A NEWSLETTER FROM
MANNHEIMER SWARTLING

AUGUST 2010

Newsletter Russia

FOR ADDITIONAL INFORMATION PLEASE CONTACT:

Dr. Christoph Dengler
chd@msa.se
tel: +7 (921) 181 66 78

MOSCOW
Romanov Dvor Business Center,
Romanov per. 4,
125009 Moscow
tel: +7 (495) 380 32 80

ST. PETERSBURG
Sweden House
Malaya Konyushennaya str., 1/3 A
191186 St.Petersburg
tel: +7 (812) 335 23 00

THIS NEWSLETTER IS DISTRIBUTED SOLELY FOR INFORMATIONAL PURPOSES AND SHOULD NOT BE REGARDED AS LEGAL ADVICE. THE NEWSLETTER MAY BE QUOTED AS LONG AS THE SOURCE IS SPECIFIED.

New law – new problem: New Russian Drug Act and foreign clinical trials – are they accepted?

I. SUMMARY

The new Russian Federal Act No. 61-FZ "On the Circulation of Medicinal Products" of 12 April 2010 (the "Act") enters into force on 1 September. It does not accept the results of international clinical trials which are conducted entirely outside of Russia, even if they were conducted in conformity with Good Clinical Practice (GCP). The results of GCP-compliant international trials are only accepted if they were conducted at least in part in Russia. This restriction leads to either Russian clinical trial sites being included in ongoing international trials or to at least a partial duplication of clinical trials to obtain a marketing authorization in Russia.

II. INTRODUCTION:

The development of a pharmaceutical drug is a time-consuming, difficult and expensive process costing up to one billion US Dollars or even more for a new drug. The bulk of the research and development expenses is caused by the full series of clinical trials. These trials, in particular phase III trials, entail as a rule international multi-centre trials in numerous countries.

MANNHEIMER SWARTLING

It is a common international practice in various countries for the results of such international multi-centre trials to be mutually accepted by regulatory authorities in such countries if certain requirements are met, and these include the following[1]: To begin with, clinical trials must be conducted in compliance with the standards of the International Conference on Harmonisation (ICH) and GCP[2]. These regulations provide a unified standard for the European Union, Japan, the United States, Australia, Canada and others. Hence, the countries following the guidelines follow the same standards. Secondly, independent official inspections secure, or at least are to secure, in practice the proper application of these uniform standards. Thus, to verify compliance with GCP, clinical trials sites, documents, records, quality assurance agreements and the like are inspected. This includes the design of the study and the favourable opinions of the ethics committees being reviewed. Likewise, official reviews may be made by the competent authority with respect to the manufacture of the study drug to confirm proper adherence to Good Manufacturing Practice. Furthermore, with respect to pre-clinical data, authorities may investigate conformity with Good Laboratory Practice. The final approving inspection report or inspection certificate helps the results of a foreign clinical trial to be accepted.

Thus, for example, in the European Community, according to directive 2001/20/EC an inspection of GCP compliance carried out by member states is carried out on behalf of the community and the results are accepted by all member states.

It is also necessary to review whether foreign clinical data can be extrapolated to the population of the relevant country for which the applicant seeks a marketing authorization by relying in part on such foreign data as a basis for its registration.[3] This reflects the concern that ethnic differences may affect the medication's safety, efficacy, dosage and dose regimen.

In Russia, clinical trials need to be conducted in conformity with GCP, i.e. the National Standard of the Russian Federation GOST-R 52379-2005 Good Clinical Practice (Надлежащая клиническая практика). This has been confirmed by Order No. 232-st of the Federal Agency for Technical Regulations and Metrology of 27 September 2005. This document is identical to the Consolidated Guideline on Good Clinical Practice issued by the International Conference on Harmonization of Technical Requirements to Registration of Pharmaceuticals for Human Use (ICH GCP). However, the Act draws a distinct line between clinical trials conducted outside of Russia and accepts their results only in certain circumstances, as set forth below.

III. SITUATION IN RUSSIA

1. CURRENT SITUATION UNTIL 1 SEPTEMBER 2010

In the current Federal act No. 86-FZ "On Medicines" of 22 June 1998, which will be replaced by the Act, the results of GCP-compliant international clinical trials can be accepted in Russia, even though conducted outside of Russia. Para. 9 of section 19 of the act "On Medicines" merely states that the applicant shall submit to the competent Federal authority in the application for a marketing authorization, amongst other documents, the "results of clinical trials of the medicinal product".

2. LEGISLATIVE PROCEDURE OF THE ACT

Already in the course of the legislative process of drafting the Act, the Russian Association of Clinical Trials Organizations ("ACTO") has cautioned Russian legislators against refusing to accept the results of internationally conducted studies, even if they are conducted in line with GCP. Otherwise, companies with a global presence might be forced to duplicate their studies. Despite the concerns raised by ACTO, the Russian lawmakers did not follow its suggestions.

3. NEW ACT AND CLINICAL TRIALS

The Act for the first time provides for a clear definition of clinical trials and even of international multi-centre clinical trials. In para. 41 of section 4 of the Act a clinical trial of a medicinal product (клиническое исследование лекарственного препарата) is defined as *"an investigation of diagnostic, therapeutic, prophylactic, pharmacological properties of a medicinal product in the process of its application to human or animal subjects, including the process of absorption, distribution, metabolism and excretion, through the use of scientific methods of assessment for the purposes of gaining evidence about the safety, quality and efficacy of a medicinal product, as well as data regarding adverse reaction to the use of the medicinal product by humans or animals and concerning potential interactions with other drugs and/or food;"*

In para. 43 of the same section 4 it is stated that an international multi-centre clinical trial is

"a clinical trial of a medicinal product for medical use which is conducted by a drug developer in different countries based on a uniform study protocol for the clinical trial of the medicinal product."

Moreover, the Act explicitly provides for international multi-centre trials to be covered by an authorization process supervised by the Federal regulatory authority, namely the Federal Service on Surveillance in Healthcare and Social Development, also known as Roszdravnadzor (Росздравнадзор), see section 39 of the Act.

Interestingly, the process of applying for a marketing authorization is already started as soon as the applicant submits to the Russian regulatory authorities the results of the favourable expert evaluation and the opinion of the ethics committee, which are necessary to allow the conduct of clinical trials, see section 13 para. 3 of the Act. The time period for conducting the clinical trial is not calculated by stopping the clock for deadlines of the authorization procedure as a whole. Hence, the Act assumes as a general rule that, when an application is made for a marketing authorization, clinical trials still need to be conducted in Russia. It shall be noted that according to section 18 of the Act the applicant shall submit the registration dossier to the Russian regulatory authorities in the form of Roszdravnadzor, which competence in the matter could be delegated elsewhere within the control of the Ministry of Public Health and Social Development of the Russian Federation (Минздравсоцразвития РФ). Such dossier has to contain the pre-clinical data, the draft study protocol of the clinical trial to be conducted, the investigator's brochure, the informed consent of the study subjects etc.

An exception to this rule of submitting the outline of a future clinical trial is the submission of the results of such international multi-centre trials which "have been in part conducted on the territory of the Russian Federation". Such results may be included already in the registration dossier to be submitted in the application of the marketing application, see sections 14 para. 2.1)b) and 18 para 3.15) of the Act. This means that only those international trials are accepted which have included Russia within the trial on the basis

[1] For the US and the practice of the Food and Drug Administration (FDA) see in particular 21 CFR 312.120.

[2] See for example 21 CFR 312.120(c)(1).

[3] See in detail ICH Topic E 5 (R1) Ethnic Factors in the Acceptability of Foreign Clinical Data.

of a uniform study protocol. The Act leaves open how many clinical trial sites must be included. It may be argued that the inclusion of one clinical trial site might be sufficient. However, some clinical research organisations recommend including at least two clinical trial sites in Russia to reduce any risk that the results of merely one site are considered insufficient to protect the health of Russian citizens. Others advise that a single centre might be adequate if the percentage of Russian patients is sufficient relative to the overall number of patients participating in the study.[4]

The purpose of the new regulation is that clinical trials should be conducted as from now at least partly in Russia. This seems to be the manifestation of the overall strategy of Russian government to create more business revenues and high-tech knowledge in the country. Foreign companies should not only deliver finished products to Russia but should (be forced to) "localize" a part of their value chain in Russia. This finds its expression in section 38 para. 1.1 of the Law. This provision prohibits clinical trials with respect to safety and tolerability with healthy volunteers if a new study drug to be tested is produced outside the Russian Federation. Thus, clinical trials with healthy volunteers (as a rule phase I) targeted to evaluate safety and tolerability may only be conducted in Russia with locally produced study drugs. However, this may also be seen as protecting the healthy volunteers in the case of first study drug administration in human beings.

Moreover, it is evident that Russia wishes to have more control over drugs entering its market and desires to be more involved in early assessment and testing of the drug's safety, efficacy and quality.

Following the requirements of the Act, if international clinical trials are conducted without Russia's participation, their results will not be accepted in an application for a marketing authorization. Nevertheless, the applicant seems to have the discretion to include such data in his application for the marketing authorization, section 18 para. 4. Moreover, ICH requires in any event the inclusion of summaries of clinical trials previously conducted in the documents submitted for a marketing authorization (with international companies following the ICH guidelines)[5]. This seems to extend to the willingness of the authorities to review a rather detailed description of all clinical trials.

4. ETHICAL PROBLEMS

As the Act does not accept the results of international clinical trials conducted without including Russia, it leads necessarily to an additional conduct of clinical trials in Russia. This applies also to pivotal studies and might raise ethical questions:

a) Firstly, any repetition of clinical trials may mean that data already gained is unnecessarily duplicated.

   The Helsinki Declaration developed by the World Medical Association emphasizes in section 21 of its chapter B. Principles for all Medical Research that *"medical research involving human subjects may only be conducted if the importance of the objective outweighs the inherent risks and burdens to the research subjects."*

   The same basic ethic principle is laid down in directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the community code relating to medicinal products for human use. Even though not applicable in Russia, the directive reflects common ethical standards. It states in its section (10) of its preamble that *"there are reasons of public policy for not conducting repetitive tests on humans or animals without over-riding cause."*

b) Secondly, any repetition may lead to a delay in receiving marketing authorization for innovative products and result in a delayed access of patients to advanced, even life saving drugs. This concern is shared by the All-Russian public organisation "League of the Protectors of Patients". In its conclusion about the draft Act, the League states that the process provided for in the Act contradicts the worldwide practice of accepting the results of international trials conducted in conformity with GCP. Moreover, the League complains that such approach creates an administrative hurdle which delays the patients' access to the drug by an unjustifiably long period.

IV. CO-OPERATION WITH EUROPEAN UNION AND US

Interestingly, the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA) have agreed jointly to collaborate on international GCP inspections in light of an increasing number of clinical trials outside the "traditional Western European and North American research areas".[6] In the EMA strategy paper for acceptance of clinical trials conducted in third countries of December 2008 the EMA wishes to monitor in a more transparent way compliance with GCP and ethical standards in the process of reviewing applications for marketing authorization.

In the EMA's draft "Reflection paper on ethical and GCP aspects of clinical trials conducted in third countries for evaluation in marketing authorisation applications for medicines for human use, submitted to the EMA", published on 28 May 2010, the following is stated:

The best approach to achieving these objectives is to ensure that a robust framework exists for the oversight and conduct of clinical trials, no matter where in the world the clinical investigators' sites are located and patients recruited. An international network of regulators from all countries involved, working together to share best practices, experiences and information and working to standards agreed and recognized by all, can provide an effective platform for such a robust framework. The EMA will seek to build and extend its relationship with regulators in all parts of the world and with international organisations in order to work to achieve this.

Thus, it might be expected that the regulatory authorities, i.e. the EMA, the FDA and their Russian colleagues will jointly elaborate more precise criteria and standards on the extent to which clinical trials would need to be repeated in Russia due to the non-acceptance of the results of certain international trials.

Until such guidance is given, companies will have to seek their own way in the current situation.

V. CONCLUSIONS

The Act creates uncertainties as to ongoing or completed clinical trials which have not included Russia. The Act neither differenti-ates explicitly between the various phases I to III of clinical trials nor provides any guideline as to which trials must be repeated to get proper marketing authorization. As a delay in granting the marketing authorization might result from duplicating clinical trials, a drug developing company might further investigate the following options

[4] Some mention as rule of thumb that the percentage should not drop below a percentage of ten percent or at least forty to fifty patients, depending on the overall amount included in the study.

[5] Even though Russia is not a participant of ICH, international companies follow their guidelines and recommendations; in this case at hand see in detail the Common Technical Document for the Registration of Pharmaceuticals for Human Use – Efficacy – M4E(R1) and Clinical Overview and Clinical Summary of Module 2 Module 5: Clinical Study Reports as well as ICH E9.

[6] See the webside of EMA with further information http://www.ema.europa.eu/Inspections/GCPgeneral.html

mentioned below. However, they depend on whether the international clinical trial at hand is still ongoing or already completed:

1) INCLUSION IN ONGOING TRIALS:
A company sponsoring trials might include Russia in ongoing clinical trials with at least one, or preferably two, clinical trial sites in Russia. This seems to be the easiest way, if the same study protocol is accepted by Russian authorities and sufficient time is left.

2) CLINICAL TRIALS PHASE III IN RUSSIA:
If there is no ongoing trial which could include Russian trial sites, then it might be sufficient to start a (new) double-blind placebo-controlled phase III trial in Russia instead of re-conducting the entire cycle of clinical studies. In such event it seems advisable to obtain the explicit prior agreement of the regulatory authorities to the number of patients to be included in such trial to make sure that the quantity of patients is deemed sufficient to obtain the marketing authorization in Russia.

3) BRIDGING STUDIES:
Alternatively, if the trial has been completed and it is therefore impossible to include Russian trial sites in an ongoing clinical trial, a company might conduct (new) studies in Russia which would be analogous to the kind of studies known as bridging studies (see ICH E5) to minimize the need to conduct a full cycle of clinical studies. Their objective would be to minimize duplication of clinical data, as well as to facilitate the acceptability of foreign clinical data and allow their extrapolation to Russia. This approach might help avoiding any repetition of the entire clinical drug development program in Russia.

Currently, it is difficult to say which option is preferable and will be accepted by Russian authorities. This uncertainty might create a certain weakness for corruption in the handling of applications.

VI. RESULT

The new Act does not accept international clinical trials conducted entirely outside of Russia, even though conducted in conformity with GCP. It merely accepts such results of international trials which have been in part conducted in Russia. This requires inclusion of preferably two Russian clinical trial sites into ongoing and future international clinical trials for the results of such clinical trials to be accepted in Russia. Otherwise, clinical trials would need to be repeated to obtain a marketing authorization in Russia. However, it remains unclear to what extent additional studies must be conducted. A pharmaceutical company may offer various alternatives to satisfy Russian regulatory authorities as described above.

Mannheimer Swartling is the leading business law firm in the Nordic region (Law firm of the Year-Northern Europe, PLC Which Lawyer-2009). The firm is a full service firm with an extensive international practice. The firm has approximately 650 employees, of which approximately 450 are lawyers.

Mannheimer Swartling has offices in Stockholm, Göteborg, Malmö, Helsingborg, Frankfurt, Berlin, Moscow, St. Petersburg, Shanghai, Hong Kong, Brussels and New York.

Mannheimer Swartling has a long history in Russia. The firm opened its first Russian office in 1990 and was the first European law firm which established itself in what was then the Union of Soviet Socialist Republics. The firm's Russian practice of about 50 lawyers involves a broad range of advisory and transactional work and has two full service offices in Russia located in Moscow and St. Petersburg.

MANNHEIMER SWARTLING