

Medical writing in the Russian Federation: Promises and pitfalls

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Abstract

More and more clinical studies are taking place in Russia, making it an attractive market for medical writing. In 2011, the Ministry of Healthcare of the Russian Federation approved over 550 new clinical studies of all types, a 16% increase over the previous year. Currently, the Russian government is making huge investments in its infrastructure for drug development. Demand for medical writing is high in the rapidly growing sector of biotechnology in Russia. Because there are some differences in local requirements compared to the EU or USA, many specific regulatory aspects have to be considered by medical writers in Russia.

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More and more clinical studies are taking place in Russia, making it an attractive market for medical writing. In 2011, the Ministry of Healthcare of the Russian Federation (MoH) approved over 550 new clinical studies of all types, a 16% increase over the previous year, while in 2012 approvals of new studies for the year increased by 20%. Over 70% of all approved studies in Russia are either multinational studies or local studies sponsored by foreign companies.¹

Key Russian regulatory documents

Russian Federal Law #61 on 'On Circulation of Medicines', which came into force on 12 April 2010, controls all processes related to drug circulation, namely, drug manufacturing, nonclinical and clinical development, monitoring of drug safety, and state control and registration of a drug. Another important regulatory document providing guidance on conducting clinical studies in Russia is the National Standard of the Russian Federation, GOST - 52379-2005, which is an essentially translated version of International Conference on Harmonisation (ICH) Good Clinical Practice (GCP). It stipulates that all clinical studies in the

Russian Federation must be performed in accordance with GCP.²

When the clinical part of the drug development has been successfully completed in a study population omitting Russian patients, Federal Law #61 stipulates that a controlled, evidence-based confirmative study must be performed in Russia as part of the drug registration process. To justify this requirement, Russian lawmakers point to differences in the characteristics of the country's population and imperfections in the legislation for the acceptance of foreign studies. Therefore, a phase III study must be conducted in Russia, and this is not considered a violation of GCP. However, no specific national guidelines on the minimum acceptable number of patients or the choice of primary endpoints have been developed.

Therefore, medical writers must study all available ICH general guidelines on study design and specific guidelines issued by regulatory agencies (e.g. FDA, EMA, and Health Canada) and make a scientific judgement on which guideline is applicable to a particular study. After that, the medical writer must work closely with statisticians to create study designs that will meet the study objectives within the study's budget. Validated software for sample size calculation and publically available study results must be taken into consideration to determine the sample size. In our experience, and according to verbal communication with experts from regulatory authorities in Russia, it is generally accepted that objective clinical criteria are preferred over pharmacodynamic parameters as primary endpoints, although no official guidance has been issued on this matter.

Federal Law #61 also prohibits phase I clinical studies involving healthy volunteers with 'medicinal products manufactured outside the Russian Federation'.³ Medical writers therefore have to think about alternate study designs involving patients instead of healthy volunteers as is the case for phase I studies with certain types of drugs, like antipsychotics, or anti-tumour agents.

Bioequivalence studies

Since the Russian MoH approved the guidance on conducting bioequivalence studies in 2008, the number of these studies conducted in Russia has increased almost four fold, from 85 in 2011 to 300 in 2012.¹ According to Federal Law #61, bioequivalence studies are performed to assess the extent and rate of absorption of the active substance of investigational drug in comparison with that of a drug registered in the State Drug Registry.³ For drugs possessing systemic effects after extravascular administration (e.g. oral, topical, or rectal), pharmacokinetic equivalence between a generic and registered drug is a guarantee of the drug's therapeutic equivalence and similar safety profile. The requirements for bioequivalence issued by the MoH differ from those issued by other regulatory agencies (e.g. EMA, FDA, and Health Canada) in the following aspects:

- Russian bioequivalence studies may only be performed in people aged 18–45 years, and the minimum number of volunteers should be at least 18.
- Medicines administered by the parenteral route, via inhalation, and by the enteral route as solutions need to undergo prior therapeutic equivalence studies.
- The washout period between treatment periods has to be at least six half-lives of the drug substance. The acceptable interval between blood samplings is at least four half-lives of the drug substance.⁴ According to the WHO, the minimum required washout period has to be five half-lives of the drug substance or at least 7 days.⁵ Health Canada requires this period to be 10 half-lives but not more than 4 weeks.⁶

When a foreign sponsor wants to conduct a bioequivalence study in Russia and provides a protocol written in accordance with the European or the American guidelines, local medical writers must adapt the protocol to the national legislation and requirements. In addition, attention should be given to the nonclinical comparative toxicity studies of the generic and original drug. These studies are generally demanded by the regulatory agency and should be described in the investigator's brochure and protocol. A renewal of the guidance on bioequivalence is expected, but the impact of the proposed changes cannot be assessed because the draft version has not been made publically available.

Another problematic area is writing protocols on biosimilar drugs. Currently, many companies are developing such drugs and are interested in developing them in Russia. Again, the first challenge is

study design and medical writing for such studies because there is no national guidance on pre-clinical or clinical development programs for biologicals. Moreover, current Russian legislation does not give a definition of a biosimilar drug.⁷ Medical writing on biosimilars is complicated and requires multiparty knowledge. Because there are no specific national guidelines on biosimilars in Russia, medical writers have been referring to EMA's general and product-specific guidelines like 'Guideline on similar biological medicinal products containing monoclonal antibodies' for development of clinical and preclinical programs. The EMA's guidelines are quite precise and stringent, so compliance with these provides a better chance of approval of a drug in Russia. Currently, several clinical studies of biosimilars and biobetters from local and foreign pharmaceutical companies have been approved by the Russian MoH and are on-going.

While planning a clinical study to show comparability of pharmacodynamics and pharmacokinetics of a biosimilar and the original drug, the following aspects must be considered:

- Choice of the study population: healthy volunteers or patients?
- Choice of pharmacokinetic parameters of interest
- Availability of relevant pharmacodynamic markers of efficacy
- Determination of a required sample size
- Study cost, including the cost of the original drug

To design a pivotal study to show the similarity of a biosimilar and the original drug, the availability of relevant pharmacodynamic markers of efficacy need to be considered as stated in the EMA's guideline.

Orphan drugs

Absence of orphan drug status is another problem that we face in Russia during the drug development process. The terms of orphan disease and orphan status were first defined in Russian legislation in 2011. However, no initiatives have yet been taken to promote such product discovery by Russian companies. Developing an orphan drug in Russia is challenging because the number of trial participants cannot be lowered. Statistically, there are no exceptions for an orphan drug study, and as many patients as a regular study must be enrolled.

Expert advice from regulatory authorities in Russia

Another problem we face when developing clinical study programs is the lack of scientific advice from

regulatory authorities in Russia. To obtain the opinions of regulatory experts, sponsors and contract research organisations often have to resort to unofficial expert recommendations from the MoH. This expert opinion obtained in this manner may not be reliable and is not supported by any written documents. In addition, different experts may have different point of views on the same issues.

To obtain the official opinion of regulatory authorities in Russia one must apply for approval of a clinical study that takes 35 working days. In case of refusal of permission to conduct a clinical study, the authorities issue a letter with recommendations for modifications in the study proposal. But even after all the recommendations are accepted, the MoH is likely to issue a second list of requirements, with no guarantee of acceptance.

Unlike Russia, scientific advice is a routine practice in the USA and Europe and features such as the study design, primary endpoints, choice of control group can be disputed and a modified protocol draft can be submitted for review by the experts. When the expert joins the discussions, the sponsor can defend its point of view and provide evidence that the authorities had misunderstood or were wrong. In Russia, this situation is difficult to imagine outside an arbitration court.

Ongoing improvements to Russian regulatory requirements and infrastructure

Russia's Federal Antimonopoly Service requires that amendments to the Law #61 be introduced to simplify the procedure for registering orphan drugs. Changes to be implemented in 2013 include introducing an expedited registration procedure for orphan drugs and first-to-market generics. For orphan drugs, data obtained from pre-clinical and clinical studies conducted abroad according to Good Laboratory Practice and ICH-GCP will be acceptable in Russia.

Currently, the Russian government is investing heavily in its infrastructure for drug development. The demand for medical writers is substantial because the biotechnology sector is growing rapidly. Because Russian universities do not offer courses in medical writing, medical writers usually are medical doctors or those who have advanced degrees in

medicine or natural sciences. Typically, successful medical writers have experience in nonclinical and clinical drug development and have trained abroad in medical writing. These professionals can only gain experience by working in pharmaceutical companies or contract research organisations and, thus, are considered an extremely valuable workforce.

Conclusion

Although there are many formal barriers to conducting clinical studies in Russia, current governmental legislation has increased the demand for clinical studies conducted in Russia. Therefore, we are looking forward to improvements in the regulations and are working to elevate our medical writing to the highest international standards.

References

1. Russia, The registry of Approved Clinical Trials [Реестр выданных разрешений на проведение клинических исследований лекарственных препаратов] [homepage on the Internet]. c2011 [cited 2013 February 16]. Available from: <http://grls.rosminzdrav.ru/CIPermissionReg.aspx>
2. Russia, National Standard of the Russian Federation. GOST R 52379-2005 'Good Clinical Practice' [ГОСТ Р 52379-2005 'Качественна клиническая практика']. c2005 [cited 2013 March 14]. Available from: State Law Publisher.
3. Russia, Federal Law #61 on Circulation of Medicines [Федеральный закон от 12.04.2010 года № 61-ФЗ 'Об обращении лекарственных средств'] c2010 April 12 [cited 2013 March 14]. Available from: State Law Publisher.
4. Russia, Operating Instructions 'Execution of Good Bioequivalence Studies of Drugs' [Методические указания «Оценка биоэквивалентности лекарственных средств»], c2008 [cited 2013 March 14]. Available from: State Law Publisher.
5. World Health Organization. Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability. c2005 [cited 2013 March 14]. Available from: http://www.who.int/medicines/services/expertcommittees/pharmprep/QAS04_093Rev4_final.pdf
6. Health Canada. Comparative bioavailability standards: formulations used for systemic effects. c2012. Available from: http://www.learnandconfirm.ca/resources/gd_standards_ld_normes-eng.pdf
7. OCT attending and presenting at the Adam Smith Conference in Moscow [homepage on the Internet]. c2012 [cited 2013 March 14]. Available from: <http://www.oct-clinicalstudies.com/?q=content/oct-attending-and-presenting-adam-smith-conference-moscow>.

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