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RESEARCH ARTICLE

Case Studies Showing Comparison between CIS Countries and EU Regulatory Frame Considering the Development of Russian Regulatory Legislation and Marketing Authorization of Herbal Medicinal Products

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ABSTRACT
A European study on current regulatory legislation in the CIS Countries & Marketing authorization of herbal medicinal products in CIS countries was done for comparing the current regulations of both in CIS countries along with EU regulations. In this study includes not only marketing authorization but also the basic principles of the clinical trials required for registration procedures as well as some regulatory aspects of successful market access and post-marketing maintenance activities.
Key words: Herbal medicinal products, Marketing Authorization, EU & CIS Regulatory Legislation.

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CONTENTS

1. Introduction

Since the early 1990s, the new countries originated from ex-Soviet Union republics, often also called CIS (the Commonwealth of Independent States) countries, have increasingly attracted the attention of global pharmaceutical players all over the world. Also, high-quality medicinal products based on sound scientific documentation from European companies are usually very well accepted by all stakeholders in the CIS market: health care practitioners,

patients and the regulatory authorities. Also, high-quality medicinal products based on sound scientific documentation from European companies are usually very well accepted by all stakeholders in the CIS market: health care practitioners, patients and the regulatory authorities This work is based on case studies of the development of Russian regulatory legislation and marketing authorization of a herbal medicinal product in these countries as compared to the EU regulatory frame.

Scope of the Work:

The scope of this work includes not only the initial MAA, but also the basic principles of the clinical trials required for registration procedures as well as some regulatory aspects of successful market access and post-marketing maintenance activities. Other related, mainly commercial/marketing topics such as fees, pricing, reimbursement, site of manufacture in the region, and rules for advertising were regarded as beyond the scope of the discussion. For the same reason, aspects specific to the different groups of medicinal products, such as patents and data exclusivity periods, local rules on a bioequivalence for the generics, marketing authorization of orphan products, rules for biological products/ biosimilars, homeopathics and veterinary products have not been covered. In detail but are touched upon where relevant. Since the regulatory framework evolves rapidly, searches for new data and a thorough update should be done before basing any regulatory strategies or conclusions on the content of this thesis.

Subject of the MAAs:

Pursuant to Article 13 of the law, marketing authorization is necessary for the following groups of products:

- Original medicinal products.
- Generics.
- New combinations of already registered medicinal products.
- New pharmaceutical forms and strengths of already registered medicinal products.

Marketing Authorization:

The goal of pharmaceutical regulatory affairs:

Every pharmaceutical company's goal is to get its drugs to market, and if you work in pharmaceutical regulatory affairs, achieving marketing authorization for your medicinal product is often the most satisfying aspect of your job. Here's what you need to know about the marketing authorization application process (and the technical jargon) for regulatory affairs in the pharmaceutical industry.

The following reasons were given for MAA:

- EU regulatory rules concerning imports from third countries are to be adopted.
- The importer in the EU must be the person or legal entity completely responsible for the imported medicinal product.
- Quality assurance and auditing in compliance with current GMP rules are to be implemented.
- The importer will be responsible for the possible complaints or recalls of batches from the market, if necessary application form, SMF, information on QP.
- A GMP audit of the manufacturer has to be conducted before the contract is signed.
- Qualified personal, especially a qualified person (QP) for GMP, have to be involved and declared.

Extension of the procedure for marketing authorization:

In February 2012, an MoH introduced new rules on the interactions between the pharmaceutical department of the MoH and the national expert body. As per amended Decree No. 98, the MoH assumed responsibility for communication with the applicants and for final decisions concerning MAAs, renewals, variations and requests for CTAs after their assessment by the expert body. Two new structures were implemented to perform these new duties:

- Service centre "Single point of contact" for direct communication with applicants within the structure of the expert body;
- Standing Committee for Marketing Authorization of Medicinal Products.

New regulatory initiatives:

- Decree No. 426, as amended (including 18 valid annexes) lays down the procedure for assessment of new submissions, renewals and variations[10] by the National expert body. The following modifications to the assessment procedures are to be implemented in the near future within the scope of further adaptation of the EU legislation on quality, safety and efficacy of the medicinal products.

Regulatory Authorities:

- Expert assessment of dossiers submitted within the scope of initial marketing authorizations, renewals and variations;
- Provision of different types of scientific advice;
- Issuing of assessment reports;
- Assessment of requests for CTAs;
- Evaluation of the quality of the medicinal products under submission and their compliance with the documentation provided;
- Pharmacovigilance activities;

2. Case Study

- Herbal medicinal product - actual regulatory requirements for marketing authorization in Russia.
- Scenario for the case study
- Justification for choice of case study
- A special scenario is described to customize the case study of the MAA of a medicinal product in the CIS countries. A herbal product was chosen.
- A fictitious, medium-sized, family-owned German pharmaceutical company "Phytopharmaka GmbH" produces a fictitious herbal medicinal product "Wunderherb" which has been on the market in Germany and Switzerland for the past 10 years. Some marketing authorizations on the basis of German Certificate of a Pharmaceutical Product (CPP) also exist in the different Ex-EU countries, but not in the CIS as yet. The active substance in Wunderherb is an extract of a fictitious plant, "Phyto herbalis".

Basic conditions for the MAAs in the CIS countries:

- Legal definitions
- Medicinal product

EU legislation distinguishes between two concepts in the definition of medicinal products: by their presence in the human body (any substance or combination of substances present in human beings for treating or preventing diseases) or by their function (used in or administered to human beings for the restoring, correcting or modifying of physiological functions by pharmacological, immunological or metabolic actions, or for making a medical diagnosis)[14]. Russian legislation does not differentiate in this way.

Type of the applications:

- Full MAA
- WEU Application
- THMP application

Presentation and format of the dossier for initial submission of MAA in Russia compared to EU requirements: The current requirements for the content of the EU dossier for application are set out in Annex I to Dir. 2001/83/EC as amended. Details of presentation and format of the dossier are described in detail in the Eudralex Volume 2B "Presentation and content of the dossier: Notice to Applicants".

Preparation of the documentation with special requirements for Product information:

As a rule, the following special aspects concerning product information apply to all CIS countries:

- There are no differences between SmPC and PIL, since only one common document for both patients and health care professionals (HCP) is approved at the end of procedure. This is referred to below as the product information leaflet (PIL), which has to be put in the each secondary package along with the medicinal product.
- Usually there are some requirements regarding minimum font size, although readability testing is not required.
- Color mock-ups of the outer and immediate packaging have to be approved.

Preliminary conclusions and advice for the case study:

- The preceding chapters describe the requirements for the MAAs and dossiers for initial submission in Russia. The following answers to the questions raised by the "Wunderherb Project Team" were prepared by the Regulatory Affairs Manager of Phytopharmaka GmbH based on the information collected on the initial MAA in the Russia.

FDA's Strategic Plan for Regulatory Science:

- ✓ To meet this need, FDA has developed a strategic plan for regulatory science, the science of developing new tools, standards, and approaches to assess the safety, efficacy, quality, and performance of FDA-regulated products. This plan identifies eight priority areas of regulatory science where new or enhanced engagement is essential to the continued success of FDA's public health and regulatory mission.

Modernize Toxicology to Enhance:

1. Product Safety
2. Implementation Strategy
3. 3.Public Health Impact

Safety Considerations: In combinations when one is a new molecular entity

Conduct general toxicology: Genetic toxicology, pharmacology, safety pharmacology, PK/ADME, general toxicology, Reproduction and developmental toxicology, carcinogenicity. Conduct 90-day bridging study with the combination in most appropriate species in combinations of two or more new molecular entities.

Adverse Event Reporting

Manufacturers of combination products should request that post marketing requirements be included in pre-approval discussions with the agency.

1. Device malfunction reporting Malfunctions associated with a death or serious injury reporting may be necessary.
2. Five-day MDR reporting: The MDR regulation requires reporting of:-
   - Any reportable event that necessitates
   - premedical action to prevent an unreasonable risk of substantial harm to the public health
   - Any MDR reportable event for which *FDA* has made a written request for the submission of 5 day report.

Examples of Russia Approved Products:

Absorbable Collagen Sponge with Genetically Engineered Human Protein

- Iontophoretic transdermal system for fentanyl
- Dermal Iontophoresis System
- Absorbable Collagen Sponge with Genetically Engineered Human Protein
- Surgical Mesh with Antibiotic Coating
- Paclitaxel-Eluting Coronary Stent System
- Tositumomab and Iodine I 131 Tositumomab

Other possible considerations when devising a development plan for a product incorporating a drug/biologic constituent include:

- *In vivo* pharmacokinetic (PK) studies may be necessary to assess changes in formulation, strength, route of administration, dosing, population or other factors that may alter the extent or time course of systemic exposure. These studies might be used to determine drug release kinetics such as release rate, local peak concentrations of the drug, local distribution and systemic bioavailability (Cmax, Tmax, etc.).
- Dose ranging or dose finding studies in humans may be appropriate to determine dose adjustments for safety/effectiveness when therapy is targeted to a local site.

Additional Perspectives:

A. Clinical Investigation

B. Manufacturing considerations

C. Reliance on information not developed by the applicant

3. Results and Discussion

As has been demonstrated above by case studies, the Russian Federation young and rapidly evolving systems of regulatory legislation, based on the Soviet heritage. Many changes to the scope of the laws on the approval and marketing of medicinal products have been adopted in the last few years, and numerous forthcoming amendments are already scheduler for 2013. Russia appears to be more conservative and intent upon having its own way as far as legislation is concerned, although they are considering European and non-European elements of regulatory legislation more and more, driven policies in the field of authorization and marketing of medicinal products, although some distortion does occur on a local level.

4. Conclusion

All terms used in the thesis are in compliance with the current European regulatory terminology for human medicinal products. The scope of this work includes not only the initial marketing authorization applications, but also basic principles of the clinical trials required for registration procedures as well as selected regulatory aspects of successful market access and post marketing maintenance activities. The thesis concludes with recommendations to EU-based pharmaceutical companies who wish to apply for marketing authorization in the CIS region.

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