Generic Drugs and Biosimilars

It is well known that the Russia Federation has a strong generic drug market. A generic medicine is defined as a medicine that contains the same active pharmaceutical ingredient (API) or a combination of the same APIs in the same dosage form as the original or innovator medicine and is introduced into circulation after an original medicine. Russian law also provides an “accelerated” marketing approval (MA) procedure for generics. Under this “accelerated procedure”, a MA Applicant submits information obtained from clinical trials of the medicine and published in specialized literature, as well as documents containing the results of bioequivalence and/or therapeutic equivalence studies of the medicine seeking MA.

While Russian law allows for the registration of biological products (Biological products are medicinal products containing a biological active substance. A “biological active substance” is a substance that is produced by or extracted from a biological source that requires for its characterization and determination of its quality a combination of physico, chemical and biological testing, along with its production process and control), it does not define a “biosimilar”, nor does it provide a regulatory framework for the accelerated approval of biosimilars. Nonetheless, Russian legislation on the registration of medicinal products (Russian Federation Law No. 61-FZ On the Circulation of Medicines) is expected to be revised in the near future and the requirements necessary conducting clinical studies for
biosimilars is under much discussion.

Because no accelerated marketing approval procedure currently exists in the Russian Federation for biosimilars, a full clinical development program must be completed. Thus, the submission of documents and timelines for biosimilars is the same as for the registration of a biological product (which is considered to be a “pharmaceutical product”). Generally, the marketing approval procedure involves the following four sequential steps:

1. Creation of a registration dossier for submission to the Ministry of Healthcare (MoH) including documents necessary for initiating clinical studies;
2. Conducting clinical trials;
3. Evaluation of the drug quality and expected benefit to possible risk ratio; and
4. Decision by the MoH.

**Step 1: Registration dossier**

An Applicant must submit a registration dossier to the MoH. The dossier must be submitted in Russian or translated into Russian and must contain the following six components (portions of which are submitted at different points in time during the marketing approval process):

1. Administrative documents;
2. Description of the pharmaceutical properties of the pharmaceutical product;
3. Data about the manufacturing of the pharmaceutical product;
4. Data regarding quality control of the finished pharmaceutical product;
5. Data regarding the preclinical pharmacological and toxicological studies of the pharmaceutical product; and
6. Data regarding the clinical studies of the pharmaceutical product.

All of the data required for Russian registration of a pharmaceutical product is the same information required for a European registration. Therefore, if an Applicant already has a European dossier, a separate, new dossier is not required for Russia (other than translating the European dossier into Russian). Other documents required for registration include:

1. A Certificate of Pharmaceutical Product (A [WHO model certificate](WHO model certificate) can be used);
2. A GMP Certificate of the finished API manufacturer; and
3. A Manufacturing License of the finished API manufacturer.

**Step 2: Clinical Trials**
All pharmaceutical products must undergo clinical studies during the registration process. The scope of the clinical studies depends upon: (a) pharmaceutical product type, form and route of administration (original or generic); (b) pharmacotherapeutic group and indications for use; (c) scope of clinical trials conducted abroad (Clinical studies conducted abroad do not have to be repeated; nonetheless, a manufacturer is not exempt from conducting at least one clinical study in Russia. However, the clinical studies conducted abroad influence the scope (number of patients, indications) to be conducted in Russia); and (d) whether an international, multi-center study was conducted and whether part of the study was conducted in Russia (If Russia was included then additional studies probably will not be needed).

Specific permission must be obtained in advance from the MoH to conduct clinical studies. Specifically, an Applicant must submit a registration dossier, fee and a protocol for conducting clinical studies. The MoH will review the dossier and send it for two parallel evaluations. The first evaluation is an ethical evaluation by the Ethics Committee. The second evaluation is an evaluation for purpose of granting a clinical study by the Federal State Budgetary Institution “Scientific Center for Evaluation of Medicinal Products” (FSBI SCEMP). If a positive evaluation is received from both the Ethics Committee and FSBI SCEMP, the MoH grants permission for the Applicant to conduct clinical trials.

The length of the clinical trial period depends on the study type, duration of treatment, etc. Typically, the clinical trial period lasts at least six months although on average, it is approximately 10-18 months. During the clinical study period, the registration procedure is suspended.

**Step 3: Evaluation**

After completion of the clinical trials, Applicant submits a clinical trial report, a fee and an application for renewal of the registration procedure to the MoH. After the submission, registration resumes and the registration dossier is forwarded to the FSBI SCEMP for two evaluations: (a) a drug quality evaluation; and (b) an evaluation of the expected benefit to possible risk ratio. For drug quality evaluation, the FSBI SCEMP examines the Applicant’s drug quality control procedures as well as samples of the drug. Additionally, for the expected benefit to possible risk ratio, experts from the FSBI SCEMP examine the registration dossier, clinical study reports and provide an opinion (positive or negative) on the drug efficacy and safety. The FSBI SCEMP’s opinions on the drug quality and expected benefit to possible risk ratio are forwarded to the MoH.

A marketing authorization is issued for five years. After five years, the manufacturer applies for confirmation of the registration at which point the marketing authorization is issued for an unlimited amount of time.

**Biosimilars approved in Russia**

Several “biosimilars” have been approved in Russia. These include epotein beta, interferon beta-1b and filgrastim. Just recently, in April 2014, Biocad Pharmaceutical Company received marketing approval from the MoH for its rituximab
biosimilar, BCD-020. BCD-020 will be marketed as AcellBia and is the first monoclonal antibody biosimilar to receive approval from the MoH. As part of its dossier, Biocad supplied data from a randomized multicenter clinical study comparing the pharmacokinetics, pharmacodynamics, safety, and efficacy of BCD-020 to the innovator rituximab. Experts at the Research Center at the MoH reviewed the clinical trial efficacy and safety data in patients with B-cell lymphoma and concluded that there were no meaningful differences between BIOCAD’s rituximab biosimilar and the originator drug.

AcellBia is produced in a special economic development district outside of St. Petersburg. Biocad has reported that it is finishing clinical trials of two more monoclonal antibody biosimilars, bevacizumab and trastuzumab (biosimilars of Herceptin and Avastin by Roche), that will be produced at the same facility. On May 22, 2014, Biocad was acquired by Pharmstandard and Russian investment company Millhouse.

This post was written with contributions from Vladislav Ugryumov of Gowlings.

©2020 MICHAEL BEST & FRIEDRICH LLP

Source URL: https://www.natlawreview.com/article/overview-biosimilars-russian-federation