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RESEARCH ARTICLE

ROLE OF EURASIAN ECONOMIC COMMISSION IN GLOBAL CLINICAL RESEARCH AND DEVELOPMENT

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ABSTRACT

Background: Eurasian Economic Commission (EEC) was established in 2014 by Belarus, Kazakhstan, Russia, Armenia and Kyrgyzstanas a regulatory body of the Eurasian Economic Union (EAEU).EEC's goal is to unite participated states under the uniformed regulations for the development, registration, production, and circulation of medical products.In 2016, the EEC created and released about 40 regulatory documents for medical drugs and devices and half are currently under revision.

Rationale: The United States Food and Drug Administration (FDA), European Medicines Agency (EMA), Japanese Ministry of Health, Labor and Welfare (MHLW) and other international organizations constantly revise and update regulations and guidelines for development and registration of medical products. They admit that existing process is long, expensive, and contains multiple gaps that motivate to look aggressively for novel approaches in clinical research. Therefore, it is an interest to understand if recently formed EEC has developed innovative ways to build pharmaceutical industry in the EAEU.

Objective: The aim of this paper is to understandif EEC'sprogression in building domestic pharmaceutical industry carries scientific values and novel approaches that can be sharedwith theother global players in the field of clinical research.

Method: To review and evaluate EEC's signed-off regulationsin terms of consistency with theworld-wide standards, and/or possession of innovative scientific approaches.

Conclusion: The developed by EEC regulations are consistent with international industry in terms ofconduct and supervision of clinical trials. There is little progress regarding the discovery and development of new medical products, possiblybecause of lack of scientific and analytical background underlying committed clinical research. There is no intention ofaligning with the global movement towards developing innovative approaches in clinical research.The author proposed some thoughts about alternativesthat could have been considered to build up anadvanced pharmaceutical industryin the EAEU.

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INTRODUCTION

Federal Law No. 61-FZ "On Circulation of Medicines" is the major legislation that regulates pharmaceutical industry in Russia from 2010.(The Russian Federation, 2010)In 2014, Pharma 2020 Russian Federation initiative set up a goal to develop innovative pharmaceutical and medical industry in Russia that will be in alignment with the world-wide standards.(http://pharma-2020.ru/) The expected increase in domestically manufactured medical products' market share should be from 22% of sales in 2010 to 50% by 2020 where at least 90% of drugs from the List of Vital and Essential Medicines (ZHNVLP) will be manufactured in Russia. (http://pharma-2020.ru/) However, from 2014 to 2016, there was a decrease in Russian-/Russian-foreign partnership manufactured drugs from 68% to 65%. (International Society for Pharmacoeconomics and Outcomes Research, 2016) This fact was explained by political and economic problems. Theother reasons have not beeninvestigated. The author hypothesized that the newly developed regulations worked only for conduct and supervision of clinical trials, and scientific background underneath the developed regulations still has to be understood. The Russian Federation,the Republic Armenia, the Republic of Belarus, the Republic of Kazakhstan is member states of the Eurasian Economic Union (EAEU) with a population of 182.7 million people overall. (Eurasian Economic Commission: Eurasian Economic Integration: Facts And Figures, 2015)In 2014, Eurasian Economic Commission (EEC) was formed as a permanent regulatory body of EAEU.

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(Eurasian Economic Commission: Eurasian Economic Integration: Facts and Figures, 2015; http://www.eurasian commission.org/en/Pages/ default.aspx) The first regulation on clinical studies was published in December 2015 and included detailed rules for development and registration of medical products in the EAEU.(The Eurasian Economic Union: Rules for registration and examination of human medicines, 2015)Since that, there has been significant progress toward developing the legislation on pharmaceutical industry in the EAEU.Global medical and public health authorities are facing potential breakthrough in clinical research using novel approaches and advanced technologies. It was expected that EEC had choseninnovative approach based on the historical, economical, and technological infrastructure of the Eurasian region to progress fast in the public health arena.The aim of this paper was to evaluate if EEC's signed-off regulations are consistent with the world-wide standards or represent an innovative approach suitable to the Eurasian region. The clear vision of chosen direction will help to understand what role EECwill take among the global key stakeholders, like FDA, EMA, or JMHLW.

Launch of EEC regulations

Major Legislation to Regulate Pharmaceutical Industry in Russia

In September, 2010, the Russian government enacted a Federal Law No. 61-FZ "On Circulation of Medicines" to regulate the pharmaceutical industry. (The Russian Federation, Federal Law #61 on Circulation of Medicines, 2010) The Ministry of Health and Social Development (MoH) became the main regulatory authority for clinical trials. The National Ethics Council (NEC) and the Scientific Center for Expertise on Medical Application Products are two parts of MoH. To be approved, all applications must be submitted to MoH and be signed off by both NEC and Scientific Center. Local Ethics Committees (LECs) participate in the process along with the NEC in parallel, or in succession manner. Documentation on all types of safety reporting must be submitted to both, the MoH and the Federal Service on Surveillance in Healthcare and Social Development of the Russian Federation (Roszdravnadzor/ RZN). Safety and pharmacovigilance is the main responsibility of RZN. Statement of Intent on Collaboration was signed between the FDA and RZN in 2010, and all RZN inspectors were trained by the FDA. (Statement of Intent on Collaboration, 2010) The progress of a new law can be recognized with the two major points. First, new regulations required that Principle Investigators had at least five years of trial experience and be certified specialists in the classification of diseases. It means that a highly educated and motivated medical staff well trained in Good Clinical Practices (GCP) conduct clinical trials in Russia. Second, legal protection of privacy information of clinical trial participants was a strong step forward. Article 18(6) of the Federal Law on Circulation of Medicines prohibits disclosure or use the information about the results of preclinical and clinical studies for commercial purposes or for state registration without the applicant's consent for 6 years from the date of state registration of the medicine. (The Russian Federation, Federal Law #61 on Circulation of Medicines, 2010) Along with that, the accession of Russia to the World Trade Organization (WTO) in 2012 induced further improvements of the confidentiality and personal data law to align with European legal standards. In September, 2012, the European Commission conducted a thorough analysis of Russian clinical trial regulatory system and published areport *Cooperation in the field of clinical trial.* (The Report: Cooperation in the field of clinical trial, 2012) The equivalence of the respective legislative framework for the conduct and supervision of clinical trials in the EU and Russian Federation was admitted. (The Report: Cooperation in the field of clinical trial, 2012)The respective legislation, fast recruitment rate, and lower cost attracted conducting clinical trials in Russia. In 2016, 71 of 105 new drugs approved by EMA were tested in Russian sites according to the orange paper prepared by Synergy Research Group. (Orange Paper for 2016)

The political crises and new sanctions against Russia promptedRussian governmentto push local production of medicines in Russia as was expressed in the resolution that took effect in January 1, 2017. Comparing second quarter of 2017 with the second quarter of 2016, there was 32% decrease in the number of bioequivalence studies (BE), and 25% decrease in local clinical trials (LCT) in Russia. (Orange Paper for 2017)The data suggeststhat new regulatory guidelines were developed in terms of "conduct" of clinical trials, but not in terms of "discovery" and "development" of the new products.

EAEU Legislation to Regulate Pharmaceutical Industry

Eurasian Economic Commission (EEC) was established in 2014 with a goal to develop unified rules for the EAEU to regulate common pharmaceutical market of medicines that started operating from January 1, 2017. The Rules include conduct of clinical trials, manufacturing, registration and examination, requirements for labeling and instructions for medical use. (Eurasian Economic Commission: Eurasian Economic Integration, 2015; http://www.eurasiancommission. org/en/Pages/default.aspx; The Eurasian Economic Union: Rules for registration and examination of human medicines, 2015) The Rulesspecify detailed requirements for submission an application for registration, and format and content of the registration dossiers for various groups of medicines. (Eurasian Economic Commission: Eurasian Economic Integration, 2015; http://www.eurasiancommission.org/en/Pages/default.aspx;The Eurasian Economic Union: Rules for registration and examination of human medicines, 2015)The basis for the Rules was taken from the best international practices, particularly *The International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use* (*ICH*) withadditional recommendations from the experts of the qualified authorities and representatives of business communities of the EAEU Member States. (Eurasian Economic Commission: Eurasian Economic Integration, 2015; http://www.eurasiancommission.org/en/Pages/default.aspx;The Eurasian Economic Union: Rules for registration and examination of human medicines, 2015) In other words, the Good Manufacturing Practice (GMP) (EEC Council Decision No. 77), Good Clinical Practice (GCP) (EEC Council Decision No. 79), Good Distribution Practice (GDP) (EEC Council Decision No. 80), Good Pharmacovigilance Practice (GPP) (EEC Council Decision No. 87), etc. are well known ICH guidelines that were translated, reviewed and adapted by EEC to ensure that safe, effective and good quality medicines will be successfully circulated within the whole Union.

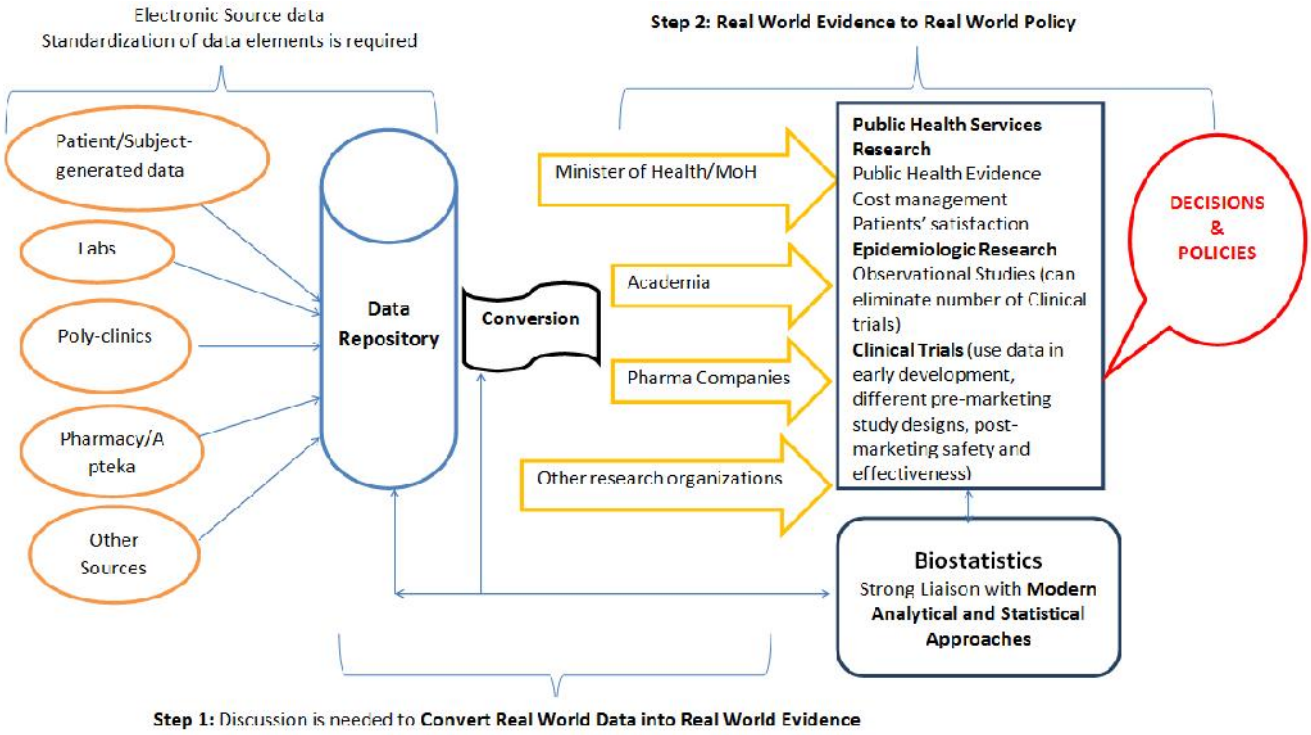

Figure 1. Schema of Evidence-Based Public Health

DISCUSSION

The EEC regulatory system must be in alignment with the international standards because the same international guidelines were translated and reviewed by the experts from the committeefor further adaption by the member states of the EAEU. However, such approach has some pitfalls. First, there are possible mistakes in translation and interpretation of westernized policies just by chance. Second, understanding of underlying rationale of the international requirements requires knowledge of the evolution how and why they were developed. Third, the translated guidelines are living documents that are constantly under revision and updates by the experts from different scientific fields. It means that in addition to business experts worked in the EEC, there should have beenmedical, biostatistical and public health experts with practical expertise and strong scientific background in the field of clinical trials in orderto give confidence in the re-evaluation of the criteria for safety, efficacy and quality of the developing by EEAU medical product. Finally, in terms of business organization, it seems that there is no separation for review and approval of generics inside MoH or other similar authorities from EAEU. In other words, having a goal to increasedomestic production of generics, there is no stand alone "office of generics". The well-known offices of "fast tracks" that concentrate on fast approval of generics and/or other medicine under demand (drugs for HIV, cancer, etc.) are proven to be efficient and productive providing short cut to the market. The offices of "fast tracks" work under different (usually abbreviated) regulations and processes.

Soviet Union did not appreciatescientific value of randomized controlled trials and/or observational studies. A glance into the academic curricula of the major universities identifies missing courses in principles of research methodology, biostatistics, clinical trials, and epidemiology. For example, the Former Soviet Union defined epidemiology as a field of medical science that studies infectious diseases, and the concept of vast observational research did not and still do not exist. (VasiliyVlassov, 2000; Vasiliy V Vlassov and Kirill D Danishevskiy, 2008)Therefore, developing the Eurasian guidelines from the evolutional stand point of member states may have been unique and interesting idea. This would require a developing of novel concepts supported by scientific, clinical, and bio-statistical methodology along with advanced technological achievements of conducting clinical research. Apparently, this approach was not considered because of lack of time and investments or absence of scientific background and education in this field. From the EEC news in May 5, 2017, the Board Member (Minister) of technical regulation Valery Koreshkov said: "The Commission, together with the best experts from the five Member States of the EAEU has prepared all the necessary documents for the effective operation of the common medicines market, taking into account the world practice….They are aimed at removingadministrative barriers in manufacture and approval of medicines for circulation in the markets of the Union countries." (http://www. eurasiancommission.org/en/nae/news/Pages/5-052017.aspx) The statement admits that released regulations target manufacturing, circulation and marketing of approved medicine but not clinical research in discovery and development of innovative products. The alignment with Western standards is happening in the level of study conduct and supervision, whereasscientific aspects of study design, clinical and statistical methodology were not grasped. For example, the role of protocol writing is assigned to medical writers who are not familiar with such aspects and do not have proper scientific advice from regulatory authorities because those are not experts in this area. (Eugenia Radkova and Irina Petrova, 2016) The deficiency of highly-qualified personnel in biostatistics is clearly seen through the statistical planning of the studies, as well as final data reporting and interpretation. For example, bioequivalence studies require a minimum of 12 subjects with a statement that "calculation of sample size should be performed". (Rules for Conducting Bioequivalence Studies of Medicines of the Eurasian Economic Union, 2015)

However, the branch of the biostatistics that justifies sample size for the study based on the scientific rationale is not used or not popular because every study protocol has temptation to enroll the minimum allowed number of subjects. Data sets collected on studies with Russian patients may be requested by the authorities to reproduce the results.(Rules for Conducting Bioequivalence Studies of Medicines of the Eurasian Economic Union, 2015) However, there are no data standards like Clinical Data Interchange Standards Consortium (CDISC), orrequirements for the use of validated software for statistical analyses like SAS®. Data can be submitted in Excel (Rules for Conducting Bioequivalence Studies of Medicines of the Eurasian Economic Union, 2015) and can be analyzed in R;both are considered invalidated software systems by the FDA/EMA/JMHLW.

EEC recommendation for development of the multiple united information databases of medicines like safe and banned medicineand adverse effects of medicines including notification or ineffectiveness (Overview Of Legislative Developments in Medicines' and Medical Devices' Circulation Domains within the Eurasian Economic Union, 2015)is great andnecessary. However, are such requirements realistic from the perspective of technical infrastructure of the member states? What is the estimated time frame for their development? For example, it took more than a decade for world-wide experienced parties to develop standard requirements for clinical data named CDISC, and work is still in progress. If databases have not set up yet, this task is not in the radar for the coming decade. Lastly, EEC does not plan to become a member of ICH. It seems that member states of the EAEUdo not fully understand the flexibility of the international harmonization practice. All existing and approved guidelines undergo multiple revisions and updates and require experts in the field constantly review and update them based on international practice. Are the members of the EE committee ready and properly equipped to join this process?

Other approaches

The review of other possible approaches to build and advance EAEUpublic health and clinical research was not the goal of this paper. However, the author yielded tothe temptation of sharing some ideas. These thoughtsmight be also helpful to understand the points brought up in the earlier sections. The idea about "evidence-based" clinical research is not new. Some good examplesin utilizing this idea is successful achievements by the non-profit TransCelerateBioPharma organization that consists of 13 major Pharma companiesin multiple therapeutic areas, (Risk-Based Monitoring Update, 2016; Strategic Priorities; Trans Celerate Bio PharmaInc. 2017) and a progress of Clinical Trials Transformation Initiative (CTTI) with more than 80 members onboard.(Clinical Trials Transformation Initiative; https://www.ctti-clinicaltrials.org) Currently, EAEU is facing a question how to re-organize and unite public health system without having a burden of "old" process and regulations in pharmaceutical industry. Therefore, EAEU has a unique opportunity to jump into the advanced concepts that author summarized and presented schematically in Figure 1. Through the advanced technology and abundance of electronic data records (EDR) form the doctor's office, medical hospitals, and other clinical and administrative offices, the collection ofReal World Data (RWD) became real and available in terms of public health and clinical research. Moreover, patients create their own websites and blogs where they share experiences and best practices aboutmedicine and medical care. The effort should be made to standardize elements of those data based on the questions, issues, or hypotheses that users like MoH, Academia, and Pharma companies are willing to investigate. The next two steps will be toutilize theRWDfor deriving comprehensivereal world evidence (RWE) by means ofanalytical research methods, and then to usethe evidence formaking regulatory decisions. RWD/RWE is extremely valuable where conduct of RCT is difficult, infeasible, unethical, or cost-ineffective. RWD/RWE can be heavily employed in early development as well as safety evaluation of post-approval medical products and giving additional insights about efficacy. RWD is the best source for conducting observational studies, and studies to evaluate public health services. Moreover, biostatistics plays one of the leading roles in the whole process suggesting innovative study designs, advanced methods of analyses, and modeling and simulation. It was clear that protocol simulation and predictive modeling eliminatesthe number of unnecessary clinical trials with little efficacy and questionable safety. Pragmatic clinical trials (PCT), umbrella or platform trails will become popular due to vest variety of comparisons in the more diverse populations. All of these factors give enormous financial and resources saving along with placing EAEU clinical research and pharmaceutical industryon the top level of quality and trust. If EAEU concentrate on this approach, member states will get an advanced Evidence-Based Public Health.

Conclusion

In general, EEC regulatory system is in alignment with the international standards for drug development in terms of study conduct and supervision. The primary goal to increase domestic production of the medical products leads to fast approval of generics keeping the low level of scientific knowledge and expertise in the area of clinical research and development of innovative medicine. These factors can be partially accountable to a 21% decrease of all type approved studies in Russia only in the second quarter of 2017, and 25% decreaseof local clinical trials (LCT) from the last year's number based on the orange paper form Synergy Research group. Lack of standardized data structure and validated software leads to questionable results from the analyses of approved products. Lack of experts in biostatistics leads to poor study designs along with questionable reporting and interpretations of safety and efficacy data of approved products.

In summary, translation of existing guidelines from the countries with different evolution and infrastructure brings into question the quality of EEAU products. To advance fast in the area of clinical research, pharmaceutical industry, and public health, EEC should have considered alternative approaches like the idea of evidence-based public health that incorporates modern technologies on the basis of three-dimensional science: medical, clinical and biostatistics.

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