REVIEW ARTICLE

Regulatory pathway for generic and new drug registration in China and Russia

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Abstract

Objectives: The objective of present work is to understand the regulatory requirements and registration process of generic and new drugs in China and Russia. **Methods:** The dossier for the generic and new drugs should be submitted in electronic common technical document (eCTD) format to both the countries China and Russia, since both countries follow the same format of eCTD. All the modules of CTD are almost same for both the countries except module 1. Module 1 differs from country to country. **Results:** In China, drug marketing authorization applications, drug clinical trial application drug registration applications and supplemental applications which are required for manufactured products that are reviewed by the Drug Evaluation Center of National medical products administration (NMPA). In Russia, the National Centre of Pharmaceutical products (FGU) oversee the quality, effectiveness, and protection of all the generic and new drug products. **Conclusion:** From the current study, it was concluded the regulatory authorities of both China and Russia have almost the similar regulatory documents and requirements for the approval of generic and new drugs. The major difference is found in the language submission of dossiers. Roszdravnadzor allows Russian language while NMPA allows submission by using standard Chinese language in China. The safety, efficacy, quality of the drug products is the main objective of both authorities.

Key words: ANDA, eCTD, NDA, national medical products administration, roszdravnadzor

INTRODUCTION

The Regulatory Authority of Russia is Ministry of Health of Russian Federation. In Russia, The Social Development and Ministry of Healthcare is the in Charge of Health Care System, it is supervised by Social Development Supervision and Federal Service on Healthcare. State policy was established by the Ministry of Health. The Ministry of Health also provides regulation for administrative healthcare governing pharmaceutical manufacturing, pricing, and distribution. The Federal Health Service (Roszdravnadzor) is in charge of the monitoring and supervision of this process.[1]

Russian Pharmaceutical Industry is divided into over-the-counter drugs and prescription drugs. Sales of prescription drugs have consistently taken the largest portion of the industry, accounting for 61% of total industry revenue in 2016. With a market share of 64.5%, generic drug sales dominate the prescription market. They account for only 39.4% of total pharmaceutical sales.[2]

The National medical products administration (NMPA), which is responsible for overseeing the regulation of all types of pharmaceutical products in China, including medical devices was formerly known as China food and drug administration (CFDA). The CFDA was established by the State food and drug administration. The Drug Evaluation Center of the NMPA examines supplemental applications, drug registration applications, drug marketing authorization applications, drug clinical trial applications for manufactured products in China (CDE).[3]

The second-largest pharmaceutical market in the world is in China, yet it is also the most complicated. It is one among

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the emerging pharmaceutical markets in the world. The pharmaceutical sector is becoming more challenging and complicated due to strict laws and regulations governing the clearance of new drugs and medical devices. NMPA controls drugs through a variety of standards and procedures to assure their safety, quality, and efficacy.[4]

METHODS

China regulatory framework

Legislation

1. Drug administration law (revision, effective on December 01, 2019)
2. Vaccine administration law (new, effective on December 01, 2019).

Russia regulatory framework

Laws and legislation

The federal law on the distribution of pharmaceutical products, enacted in 2010, required previous legislation. The national approval process, however, would be phased out by the end of 2020. As a result, legislative and regulatory provisions are limited. Furthermore, regulatory standards frequently mimic but do not evolve legislative laws. As a result, such regulations provisions may be considered obsolete. Pharmaceutical law is distinct from other types of healthcare laws, such as medical device or cosmetics regulations.[5]

Electronic common technical document (eCTD) structure for the registration of drug products in Russia and China

1. Module 1: Administrative information
2. Module 2: CTD Overviews and Summaries
3. Module 3: Quality
4. Module 4: Reports on Non-clinical studies
5. Module 5: Reports on Clinical studies.[6,7]

CTD

The structure of CTD is represented in Figure 1.

RESULTS AND DISCUSSION

Generic drugs (ANDA) approval process in China

Applicant need to submit applicant part as well as restricted part of drug master file (DMF) to the CDE of NMPA. Along with applicant and restricted part, a comparison table of

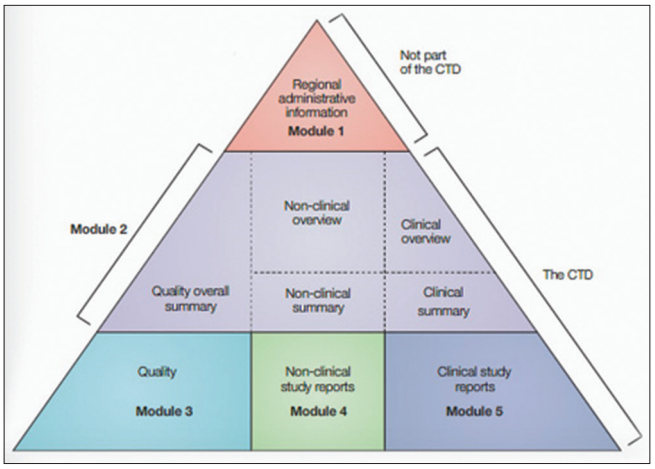

Figure 1: ICH-CTD triangle for dossier submission

Innovator and Generic drug product is also to be submitted. This comparison table includes various data such as Batch analysis data, Stability data, Reference standard data, and Impurity profile data. The authorized Chinese agent will convert it to Chinese language and submitted it to CDE. A timeline of 12 months is required for generic drug approval proposal review and GMP/GCP inspection will be carried by CFDI.

Following receipt of the application dossier, CDE will review it for completeness of the dossier and if it complies with the regulations, will accept it. The generic drug submission along with API's, packaging materials and excipients will be examined by CDE during the technical review. The effectiveness, safety, and quality of the drug will be examined on the basis of application dossier, sample testing and the findings of the site inspection. If the decision goes in favor of applicant, NMPA will provide an import drug license for the ANDA registration. The overall timeline for ANDA submission to approval can take approximately 12–16 months. CDE's technical review time period is around 200 working days, which could be exempted to another 1/3 more time, if material supplementation is required.[8]

The generic drug approval process and ANDA review in China is represented in Figure 2.

New drug approval process in China

After the completion of the clinical trial for an innovative new drug, NDA applicant can develop requirements for registration and verify the procedure of large-scale manufacturing and ultimately submit an application for drug registration. In accordance with the regulations for drug registration (SAMR Decree No 27), application requirements must be produced and submitted to CDE. CFDI-NMPA will carry out for-cause on-site inspections of safety controls throughout the processes of production, drug product development, distribution, and uses of drug product. Therefore, while applying for NDA registration, the producer or the drug

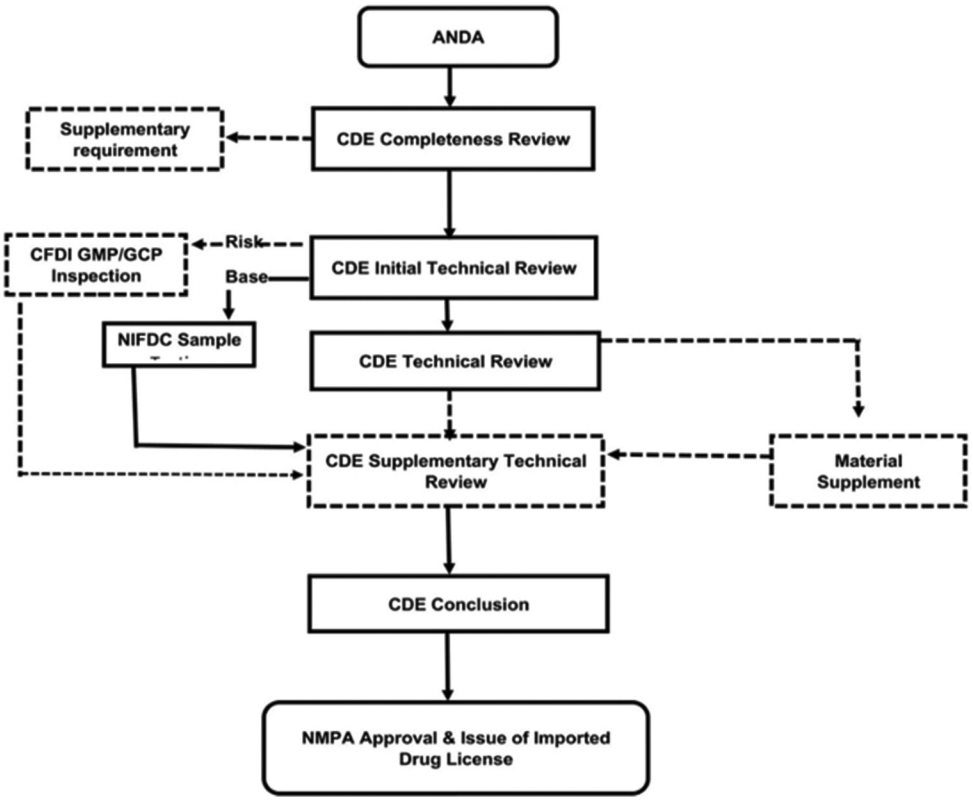

Figure 2: ANDA review and generic drug approval process in China

product's market authorization holder should be completely prepared for NMPA inspection when requesting for NDA registration. After obtaining the application dossier, CDE will examine it for completion; if no errors are discovered, the application will be approved. CDE examiners will look at the finished dosage form together with any relevant packaging components, active pharmaceutical ingredients and excipients during the technical evaluation. On the basis of application dossier, the outcomes of the testing of sample and site inspection, the safety, quality and efficacy of the drug will be carefully reviewed. After the final confirmation of the review process, the NMPA will issue a New Drug Certificate for the NDA registration of new drug products.[9]

The NDA review and approval process in China is shown in Figure 3.

Figure 3: NMPA review and approval process for NDA in China

Generic and new drug product registration in Russia

In Russia, registration procedure for drugs mainly takes place in three steps. During the initial step, all the essential documentation for the dossier is gathered by the applicant. Before submitting it to the National Center of Pharmaceutical Products Expertise (FGU), it must be translated into Russian language. Assigning the file to the right experts at the Institute of Preclinical and Clinical Expertise and Institute of Products Quality Control for the examination of efficacy, quality and safety is the second step, which is possibly the longest and most complicated of the entire procedure. The third step involves finishing this evaluation and submitting the entire dossier to Roszdravnadzor in order to get product certificate for the registration of drugs. Although both Generic and New drugs must complete all three stages of the registration process, generic products may be excluded from few of them, whereas new drugs must go through all the three steps. The requirement of clinical trials in Russia is one of the examples. While this is mandatory for new drugs, generics rarely require bioequivalence tests, which do not have to be undertaken in Russia. The necessity of undertaking more clinical trial studies or delay involved when additional

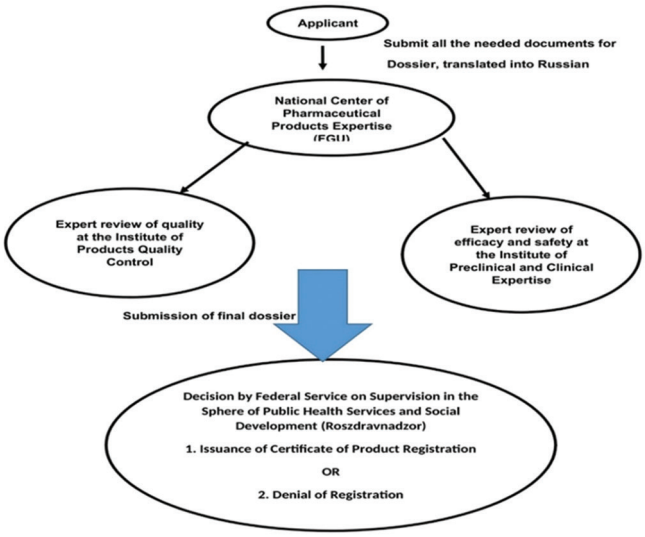

Figure 4: Registration process for generic and new drug in Russia

clinical data is requested by the state authorities implementing a quality control which will increase the timeline of the registration. Generally, in Russia it takes approximately 24 months of time period after the submission of dossier for the registration of both generic and new drugs.[10,11]

The generic and new drugs registration procedure in Russia is illustrated in Figure 4.

CONCLUSION

One of the basic similarities in Russia and China is Certificate of Suitability (COS) can be instead of DMF. Since the DMF is already approved by the European directorate for the quality of the medicine (EDQM) in order to save authority time and to get easy approval, both the China and Russia authorities accepts the COS. EDQM is the only agency which approves drug substance information without reference of drug product application. Both the regulatory authorities have almost the similar documents and regulatory requirements for the approval of NDA for new drugs. The major difference is the submission language. Roszdravnadzor allows Russian while NMPA allows submission by using standard Chinese language. The NMPA also requests for a local mediator or representative for the marketing authorization submission to the authority. Both the authorities accept the dossier through electronic submission of CTD. The efficacy, safety, and quality of the drug and pharmaceutical products are the main objectives of both authorities.

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