptions apply) an "Accelerated procedure for expert examination of Medicines" is in place (1, Article 26). Due to the fact that the pharmaceutical market in RF is dominated by generics, this provision is of high importance

4.3. Control of compliance with GCP rules in clinical trials; Enforcement

4.3.1. Organisation of control of compliance with GCP rules; Regulatory/legislative basis and scope

Federal law no. 294-FZ [4] gives general provisions for the control, supervision/surveillance of legal entities and individual entrepreneurs by State and/or Municipal bodies. Controls are allowed only once in three years, except of institutions in the public health, educational and social area, and controls must be announced in advance (minimum three business days before the scheduled inspection).

Thus, the RZN publishes on its website each year in advance a list of institutions which will be inspected. For this year 112 inspections have been announced. Inspectors from the RZN are supported by more than one hundred inspectors located in the various regions of the RF [12]. However, as in some regions no clinical trials are conducted, not all regional inspectors work full-time, and/or execute other duties in public health. Details of the 79 regional RZN offices are listed in Appendix 1 of Executive Order no. 1091 [23].

About 100 staff members work in the area of GCP regulation, the total number of RZN staff is more than 1.000.

This Order covers both preclinical and clinical studies and entitles the RZN to perform "scheduled and random inspections of the legal entities that organise and hold preclinical studies and clinical trials". Reports of inspections from the regional RZN branches are processed centrally by the RZN.

In the following, provisions are given on the Rights and obligations of the inspector(s) and the inspected persons during the inspection, Guidance on the conduct of an inspection, those items which might be inspected (facilities, products, documents, etc.). These provisions have just been described in more detail by Federal law no. 93-FZ, which amends [1], Article 9 "Governmental Control (Supervision) in the Sphere of Circulation of Medicines".

There are stringent time limits for performing inspections: field checks on small companies shall not exceed 50 hours, for "micro-enterprises" 15 hours. Inspections are limited to a maximum of 20 days; however, the average time for inspections is 3-5 days.

Concerning **IMPs** in RF the "Rules on manufacturing practice" must be followed; the respective National standard GOSTP52249-2009 [25] is a non-legally binding recommendation Verification that IMPs are manufactured under the "Rules on manufacturing practice" is assessed by RZN GCP inspectors during their on-site inspections.

This holds true also for **Inspections** on the "Rules on Laboratory practice", which are performed at institutions and investigators on a list published by the RZN

Medical devices

Medical devices are regulated and receive marketing authorisations from the RZN.



4.3.2. Type of inspections performed

There are two types of Scheduled inspections: (1) Document inspections and (2) Field inspections. So-called "Random checks" (inspections) can be ordered only in defined cases: (1) "prevention of causing injury to people's lives and health, (2) failure to remedy findings in inspections/breaches of regulations, (3) RZN receives information on unlawful actions at a site, (4) the President of the RF and/or the prosecutor orders an inspection. Anonymous accusations are not considered for triggering an inspection. Like for scheduled inspections, random checks (i.e. for-cause inspections) focus on the inspection of documents and/or as a field check (i.e. a site-inspection).

GCP inspections at clinical sites always include <u>all</u> aspects of the site/study: facilities, personnel, equipment, QA-system(s), clinical chemistry lab, eligibility of study participants, record keeping, etc. There are in general no inspections conducted focussed on specific aspects of a site or a study, like described in the guidances for the conduct of inspections (Chapter IV "Inspections" of [32] in EU

There are no specific, separate inspections performed concerning Clinical laboratories, Computer systems, Sponsor and CRO Phase I units, Record keeping and archiving of documents, Bioanalytical part, Pharmacokinetic and Statistical Analyses of bioequivalence trials [*D15*]

4.3.3. Conduct of GCP inspections

An inspection is carried-out with at least two officials, in general an inspector, who is supported by a consulting specialist familiar with peculiarities of the site to be inspected, the therapeutic area the study drug belongs to, etc. If necessary, more specialists/experts are invited to participate in an inspection.

After the inspection a report must be produced listing all findings and the measures to remedy them, in principle a CAPA action. Breaches of the law are reported to the enforcement authorities, if criminal activities are suspected, the prosecutor's office is informed accordingly. Results of the inspection are made public on the RZN website and may be presented (on their request) to other Federal bodies, *e.g.* the Ministry of Internal Affairs or Federal Security Service, or may even be requested personally at the RZN offices or by phone. This website has a public and a restricted access part in order to ensure confidentiality of the inspection results.

So-called "random field-checks" can be done only after an respective Order has been issued by the Head or Deputy Head of the RZN and approval from the prosecutor's office of the region where the entity to be inspected has its seat. In emergency cases RZN has the right to inspect the incumbent site immediately without an advance notifying, but needs to seek approval from the Prosecutor's Office within 24 hours. In cases, which need immediate action, e.g. life-threatening situations for study participants, the RZN asks the MHSD to take legal/administrative steps to e.g. stop the trial. This holds true also for situations the Ethical Council comes to the conclusion that a trial needs to be prematurely terminated or to suspend its approval/favourable opinion of a trial. Such legal/administrative actions can be ordered only via the MHSD.



However, until now the RZN didn't request the MHSD to prematurely terminate a clinical trial or to issue an amendment to a study protocol (Information from the RZN; lit.12).

The form and contents of an order to conduct an inspection, as well as the form and contents of the inspection report are defined precisely and the report must be issued immediately after the inspection has been finished. In cases of a possible direct impact on study participant's health or lives, RZN has the right to immediately stop the source which causes the danger via an order issued by the MHSD.

Inspection reports must be sent to the Head of the "Division of Clinical trials control" on a quarterly basis for further processing. The results, possible conclusions, proposed actions etc. derived from the reports must be reported to the Head of RZN and afterwards put on the official RZN website. A flowchart describing this process from acquiring data from inspections till its publication on the RZN website can be found as Appendix 3 to this Decree.

The provisions foresee also the possibility to repeal the decisions of *e.g.* results of an inspection, incorrect actions of RZN officials, etc. The procedure, including a list of responsible persons to whom a complaint can be sent (by e-mail or in writing), is provided (Articles 68-71). Complaints must be answered within 30 days after receiving the request.

Violations of the provisions laid down in the respective regulatory/legislative documents (Laws, decrees, etc.) are subject to legal actions described in the Federal Law no. 79-FZ.

This law, which deals with the general aspects of delivering public services, gives provisions concerning impartiality, transparency, rules for dealing with possible conflicts of interest and confidentiality of information are regulated by Federal Law 79-FZ.

In cases the inspection reveals "Findings", the RZN issues an Executive Order that the inspected entity has to submit an appropriate CAPA plan to the RZN, in particular a description of those planned measures to remedy the identified findings. The RZN may consider a reinspection to control that the CAPAs have been successfully implemented.

4.3.4. GCP-Inspections conducted in RF

From 1997 to 2009 eight GCP inspections, requested by the **CHMP**, were conducted, of which 3 took place in 2008, but none in 2009. Until now more than 11 inspections were executed, largely with favourable results and where problems have been identified, they were related more to sponsor deficiencies rather than deficiencies of the RF system or clinical sites

The **FDA** did 83 GCP inspections from 1995 till February 2012 [lit.5,9,10,11]. The outcome of the (study-orientated) FDA inspections was: 53 inspections, 64% NAI (No Action Indicated), 29 inspections, 35% VAI (Voluntary Action Indicated), and 1 inspection, 1% OAI (Official Action Indicated). The three most common GCP violations were: Failure to follow the protocol/investigational plan (20%), Inadequate and/or inaccurate records (20%), and Failure to report adverse drug reactions (4%) [lit.5,10,11]. FDA concluded after a marketing application related inspection, that data is considered reliable in support of the application [lit.5].



The **Roszdravnadzor** itself performed 387 inspections between 2005 and 1Q/2012 [4]. In 2011 RZN conducted 85 inspections, for this year 112 inspections are planned

No inspections are conducted outside the country [D16]

Training

Co-operation agreements exist between the RZN and the FDA [lit.3] as well as a training program for inspectors ("Train-the-trainer" programs) [lit.8].

RZN GCP inspectors regularly participate in International workshops on ethical and GCP aspects of clinical trials organised by the EMA.

According to Federal law no. 79-FZ, civil servants must attend at least one training course in 3 years. These trainings however are focussed on administrative, legal issues, not on scientific or specific job requirements.

Training for the scientific personnel at the MHSD and RZN is organised by the Department for Continuous professional training at the Expert Centre of the MHSD. These training courses are open also for participants from the Industry, CROs, etc.

4.4. Drug safety, Pharmacovigilance

The Russian Federation joined the WHO International Drug Monitoring Program in 2004 [lit.10]. The "Division of Drugs efficacy and safety monitoring" of the "Department for the State Quality Control of Medicinal products" of RZN is the responsible competent body in the Drug safety/Pharmacovigilance sector. It is supported by the regional RZN offices, which directly report to the Department by adding new, updated safety information into a database hosted by the RZN. Since November 2009 also SUSARs are monitored and entered into the database [lit.12].

The "On Circulation of medicines" Law [1] stipulates in Chapter 13 "Safety Monitoring of Medicinal products being in circulation in the Russian Federation", Article 64 "Safety Monitoring of Medicinal Products" that only "products in circulation" are subjected to a safety monitoring. However, [1], Article 4 (28) inexplicably defines that circulation of medicines includes also clinical trials. However, in contradiction to the aforementioned, in Article 3 it is requested that interactions between products in <u>circulation</u>, *i.e.* registered drugs, <u>and</u> investigational medicinal products applied in clinical trials, must be reported to the RZN.

The procedure (Point 1) described in Decree no. 757n [18] concerning safety monitoring limits this rules for "registered drugs in circulation in the RF". However, in Point 2 the scope of safety monitoring is expanded on "side effects, serious and unexpected adverse reactions, and interactions with other drugs, which are revealed in the course of clinical studies". Reports need to be sent to RZN within 15 calendar days after the information was revealed. Periodic safety reports for marketed products must be submitted to RZN "within the time period starting from the registration date of the pharmaceutical product in the country where it was approved for medical use for the first time: biannually within the first two years of the pharmaceutical product registration, annually within the subsequent two years, the third and fourth year of the pharmaceutical product registration, once every year from the fifth year of the



pharmaceutical product registration". Reports need to be sent to the RZN within 30 days before the end of the reporting date.

Adverse events/Adverse reactions and follow-ups for ongoing clinical trials must be reported to the RZN [18], but some sponsors—in particular sponsors of IMCTs- report these in parallel to the Ethics Council and Independent Ethics Committees. After evaluation of the reports by the RZN, reports are forwarded to the "Department of State Regulation of drug Circulation" in the MHSD, which decides on possible actions in order to safeguard public health. The Ethics Council is informed as well. The MHSD's decision on possible actions is posted on the official MHSD website. The experts have been informed [lit.12] that the provisions of the "ICH Harmonised Tripartite guideline "Clinical safety data management: Definitions and Standards for expedited reporting, E2A" are taken into account by the RZN [37].

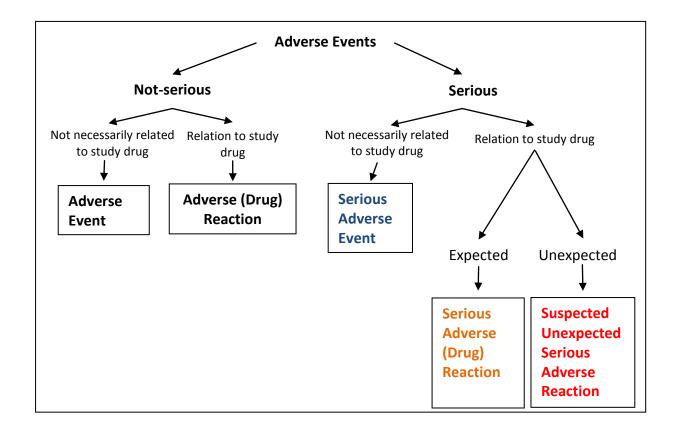
Both, Article 4, Points 50-52, and Article 64 of the "On Circulation of Medicines" Law [1] and Decree no. 757n [18], do not provide a consistent classification of Adverse events/Adverse Drug reactions: Adverse and Serious Adverse Events (SAE) are not necessarily related to a given drug, whereas Adverse (Drug) Reactions, Serious Adverse (Drug) Reactions and Suspected Unexpected Serious Adverse (Drug) Reactions (SUSARS) are connected with the application of a drug (for clarification, please refer to the Figure below).

Article 64 of the "On Circulation of Medicines" Law [1] and Decree no. 757n [18], do not provide a consistent classification of Adverse events/Adverse Drug reactions [**D17**]

So-called "Pharmacovigilance inspections" are conducted only an "emergency basis", *i.e.* not regularly.

Pharmacovigilance/Risk management plans, in particular for the early post-marketing period (when the likelihood that new safety issues of the new drug emerge), is high, are not on file. In 2011 "the RZN received more than 20.000 reports on adverse drug reactions from clinical trials.... The major share of such reports belonged to trials of oncology products or products designed for patients with serious medical conditions"[lit.12].





4.5. Participation in GCP-inspections

In the framework of this project it was considered that the experts participate in defined inspections conducted by RZN GCP inspectors; in total they participated in three inspections:

The first inspection took place on 24th and 25th of May 2012 at the Moscow City Hospital no.12. The inspection comprised the inspection of both the Hospital, its Clinical Site for conducting clinical trials in the area gastroenterology, and the documents from a selected clinical trial. As can be deducted from the Inspection Report [Annex 5], both the inspected clinical site and the assessed clinical study fulfil the requirements set by the ICH-GCP rules, despite the formal regulatory/legislative framework in RF does not require that clinical trials are conducted by following ICH-GCP rules, but by the "Rules for clinical practice" [10]. The Clinical site doesn't run a Quality Management system, this may be considered as a "Critical finding".

The site hasn't been involved in the conduct of IMCTs since several years; however, the Principal investigator informed the inspectors that he expects to be included in IMCTs in the nearest future. In essence it can be stated that the conduct of the assessed clinical trial followed the provisions given by the ICH-GCP rules.

The **second inspection** took place on 4th and 5th of June, 2012 at the Republican Hospital named after Baranov, Petrozavodsk, Republic of Karelia, Russian Federation



The **third inspection** was carried-out on 27th and 28th of June, 2012 at the Scientific Research Institute of Influenza of the Russian Ministry of Health, St Petersburg, Russian Federation.



5. Identified differences between the relevant regulations in EU and RF and recommendations

No.	Component	Issue and Recommendation	
D1	Law no. 61-	Except of so-called international multicentre clinical trials (IMCTs)	
	FZ;[1, Articles	and post-registration studies, applications for conducting a clinical	
	14, 21(2), 39]	trial in RF can only be submitted in the course of a registration	
		process	
		<u>Recommendation:</u> The link between registration process and	
		authorisation to conduct of a clinical trial might be removed	
D2	Law no. 61-FZ,	Despite all clinical trials must be conducted in compliance with the	
	[1; Article 18]	"Rules on Clinical practice", this is not an obligatory requirement	
		within the registration/marketing authorization process in the RF	
		[1; Article 18]	
		<u>Recommendation:</u> Within the MAA process in RF, compliance of clinical trials with the "Rules on Clinical practice" [10] should be	
		requested	
D3	Law no. 61-FZ,	Definitions given in the "On Circulation of Medicines" Law are not	
	[1; Article 4	always identical with the ones provided in Directives 2001/83/EC	
		and 2001/20/EC	
		Recommendation: Adopt International accepted (technical) terms	
		to facilitate an (International) exchange of information	
D4	Law no. 61-FZ;	Article 3 (5) of [1] states that the results of clinical trials conducted	
	[1; Article 3]	outside of RF shall be acknowledged based on "International trea	
		ties" and/or the principle of reciprocity.	
		<u>Recommendation:</u> This might be replaced by a phrase like "The results of clinical trials will be accepted in the marketing authori-	
		sation process, if it can be demonstrated that the trial was con-	
		ducted in compliance with GCP rules"	
D5	Decree 753n	Direct contacts of an applicant with the Ethics Council or the Expert	
	[16]	Organisation are not allowed. This is different in EU where a	
		dialogue between applicant and drug regulatory authorities and	
		Ethics Committees is considered to be beneficial	
		Recommendation: In order to quickly resolve e.g. questions of the	
		Ethics Council concerning provisions in the study protocol, direct	
D6	Law no. 294-	contacts with the applicant should be possible	
סט	FZ [4]	Contrary to EU practices, in RF inspections are free-of-charge <u>Recommendation:</u> Collecting fees for inspections could support the	
	FZ [4] 	independent status of the RZN	
D7	Law no. 61-FZ;	Clinical studies need to involve "research" and must be	
	[1, Article 38]	"scientifically sound" [24], there is no list defining allowed purposes	
	- '	for conducting clinical trials in EU	
		Recommendation: Revise this provision/harmonise with EU/ICH	
		provisions	



	T			
D8	Law no. 61-FZ; [1, Article 14, 38(1)	Clinical trials involving healthy volunteers, i.e. in phase I studies, with "medicinal products manufactured outside the RF" drugs are prohibited, but for local sponsors are permitted, also possible are phase I studies with foreign drugs involving patients Recommendation: A consistent solution should be reached: the risk for study participants is independent of the nationality of the sponsor and both in EU and RF medicinal products are manufactured according to the "Rules on Manufacturing practice"		
D9	Law no. 61-FZ; [1, Article 38]	Only defined organisations are entitled to organise clinical trials Such restrictions are not reflected in the applicable EU regulations: Article 2(e) of [32] defines that a sponsor can be an individual, a company, an institution or an organization Recommendation: This provision should be revised/harmonized with EU regulations; this might also enlarge the basis for research, because new groups of sponsors might be attracted		
D10	Governmental Decree no. 683 [7], Executive Order 752n [15]	Clinical sites for conducting clinical trials need to be accredited by the MHSD. Such an accreditation requirement is not reflected in the applicable EU regulations Recommendation: In a separate project/survey it should be evaluated whether this provision improves the safety of study participants and the quality of study-generated data, as well as its impact on the administrative burden in the clinical trial application process		
D11	Decree no. 684	Drug manufacturing licenses are issued by the Ministry of Industry and Trade, not by the Drug regulatory authorities <u>Recommendation:</u> Licensing and control should rest with the RZN or DRAs, because these organisations have the required (technical) experts		
D12	Executive Order 751 [14]	(Principal) investigators must have a 5-year experience in the conduct of clinical trials in order to be eligible as investigator in a clinical trial. Such provision doesn't exist in the EU, but exists in the national legislation of member states like Germany, where a 2-years' experience is in the conduct of clinical trials is requested for investigators *Recommendation:* In a separate project/survey it should be evaluated whether this provision improves the safety of study participants and the quality of study-generated data, as well as its impact on the administrative burden in the clinical trial application process		
D13	Law no. 61-FZ; [1, Article 43]	The law provides very strict rules concerning the conduct of clinical trials on defined vulnerable persons. Such strict rules, like on "Persons deprived of liberty", are not in place in EU. **Recommendation*: The principle of respect of the autonomy [lit.7, p.41-42] needs also to be taken into account. In a separate project/survey it should be evaluated whether this provision improves the safety of study participants and the quality of study-generated data, as well as its impact on the administrative burden		



		in the clinical trial application process	
D14	Law no. 61-FZ;	The requirement to repeat safety and efficacy clinical trials (so-	
	[1, Articles 14,	called local registration studies) whose results have already been	
	21(2), 27]	assessed in the "original" registration process, puts study	
		participants on unnecessary risk(s), generates additional costs for	
		the applicant, and postpones access of the population to modern	
		drugs.	
		Recommendation: The requirement to conduct "Local registration	
		studies" should be restricted to defined, (country specific) cases,	
		like special national medical care system/population (ethnic	
		groups)/diet	
D15	Executive	There are no specific, separate inspections performed concerning	
	Order no.	Clinical laboratories, Computer systems, Sponsor and CRO Phase I	
	1091n [23]	units, Record keeping and archiving of documents, Bioanalytical	
		part, Pharmacokinetic and Statistical Analyses of Bioequivalence	
		Trials	
		Recommendation: The regulatory scope of clinical trial inspections	
		should also include the aforementioned types of inspections	
D16	Executive	The RZN doesn't conduct inspections outside the country	
	Order no.	Recommendation: The RZN may inspect foreign applicants filing an	
	1091n [23]	MAA in RF in order to assure that GxP rules have been correctly	
		applied and the supplied documents are correct	
D17	Law no. 61-FZ;	Article 64 of the "On Circulation of Medicines" Law and Order no.	
	[1, Article 64],	757n [18], do not provide a consistent classifications of Adverse	
	Executive	events/ Adverse Drug reactions	
	Order no.	Recommendation: Include into [1 and 18] International accepted	
	757n [18]	definitions for adverse events/reactions or place a reference to	
		such standards in the text(see figure on p. 40) in order to facilitate	
		an International exchange of information	



6. Lessons learned, Summary and Conclusions

In general, it can be stated that for the conduct and supervision of clinical trials in the EU and the RF equivalence of the respective regulatory/legislative framework provisions is given. However, a number of differences exist, which have been identified and classified in the following four (4) categories:

Differences that might affect the trial participant's rights, safety and welfare, credibility of study data and thus acceptance of the clinical study results by the DRAs in EU:

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No.	Issue		
D2	Despite clinical trials must be conducted in compliance with "Rules on Clinical practice" , this is not an obligatory requirement within the registration/marketing authorization process in the RF		
D3	Definitions given in the "On Circulation of Medicines" Law are not always identical		
	with the ones provided in Directives 2001/83/EC and 2001/20/EC		
D15	There are no specific, separate inspections performed concerning Clinical laboratories, Computer systems, Sponsor and CRO Phase I units, Record keeping and archiving of documents, Bioanalytical part, Pharmacokinetic and Statistical Analyses of bioequivalence trials		
D17	No consistent classification of Adverse events/Adverse Drug reactions in the Law [1, Article 64] and [18]		

Differences, which restrict the nature and extent of trials that can be carried out in RF, in a manner more restrictive than those in EU:

No.	Issue	
D1	Except of so-called international multicentre clinical trials (IMCTs) and post-	
	registration studies, applications for conducting a clinical trial in RF can only be	
	submitted in the course of a registration process	
D7	Clinical studies can be conducted only for pre-defined purposes	
D8	Clinical trials involving healthy volunteers, i.e. in phase I studies, with "medicinal	
	products manufactured outside the RF" are prohibited, but for local sponsors are	
	permitted. Also phase I studies with foreign drugs involving patients are possible	

Country specific requirements that go beyond those applied in EU:

No.	Issue
D9	Only defined applicants/organisations are entitled to organise clinical trials
D10	Clinical sites for conducting clinical trials need to be accredited by the MHSD
D12	(Principal) investigators must have a 5-year experience in the conduct of clinical
	trials in order to be eligible as investigator in a clinical trial
D13	The law provides very strict rules concerning the conduct of clinical trials on
	defined vulnerable persons, exceeding those in EU
D14	"Local registration studies" on safety and efficacy (except for IMCTs) trials need to
	be repeated (so-called confirmatory trials) in the marketing authorisation process



Other, country-related, differences:

No.	Issue	
D4	Article 3 (5) of the On circulation of medicines Law states that the results of clinical	
	trials conducted outside of RF shall be acknowledged based on "International	
	treaties" and/or the principle of reciprocity	
D5	Direct contacts of an applicant with the Ethics Council or the Expert Organisation	
	are not allowed	
D6	In RF GCP inspections are free-of-charge	
D11	Drug manufacturing licenses are issued by the Ministry of Industry and Trade, not	
	by the Drug regulatory authorities (or the RZN)	
D16	The RZN doesn't conduct inspections outside the country	



7. Annexes

7.1. Annex 1 - List of Laws, Orders, Decrees and other regulatory documents ruling clinical trials in RF

[no.]	Law no.	Title
[1]	61-FZ (12 Apr 2010); amended by	On Circulation of Medicines
	192-FZ (27 July 2010)	
	271-FZ (11 Oct 2010)	
	313-FZ (29 Nov 2010)	
	93-FZ (25 Jun 2012)(Article 32)	
[2]	323-FZ (21 Nov 2011); excerpts	On public health protection in the Russian
	(Articles 74 and 75)	Federation
[3]	Amendments to Part Second of the	Fees for Registration/marketing
	Tax Code; extracts	Authorisation
[4]	294-FZ (19 Dec 2008)	On the protection of legal entities and
		individual entrepreneurs' rights in the course
		of state control (supervision) and municipal
		control
	Governmental Decree no.	
[5]	423 (02 Jun 2008)	On some issues of the activities of the
	321 (30 Jun 2004) Statute of the	Ministry of Health and social development
	MHSD	and of the Federal Medical and Biological
	323 (30 Jun 2004) Statute of RZN	Agency
[6]	673 (03 Sep 2010); amended by	On Approval of the rules for import and
	Decree no. 441 (03 Jun 2011),	export of biological materials obtained in
	Decree no. 1001 (05 Dec 2011)	clinical trials of a medicinal product for
		medical use into and from the Russian
		Federation
[7]	683 (03 Sep 2010); amended by	On Approval of rules for accreditation of
	Decree no. 1001 (05 Dec 2011)	Medical Institutions for the right to conduct
		clinical trials of pharmaceutical drugs for
		medical application
[8]	714 (13 Sep 2010); amended by	On Approval of typical rules for compulsory
	Decree no. 393 (18 May 2011)	insurance of the life and health of a patient
		involved in clinical trials of a medicinal
[0]	774 (20 Com 2040)	product
[9]	771 (29 Sep 2010); amended by	On the procedure of import of medicines for
	Decree no. 441 (03 Jun 2011),	medical use into the Russian Federation
	Decree no. 1001 (05 Dec 2011)	
[40]	(Executive) Order no.	Dulas for Clinical Practice in the Bussian
[10]	266 (19 Jun 2003)	Rules for Clinical Practice in the Russian
[11]	702n /22 Aug 2010\	Federation On approval of the form of notice of
[11]	703n (23 Aug 2010)	On approval of the form of notice of
		completion, suspension or termination of the



		clinical trial of the medicinal product for
		medical use
[12]	748n (26 Aug 2010)	Approval of procedure to issue permits for clinical trials of medicinal products for medical use
[13]	750n (26 Aug 2010)	Approval of rules for expert examination of medicines for medical use and forms for expert council conclusions on the results of expert examination of medicines
[14]	751 (26 Aug 2010)	On approval of the rules of maintenance of the register of investigators who are conducting (or conducted) clinical trials of medicinal products for medical use, and the procedure of placing of the register on the official website of the Ministry of Public Health and Social Development of the Russian Federation
[15]	752n (26 Aug 2010)	On approval of the procedure of publishing and placing of the list of medical institutions entitled to conduct clinical trials of medicinal products for medical use on the official website of Ministry of Public Health and Social Development of Russian Federation
[16]	753n (26 Aug 2010)	Approval of procedure to organize and conduct ethical expert examination of possibility of clinical trial of medicinal products for medical use, and the form for Ethical Council conclusion
[17]	754n (26 Aug 2010)	On approval of the procedure for maintenance, publication and placing of the register of issued permits for the conduct of clinical trials of medicinal products for medical use on the official web-site
[18]	757n (26 Aug 2010)	On approval of the procedure for safety monitoring of pharmaceutical products meant for medical use and registration of side effects, serious adverse reactions and unexpected adverse reactions in the case of application of the pharmaceutical products meant for medical use
[19]	774n (31 Aug 2010)	On Ethical Council
[20]	775n (31 Aug 2010)	On approving the procedure of review of report of need of amending the protocol of the clinical trial of the medicinal product for medical use
[21]	951n (02 Nov 2010)	On approval of the form of the register of issued permits (decisions to refuse to issue



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7.2. Annex 2 - List of regulatory/legislative Core documents ruling clinical trials in EU

#	Document	Key points
[32]	EUDRALEX The Rules Governing	Compilation of legislative and guidance
	Medicinal Products in the EU, Vol. 10,	documents in the field of clinical trials
	Clinical trials, V26, March 2012	
[33]	Directive 2001/20/EC ("Clinical Trial	Legal basis for the implementation of GCP
	Directive")	within the EU Member states
[34]	Directive 2005/28/EC	Amending Directive 2001/20/EC; Defines
		the requirements for authorisation of the
		manufacturing or importation of
		Investigational Medicinal Products (IMP)
[35]	Directive 2003/94/EC	Principles and guidelines of GMP in
		respect of medicinal products for human
		use and IMPs for human use
[36]	Directive 2001/83/EC (as amended by	The foundation of Community
	Directives 2003/63/EC, 2008/29/EC)	pharmaceutical law
[37]	ICH Harmonised Tripartite Guideline	Clinical safety data management:
	E2A	Definitions and Standards for expedited
		reporting

7.3. Annex 3 - Other supportive literature, reports, publications etc. in the sector

- [lit.1] Specific Terms of Reference-2011/276-014, Partnership for modernisation, Cooperation in the field of clinical trials, FWC COM 2011 Lot 1
- [lit.2] Clinical trials submitted in marketing authorisation applications to the EMA EMA/INS/GCP/154352/2010; 05 November 2010
- [lit.3] Statement of Intent on Collaboration between the Food and Drug Administration of the United States of America and Federal Service on Surveillance in Health Care and Social Development of the Russian Federation, FDA-Roszdravnadzor, 27 May 2010, www.fda.gov/InternationalPrograms/Agreements/MemorandaofUnderstanding/...
- [lit.4] The Blue Book, 2nd Ed., Marketing Authorisation of Pharmaceutical Products with Special Reference to Multisource (Generic) Products. A manual for National Medicines Regulatory Authorities (NMRAs); WHO, 2011; www.who.int
- [lit.5] Purohit-Sheth, T., Clinical Trial Quality and Compliance: An FDA Perspective, Bioresearch Monitoring and Inspections, FDA, CDER, www.fda.gov...UCM232756.pdf
- [lit.6] Ethics Review of Clinical Research in Pharmaceuticals; International Scientific Conference, 28-29 November 2011, Moscow; www.coe.int/bioethics
- [lit.7] Guide for Research Ethics Committee Members. Steering Committee on Bioethics (CDBI); Strasbourg, 07 February 2011; www.coe.int/bioethics



- [lit.8] Draft Agenda: (For Discussion Purposes only) Roszdravnadzor/U.S. FDA International Good Clinical Practice (GCP)/Inspection "Train-the-Trainer" Phase 3 Workshop, June 15-22, 2012
- [lit.9] Association of Clinical Trials Organizations (ACTO), Newsletter No. 1-4, Timeframes monitoring report, Other information materials, www.acto-russia.org
- [lit.10] Ravdel A., Russia: has all the required infrastructure and resources to conduct high-quality, accurate clinical trials; Journal for Clinical Studies, January 2010, p. 24-26
- [lit.11] Storozhuk, E., Astafyeva, S., Clinical Trials in Russia, Monitor, February 2012, p. 29-35
- [lit.12] Personal communications with staff from the MHSD and RZN
- [lit.13] Independent Interdisciplinary Ethics Committee on Ethical Review for Clinical Studies, www.ethicuni.ru

7.4. Annex 4 - Structure of the "On Circulation of Medicines" Law no. 61-FZ – an Overview

Structure of the "On Circulation of Medicines" Law no.61-FZ – an Overview			
Chapter 1	General Provisions		
Article 1	Subject of Regulation of this Federal Law		
Article 2	Scope of Application of this Federal Law		
Article 3	Legislation on Circulation of Medicines		
Article 4	Basic Terms used in this Federal Law		
Chapter 2	Powers of Federal Executive Bodies and Executive Bodies of		
	Constituent Entities of Russian Federation with Respect to Circulation		
	of Medicines		
Article 5	Powers of Federal Executive Bodies with respect to circulation of		
	Medicines		
Article 6	Powers of Executive Bodies of Subject of Russian Federation with respect		
	to circulation of Medicines		
Chapter 3	State Pharmacopeia		
Article 7	Development and Enactment of State Pharmacopeia, allocation of Da		
	thereof		
Chapter 4	State Control over Circulation of Medicines		
Article 8	Licensing of Manufacturing of Medicines and Pharmaceutical Activities		
Article 9	State Control over circulation of Medicines		
Chapter 5	Development, Preclinical testing of Medicines and Clinical Trials of		
	Medicinal Products for Veterinary Use		
Article 10	Development of Medicines		
Article 11	Preclinical Testing of a Medicine for Medical Use		



Article 12	Preclinical Testing of a Medicine and Clinical Trial of Medicinal Product for Veterinary Use
Chapter 6	Performance of State Registration of Medicinal Products
Article 13	State Registration of Medicinal Products
Article 14	Principles of Expert Examination of Medicines and Ethical Expert Examination
Article 15	Federal State-financed Institution carrying out Expert Examination of Medicines
Article16	Organisation of Expert Examination of Medicines for State Registration thereof
Article 17	Ethical expert Examination
Article 18	Submission and Review of Applications for State Registration of Medicinal Products and Submissions of necessary documents
Article 19	Procedure for Making Decision on Issuance of Assignment for Performance of Expert Examination of Medicines for Expert Institution and Ethical Council
Article 20	Expert Examination of Documents necessary to obtain permit for conduct of clinical trial of Medicinal product for medical use and Ethical expert examination
Article 21	Procedure for obtaining permit to conduct clinical trial of medicinal product for medical use
Article 22	Decision on conducting of clinical trial of Medicinal product for medical use
Article 23	Expert Examination of quality of a medicine and expert examination of correlation between anticipated benefit and risk from use of medicinal product for medical use
Article 24	Expert Examination of quality of a medicine and expert examination of correlation between anticipated benefit and risk from use of medicinal product for veterinary use
Article 25	Repeated expert examination of Medicines and repeated Ethical Expert Examination
Article 26	Accelerated Procedure for Expert Examination of Medicines
Article 27	Decision on State Registration of a Medicinal Product
Article 28	Registration Certificate for a Medicinal Product
Article 29	Confirmation of State Registration of a Medicinal Product
Article 30	Amendments to Documents Contained in Registration Dossier for Registered medicinal product for medical use
Article 31	Amendments to Documents Contained in registration Dossier for Registered Medicinal product for Veterinary use
Article 32	Cancellation of State Registration of a Medicinal Product
Article 33	State Register of Medicines
Article 34	Quality evaluation of Pharmaceutical substance not used in Manufacturing of Medicinal products
Article 35	Repeated presentation of a Medicinal product, which failed State registration of medicinal products for State Registration of Medicinal products



Article 36	Appeal of decision on Refusal to issue permit for clinical trials of medicinal product, or refusal to perform State Registration of a medicinal
	product
Article 37	Information relating to State Registration of Medicinal products,
	Information about Registered Medicinal Products, and Medicinal
	Products removed from the State Register of Medicines
Chapter 7	Clinical trials of Medicinal Products for Medical use, Clinical trial
-	Contract, Rights of Patients involved in trials
Article 38	Clinical trials of Medicinal Products for Medical use
Article 39	International Multicentre Clinical trial of Medicinal product for medical
	use or post-registration clinical trial of medicinal product for medical use
Article 40	Procedure for Clinical trial of medicinal product for medical use
Article 41	Contract for Clinical Trial of Medicinal product for medical use
Article 42	Finance support of clinical trial of medicinal product for medical use
Article 43	Rights of patients involved in clinical trial of medicinal product for
	medical use
Article 44	Compulsory Insurance of Life and Health of the Patient involved in
	clinical trial of medicinal product for medical use
Chapter 8	Manufacture and Making of Medicines
Article 45	Manufacturing of Medicines
Article 46	Marking of Medicines
Chapter 9	Import of Medicines into the Russian Federation and Export of
	Medicines from the Russian Federation
Article 47	Procedure for Import of Medicines to the Russian Federation and Export
	of Medicines from the Russian Federation
Article 48	Legal Entities Authorised to import Medicines into the Russian Federation
Article 49	Documents submitted to customs authorities of the Russian Federation
	when Importing Medicines into the Russian Federation
Article 50	Import of Medicinal Products into the Russian Federation for Personal
	Use and other non-commercial purposes
Article 51	Cooperation between the Federal Executive Body authorised in the Area
	of Customs and other authorized federal Executive bodies
Chapter 10	Pharmaceutical Activity
Article 52	Realisation of Pharmaceutical Activity
Article 53	Sale, transfer of Medicines by wholesalers of Medicines
Article 54	Regulations for Medicines wholesale
Article 55	Procedure for Medicines Product Retail
Article 56	Compounding and Dispensation of Medicinal Products
Article 57	Ban on sale of counterfeit medicines, poor quality medicines or infringing medicines
Article 58	Storage of Medicines
Chapter 11	Destruction of Medicines
Article 59	Reasons and Procedures for destruction of medicines
Chapter 12	State Regulation of Prices for Medicinal products for medical use



Article 61	State Registration of Manufacturer's maximum ex-works prices for vital
	and essential medicinal products and their sale
Article 62	State Registration of Manufacturer's maximum ex-works prices for
	medicinal products included into the list of vital and essential medicinal
	products
Article 63	Determination of Executive Authorities of the Russian Federation
	Constituent Entities of maximum wholesale and maximum retail mark-
	ups to actual ex-works prices of manufacturers of medicinal products for
	medicinal products for medical use
Chapter 13	Safety monitoring of medicinal products being in circulation in the
	Russian Federation
Article 64	Safety monitoring of medicinal products
Article 65	Suspension of Medicinal Product
Article 66	Information on the Results of Safety Monitoring of Medicinal products
Chapter 14	Information on Medicinal products
Article 67	Information on Medicinal products
Chapter 15	Liability for Violation of Legislation of the Russian Federation of
	Medicines circulation and compensation for harm to human health
	caused by administration of medicinal products
Article 68	Liability for Violation of legislation of the Russian Federation for the
	Medicines circulation
Article 69	Compensation for harm to human health caused by administration of
	medicinal products
Chapter 16	Final Provisions
Article 70	Declaring inoperative separate legal acts (provisions of legal acts) of the
	Russian Federation
Article 71	Enactment of this Federal Law

7.5 Annex 5 – Reports from co-inspections carried out in May-June 2012

Report of a GCP co-inspection carried out on 24 and 25 May 2012 at the clinical site, Moscow City Clinic #12

<u>Inspected clinical site</u>

Moscow City Hospital #12, Bakinskaja ul., 26, 115516 Moscow, Russian Federation Department of Gastroenterology

Persons involved in the inspection

Hospital/Clinical Site:

Mr. S.A. Salikov (MD, PhD); Chief Physician of the hospital

Ms.I.G. Tursheva (MD, PhD); Deputy Chief Physician

Ms.I.O. Sirenova (MD, PhD); Deputy Chief Physician



Ms.E.Y. Termosesova (MD, PhD); Pharmacologist

Mr. I. Fedorov (MD, PhD); Head of the Department of Gastroenterology and Prinicipal Investigator in the clinical trial which has been assessed

Roszdravnadzor Main Office:

Mr. Yuri Afonchikov (MD, PhD); Head of Clinical Trials Control Department; Lead inspector

Mr. E.S. Rogov (MD, PhD, JD); Deputy Head of Clinical Trials Control Department; Coinspector

Roszdravnadzor Moscow Regional Office:

Ms. N. Chebotarova (PhD, pharmacist)

Mr. S. Gawron (pharmacist)

Observer:

Mr. W. Gielsdorf (PhD)

Legal basis and administrative aspects of the inspection

The inspection has been set-up within the responsibility of the Moscow Regional Office of Roszdravnadzor (RZN).

The legal basis for this inspection is Order (Prikras) no. 3 from 18 May 2012, issued by the RZN Moscow Regional Office, which describes in detail the aspects of the inspection, like date and duration or the inspection (24 May till 21 June 2012), names of the RZN inspectors (in total six), which persons from the hospital/clinical site need to be available during the inspection, e.g. for interviews, which facilities/organisational units will be inspected, which documents need to be present for assessment, etc.

The Order is attached [Attachment 1] as it defines the aspects of the inspection; its legal base is Law no. 294-FZ [4], which regulates all kinds of inspections in RF, irrespectively of the area of inspection. Concerning the structure, form and contents of all Inspection Reports, the Ministry of Economic Development of the Russian Federation issued Order no. 141 from 30 April 2009 ("On implementation of provisions of the Federal Law on protection of rights of legal entities and individual entrepreneurs in the course of execution of State control (supervision) and of Municipal Control", as amended by Orders no. 199 of 24 May 2010 and no. 532 of 30 September 2011); all reports must comply with the provided form in this Order. Taking into account the different areas and issues covered by these general legal provisions, the RZN has published a checklist for GCP inspections, including adaptations taking into account the specifics of a GCP inspection. This Order (Order no. 2042-II/05 "On taking control measures" from 21 September 2005), also defines the structure and contents of a GCP Inspection Report. In addition, the RZN produced an "Internal Handbook on Inspections", which is confidential.

The legislative/regulatory basis of the (Investigator site) inspection is GOSTP52379-2005 "Good Clinical Practice (ICH-GCP)" [24] and the Executive Order no. 266 "Rules for Clinical Practice in the Russian Federation" [10]. Despite [24] has a legal status of a Recommendation, and [10] defines only "Rules for clinical practice" and is in legal force only in those parts, which



are not covered by the "On Circulation of Medicines" Law [1], the inspectors referred to these two documents.

During the opening meeting it turned out that the investigator for the last time participated in 3-4 International Multicentre Clinical trials (IMCTs) in 2008, since then only clinical trials were conducted for domestic sponsors. Neither the hospital, nor its clinical sites have yet been inspected; in 2005 the clinical site at the Gastroenterological Department has been audited by a (foreign) sponsor. The clinical site conducted in 2011 three local clinical trials and participates at present in an observational study.

The inspection comprised both the Hospital, its Clinical Site for conducting clinical trials in the area gastroenterology, and the documents from a selected clinical trial.

Inspection of the Facilities and equipment, including the Clinical site

The Moscow City Hospital #12 is one of the biggest hospitals in Moscow with more than 1.000 beds; until 2006 it was the hospital of the car manufacturer SIL, then it went into the responsibility of the City of Moscow.

Following the formal administrative procedures, like proving the legitimation of inspectors and inspection, presenting the inspection programme, etc., the inspectors checked the general legal documents concerning the hospital's accreditation to operate the hospital, including its pharmacy and clinical laboratories. This involved also the accreditation to conduct clinical trials, and the contracts between Sponsor and Hospital (there are no contracts concluded between Sponsor and investigator).

Afterwards a facilities (hospital) tour commenced and the following departments were inspected, including the available equipment:

Clinical laboratory (accreditation, QA-system)

Pharmacy (in general and the separate room for storing IMPs)

ECG recording rooms and equipment

Gastroenterology ward/rooms and equipment.

Although there are several departments of the hospital, which are involved in clinical trials, only the Clinical site, which had conducted the clinical trial selected for inspection, *i.e.* the Department of Gastroenterology, was inspected.

The inspectors ensured themselves that the legal requirements to conduct clinical trials in the area of gastroenterology are fulfilled, like that the Principal investigator and staff have the necessary qualifications, the facilities are appropriate to accommodate study participants, and the required equipment for study conduct is at hands. Special attention was drawn on the proper storage of the IMPs, both at the hospital (general) pharmacy and at the clinical site.

The following phase III-study had been chosen for inspection:

"Open, comparative, randomized clinical trial of clinical efficacy and safety of Spasmaton and Spasmalgon in patients with gastroenterological pain syndrome" (Study Code RU 03/10).

The Principal investigator was Dr. Ilya Fedorov, MD, PhD, Head of the hospitals Gastroenterological Department. The study was conducted from August 2010 till June 2011 and included 40 patients. A written confirmation of the Principal investigator that the study has been conducted "according to the national regulations on GCP and the study protocol" is on file.



Assessment of the Study documentation comprised a complete check of

- All Case Report Forms (CRFs)
- All Written Informed Consent Forms
- The Investigator Site File, including the favourable study approvals of the Institutional Ethics Committee (IRB) and the Ethics Council (of the MHSD), study protocol, Investigators brochure, Safety reporting
- The Approval from the RZN
- All Drug accountability records
- The Monitoring log
- The System for the management of biological samples
- The Source data verification, including <u>all</u> recorded ECGs, clinical laboratory results, medical history
- All Trial subject data.

There is no quality management system (QMS) in place at the site, in clinical trials the SOPs supplied by the sponsor and/or of the hospitals clinical laboratory are followed.

No computerized systems are used; for administrative (Office) work Microsoft Office is used.

No protocol deviations and/or violations were reported and there were no drop-outs or withdrawals or premature terminations. No Adverse events or other safety issues were reported.

A further check of the Drug accountability records and a general check of the hospitals pharmacy will be conducted in the following week by other colleagues of RZN's Moscow Regional Office.

After the assessment of the Study documentation the **Institutional Ethics Committee (IRB)** has been assessed for its compliance with (ICH)-GCP rules.

The IRB consists of six members, four females and two males:

- (1) Head of the IRB: MD
- (2) Clinical pharmacologist
- (3) Pathologist
- (4) Specialist for clinical laboratory medicine (external, *i.e.* not an employee of the hospital)
- (5) Gastroenterologist
- (6) Lawyer.

A detailed, written Statute of the IRB is on file, as well as a number of SOPs, which have been amalgamated into one consolidated document serving as the "Working procedures". In contrary to the Ethics Council of the MHSD, the IRB issues, besides a Yes/No decision, also so-called conditional approvals. The set quorum is n=3.

Without a favourable approval of the hospital's IRB, no clinical trial will be conducted, even if the Ethics Council (of the MHSD) has approved the study.

It has been documented that the co-investigator of the study participated in the respective IRB meeting, but didn't vote.



Conclusions

As can be fairly judged, both the inspected clinical site and the assessed clinical study fulfil the requirements set by the ICH-GCP rules, despite the formal regulatory/legislative framework in RF does not require that clinical trials are conducted by following ICH-GCP rules, but by the "Rules for clinical practice" [10].

The Clinical site doesn't run a Quality Management system, this may be considered as a "Critical finding".

The site hasn't been involved in the conduct of IMCTs since several years; however, the Principal investigator informed the inspectors that he expects to be included in IMCTs in the nearest future.

In essence it can be stated that the conduct of the assessed clinical trial followed the provisions given by the ICH-GCP rules

Report of a GCP co-inspection carried out on 4th and 5th of June, 2012 at the Republican Hospital named after Baranov, Petrozavodsk, Republic of Karelia, Russian Federation

Inspected clinical site

Republican Hospital named after Baranov, Pirogova Street 3, 185019 Petrozavodsk, Republic of Karelia, Russian Federation, Department of Haematology

Persons involved in the inspection

- Hospital/Clinical Site:
 - Dr. Elissan Shandalovich, (MD, PhD); Chief Physician of the hospital
 - <u>Dr</u>. Tamazy Karapetyan (MD, PhD); Deputy Chief Physician
 - Dra. Ekaterina Moskvina (MD, PhD); Clinical Pharmacologist
 - <u>Dra</u>. Svetlana Moshnina (MD, PhD); Haematologist
 - Dr. Alexander Myasnikov (MD, PhD); Head of the Department of Haematology
 - Dra. Anna Khilkova (MD, PhD); Chairwoman of the Institutional Ethics Committee (IRB)
 - Dra. Natalia Vezikova (MD, PhD), Professor and Head of the Acute Stroke Department
 - Dra. Irina Polskaya, Cardiologist
- Roszdravnadzor Main Office:
 - Dr. Yuri Afonchikov (MD, PhD); Head of Clinical Trials Control Department; Lead inspector
 - Dr. Evgeny Rogov (MD, PhD, JD); Deputy Head of Clinical Trials Control Department; Co-inspector
- Roszdravnadzor Petrozavodsk Regional Office:
 - Dra. Nataliya Smirnova (PhD, pharmacist), Head RZN Karelia
 - Ms. Nataliya Urchona (pharmacist), Head Office Petrozavodsk



EU Observer:

Dr Frans van Andel (PhD)

Legal basis and administrative aspects of the inspection

The inspection was set up under the responsibility of the Karelian Regional Office of Roszdravnadzor (RZN).

The legal basis for this inspection is Order (Prikras) 294, issued by the RZN Moscow Central Office, which describes in detail the aspects of the inspection, like date and duration or the inspection (4-9 June 2012), names of the RZN inspectors and staff from the hospital/clinical site to be available during the inspection for interviews and presentation of documentation.

During the opening meeting of the inspection it appeared that the hospital was last inspected by the RZN in 2007. On that occasion, the RZN inspected three CT's (two IMCT's, one local). The main outcomes of the inspection in 2007 were discussed and it was acknowledged that the inspection in 2007 generally gave good results and no major protocol violations established. The RZN did not issue any injunctions or major recommendations to the hospital on that occasion.

The inspection comprised the Haematology Department of the hospital as a site for conducting clinical trials in the area of haematology, and the documents from two selected trials (one IMCT and one national trial).

Inspection of the Facilities and equipment, including the clinical site

With over 700 beds, the Republican Hospital in Petrozavodsk is the largest hospital in the Republic of Karelia. It services the population of Petrozavodsk and has a catchment area of approximately 300,000 persons. The hospital can be described as a tertiary hospital with major facilities in most medical specialties. It functions as a training centre of medical students at the Medical Faculty of the State University in Petrozavodsk. The hospital has been the focus of a recent renovation programme and most departments have undergone significant modernization. With funds from the Federal Ministry of Health (MoH), modern laboratory and screening equipment was procured recently.

The inspection started with assessing formal administrative procedures such as proving the legitimation of inspectors and inspection, presenting the inspection programme objectives and timetable and requesting full cooperation with the inspection. It appeared the management of the hospital was well briefed about the inspection and full cooperation was granted by all staff members.

Then the inspectors checked the general legal documents concerning the hospital's accreditation to operate the hospital as well as to conduct clinical trials.

An inspection was carried out of the facilities at the Haematology Department. Facilities of the Department can be found at several locations inside the hospital. This is partly due to an ongoing renovation programme of, for instance, the laboratory section. The Haematology Department appears to be located at a section of the hospital, which is not yet renovated. The premises are generally dark and colourless and need general repair and upgrading.

At the outset of the inspection of the facilities, the inspectors ensured themselves that the legal requirements to conduct clinical trials in the area of haematology are fulfilled, such as the Principal Investigator and staff having the necessary qualifications, the facilities being



appropriate to accommodate study participants, and the required equipment for study conduct available and in good working order. Special attention was given to the proper storage of the IMPs.

The following facilities were inspected:

- Clinical laboratory (modern equipment installed in renovated sections)
- Pharmacy with respect to storing IMPs (in cellar)
- X-ray, ECG and other equipment
- Haematology patient rooms
- Localities for storing files and central archive

Inspections were carried out of maintenance reports of all equipment such as refrigerators, centrifuges. In most instances, equipment was calibrated and reports available for 2011. In addition, the RF "FSVOK" certificate of quality standards of the laboratory was issued by the RF Standard Authority and a 2012 certificate was in process. The "FSVOK" certificate is the Russian equivalent of ISO standards.

Inspection of two clinical trials

An overview was presented of on-going clinical trials in the Cardiology and Haematology Departments as follows:

- In the Haematology Department a total of 12 CT's is on-going. 10 studies are IMCT's and 3 national ones;
- In the Cardiology Department a total of 14 studies is presently on-going all IMCT's.

According to the inspectors, with a total of approximately 25 on-going trials, the Republican Hospital in Petrozavodsk has an average score as regards number of trials. In RF some hospitals feature more than 100 trials and these can be considered as large centres for CT's.

A selection was made to review one IMCT and one national trial. The international trial was "A multicentre 12 week randomized double blind placebo-controlled biomarker study of secukinumab in rheumatoid arthritis patients followed by an open label extension" (study AIN 457, sponsor Novartis, Principal Investigator Professor Nataliya Vezikova, started November 2011).

The national study was "An open prospective multicentre clinical study of safety and effectiveness of bortezomib, melfalan and prednizolon in combination with velcade" (study BOR 1, sponsor Biokag, Principal Investigator Dr Alexander Myasnikov, started March 2012).

The inspectors carried out an assessment of the following study documentation:

- All Case Report Forms (CRFs)
- All Written Informed Consent Forms
- The Investigator Site File, including the favourable study approvals of the Institutional Ethics Committee (IRB) and the Ethics Council (of the MoH), study protocol, Investigators brochure, Safety reporting
- The Approval from the RZN
- All Drug accountability records
- The Monitoring log
- The System for the management of biological samples



- The Source data verification, including all recorded ECGs, clinical laboratory results, medical history
- All Trial subject data.

With respect to the IMCT, the inspectors concluded that there were no protocol deviations and that the study patient enrolment of 50 patients in total was developing according to plan. This study did not report untoward side-effects of the treatment.

As regards the national study, since March 2012, two patients had been screened and two enrolled. However, one patient developed serious ADR's (ischaemic stroke) and was dismissed from the study. Patient enrolment was temporarily suspended and consultation with the sponsor is presently taking place to modify the study protocol.

A visit was paid to the office of the **Institutional Ethics Committee (IRB)**, dealing with issues of facilitating clinical trials in the hospital.

The activities of the IRB are regulated by order 289 of 26th of September 2011 issued by the MoH.

The present IRB consists of 12 members as follows:

- (1) Chief Physician
- (2) Two Deputy Heads of the Chief Physician
- (3) Clinical pharmacologist
- (4) Three Professors of Medicine of various specialties teaching at the Medical Faculty of the State University in Petrozavodsk
- (5) Haematologist
- (6) Representative of the Medical Faculty in Petrozavodsk
- (7) Emergency Medicine Specialist
- (8) Neurosurgeon
- (9) Lawyer.

The working procedure of the IRB is described in internal regulation 397 (2010). A detailed written Statute of the IRB is on file, as well as a description of the working procedures.

As described in the "Law on Circulation of Medicines" (Federal Law 61), for all international and local trials the Ethics Council (of the MoH) needs to give permission following application by the sponsor of the trial. Only if permission is granted by the MoH, a local IRB can act accordingly by approving (or not) to conduct a trial in the hospital.

Generally, decisions are prepared by one member of the IRB. Decisions of the IRB are always based on a majority vote of the council (i.e. 6 members plus one need to be in favour of a decision).

Without a favourable approval of the hospital's IRB, no clinical trial will be conducted, even if the Ethics Council (of the MoH) has approved the study.

Conclusions

As evidenced by the large number of IMCT's on-going, there is extensive experience at the Republican Hospital in Petrozavodsk with the application of ICH-GCP rules. It is no surprise



that both the RZN inspection in 2007 and the current one did not result in protocol violations of the IMCT's conducted. Of course this can be explained by the fact that for IMCT's the rules of ICH-GCP must be applied by the international sponsor in order for the data collected to be acceptable for registration purposes in the EU and USA.

On the other hand, the national trial inspected at the Republican Hospital did result in protocol violations. However, these were not due to violations of the ICH-GCP rules, but can be accounted for due to unforeseen serious side-effects of the study medication.

It appears that even though the RF uses its own set of GCP rules called "Rules for Clinical Practice", in fact ICH-GCP rules are followed.

The inspectors raised a number of issues which may improve the effectiveness of the work of the RZN inspecting clinical trials. One such issues may be to set up a better link between an inspection and data needs for subsequent registration of a new medication. However, issues raised by the inspectors do not directly affect the application of ICH-GCP rules.

Based on the inspection of the Republican Hospital in Petrozavodsk, Republic of Karelia, RF, it can be concluded that the implementation of assessed clinical trials is in compliance with ICH-GCP rules.

Report of a GCP co-inspection carried out on 27th and 28th of June, 2012 at the Scientific Research Institute of Influenza of the Russian Ministry of Health, St Petersburg, Russian Federation

Inspected clinical site

Scientific Research Institute of Influenza of the Russian Ministry of Health, St Petersburg, Russian Federation, Professor Popov Street 15/17, 197376 St Petersburg, Russian Federation

Persons involved in the inspection

Influenza Institute:

Prof. Oleg I Kiselev, (MD, PhD); Director of the Institute

Dra. Emilia Kutcheruk, (MD, PhD); Chief Physician

Dr. Michael Grudenin, (MD, PhD); Director of Research

Dra. Mariana Erofeeva (MD, PhD); Director of the Laboratory

Dra. Ella Deyeva (MD, PhD); Physician, Principal Investigator

Dra. Elena Esaulenka (MD, PhD); Director of the Department of Chronic Viral Hepatitis

Dra. Olesya Nikitina (MD, PhD); Co-investigator

Ms. Anna Shelesthova (RN); Senior Nurse

Roszdravnadzor Main Office:

Dr. Yuri Afonchikov (MD, PhD); Head of Clinical Trials Control Department; Lead inspector

Dr. Evgeny Rogov (MD, PhD, JD); Deputy Head of Clinical Trials Control Department; Co-inspector



EU Observer:

Dr Frans van Andel (PhD)

Legal basis and administrative aspects of the inspection

The inspection was set up under the responsibility of the St Petersburg Regional Office of Roszdravnadzor (RZN).

The legal basis for this inspection is decision number 4855445 by the State Prosecution Office in Moscow. Details of the inspection were sent to the institute by the RZN Moscow office in advance of the inspection.

During the opening meeting of the inspection at the office of the Director of the institute, Professor Kiselev, it appeared that the institute had never been inspected by RZN. However, an FDA inspection took place several years ago and no major violations in GCP were found. An IMCT was inspected at the time, sponsor Pasteur Merieux.

The inspection comprised all facilities of the institute at various departments (chronic viruses, influenza, hepatitis), the central laboratory, rooms for ambulatory treatment of patients as well as the archives.

The Research Institute of Influenza

The main task of the Research Institute of Influenza is to serve as the national reference centre for detecting influenza strains and developing and testing vaccines for its treatment in the RF. These vaccines are primarily developed for the Russian population, but some of them have also been used internationally. The institute does not manufacture vaccines itself and this is done at various sites in the country (e.g. Novosibirsk). The centre is the only scientific centre of its kind in the RF. It receives its funding from the Russian Ministry of Health (MOH) and employs approximately 400 staff. The Centre is a WHO Collaborating Centre for Influenza Research and maintains a good working collaboration with the international scientific community in influenza research in the EU and USA. The Centre participates in various international research programmes and is a collaborator in the frame of the FP7 programme sponsored by the EC. In addition to influenza, the institute focuses its research efforts on respiratory viruses, encephalitis, anti-viral drugs for children and genetic engineering.

The inspection started in the office of the Director with assessing formal administrative procedures such as proving the legitimation of inspectors and inspection, presenting the inspection programme objectives and timetable and requesting full cooperation with the inspection. It appeared the management of the hospital was well briefed about the inspection and full cooperation was granted by all staff members.

Then the inspectors checked the general legal documents concerning the institute's accreditation to conduct clinical trials.

An inspection was carried out of all facilities of the institute including various departments (chronic viruses, influenza, hepatitis), the central laboratory, rooms for ambulatory treatment of patients as well as the archives. The institute does not have in-patients beds. The facilities are available in different buildings and appeared to be in a good state of affairs with bright



localities and new state-of-the-art equipment in the laboratory and patient treatment rooms (although the exterior of some of the buildings needs some major renovation).

At the outset of the inspection of the facilities, the inspectors ensured themselves that the legal requirements to conduct clinical trials in the institute were fulfilled, such as the Principal Investigator and staff having the necessary qualifications, the facilities being appropriate to accommodate study participants, patients insured appropriately and the required equipment for study conduct available and in good working order. Special attention was given to the proper storage of the IMPs (i.e. temperature of refrigerators and storage conditions).

Inspections were carried out of maintenance reports of all equipment such as refrigerators, centrifuges etc. In all instances, equipment was calibrated and reports available for 2011 and copies of these reports included in the trial documentation.

Inspection of trials

An overview was presented of completed and on-going trials at the institute as follows:

- Completed trials 2009-2011 (three years): total 24; 13 bioequivalence studies, 5 Phase I, 3 Phase II, 2 Phase III, 1 Phase IV;
- On-going trials: total 6; 5 bioequivalence, 1 Phase I.

Most of these trials concerned bioequivalence studies of anti-viral medication. For these studies approval is needed by the MOH in Moscow as well as the local IRB. Four trials were checked for evidence of approval (MOH and IRB) and this information was indeed available in the documentation presented.

A selection was made to review one bioequivalence trial. The rationale for selecting this trial was that if GCP violations are to be found, according to RZN, these will probably most likely be in local trials and not international ones.

The trial (Number 11-14R) was "A randomized bioequivalence trial of Lorista (manufacturer Krka, Slovenia) compared to Gizaar forte (manufacturer MSD)". Sponsor of the project was Krka and PI Dra. Mariana Erofeeva.

The inspectors carried out an assessment of the following study documentation:

- All Case Report Forms (CRFs)
- All Written Informed Consent Forms
- The Investigator Site File, including the favourable study approvals of the Institutional Ethics Committee (IRB) and the Ethics Council (of the MoH), study protocol, Investigators brochure, Safety reporting
- The Approval from the RZN
- All Drug accountability records
- The Monitoring log
- The System for the management of biological samples
- The Source data verification, including all recorded ECGs, clinical laboratory results, medical history
- All Trial subject data.

With respect to the trial, the inspectors concluded that there were no protocol deviations and that the study patient enrolment of 34 patients in total was developing according to plan. This study did not report untoward side-effects of the treatment.



A visit was paid to the office of the **Institutional Ethics Committee (IRB)**, dealing with issues of facilitating clinical trials in the hospital.

The activities of the IRB are regulated by order 289 of 26th of September 2011 issued by the MoH. The present IRB consists of 12 members as follows:

- (1) Chief Physician
- (2) Three Heads of Departments
- (3) Head PhD Council
- (4) Two Professors of Medicine of virology
- (5) Infection specialist
- (6) Laboratory staff member
- (7) Specialist in documentation
- (8) External person (bacteriologist)
- (9) Lawyer.

A detailed written Statute of the IRB is on file, as well as a description of the working procedures. All trials checked contained the consent given by the MOH as well as a decision taken by the IRB.

As described in the "Law on Circulation of Medicines" (Federal Law 61), for all international and local trials the Ethics Council (of the MOH) needs to give permission following application by the sponsor of the trial. Only if permission is granted by the MOH, a local IRB can act accordingly by approving (or not) to conduct a trial in the hospital.

Generally, decisions are prepared by one member of the IRB. Decisions of the IRB are always based on a majority vote of the council (i.e. 6 members plus one need to be in favour of a decision).

Without a favourable approval of the institute's IRB, no clinical trial will be conducted, even if the Ethics Council (of the MOH) has approved the study.

Conclusions

At the institute there is extensive experience with trials in all phases of development from bioequivalence to Phase I to IV studies. The institute is a respected member of the international community in the field of influenza research and acts as a WHO Collaborating Centre.

The institute does not have in-patient beds and its primary activity is research (as opposed to other facilities inspected in the frame of this EC project, which were hospitals with a prime task to treat patients).

The prime focus on research in combination with the respected status of the institute in the international research community may be an explanation why in general terms the documentation checked on completed and on-going trials was in very good order, both at the various Departments where on-going trials are taking place as well as the archives, where information can be found on completed trials.

It was apparent that there is extensive experience at the institute with the application of ICH-GCP rules. Although the RF uses its own set of GCP rules called "Rules for Clinical Practice", in fact ICH-GCP rules are followed and no evidence could be found at the institute that this is not the case.



The results of the inspection are not surprising in the light of the fact that the institute is a prime international scientific centre in the field of influenza research and thus has adequate knowledge about how to conduct clinical trials according to ICH-GCP.

Based on the inspection of the Research Institute of Influenza in St Petersburg, RF, it can be concluded that the implementation of assessed trials is in compliance with ICH-GCP rules.

