

**European view on current regulatory
legislation in the CIS countries.
Marketing authorisation of herbal medicinal
products in Russia and the Ukraine.**

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Executive Summary

Since the early 1990s, the new countries emerging from the former Soviet Union, commonly called CIS countries, have increasingly attracted the attention of major players in the pharma business worldwide, but especially that of the European pharmaceutical industry. Two distinct trends have been identified in the evolution of regulatory legislation in the CIS countries: some countries, like Ukraine, try to adopt as much as possible of the European/ICH perspective, whereas others, such as Russia, continue on their own path, partly influenced by the heritage of the Soviet era. Since Russia and Ukraine are the two largest and most attractive CIS markets, but pursue two distinct regulatory approaches, this work is focused primarily on comparing the legislation in those two countries with the EU regulatory framework.

The history and current development of regulatory legislation, new legal initiatives, and possibilities for harmonisation with the EU rules are extensively elaborated in two case studies on Russia and Ukraine. A third case study on the marketing authorisation of a herbal medicinal product in both countries was chosen for the illustrative purposes, especially taking into account that the rules for applying for marketing authorisation in Russia and Ukraine are similar, if not identical, for both herbal and chemical medicinal products.

All terms used in this 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 authorisation 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 authorisation in the CIS region.

List of abbreviations

ACTO	Association of Clinical Trials Organizations, Russia
AF	Application Form
AIPM	Association of International Pharmaceutical Manufacturers, Russia
ATC	Anatomical Therapeutic Chemical classification system
BfArM	Bundesinstitut für Arzneimittel und Medizinprodukte (Federal Institute for Drugs and Medical Devices, Germany)
CIS	Commonwealth of Independent States
CHMP	Committee for Medicinal Products for Human Use
CMDh	Co-ordination Group for Mutual Recognition and Decentralised Procedures - Human
CMS	Concerned Member States
CoA	Certificate of Analysis
CPP	Certificate of a Pharmaceutical Product
CRO	Clinical/Contract Research Organization
CTA	Clinical Trial Authorisation
CTD	Common Technical Document
CV	Curriculum Vitae
DCP	Decentralised Procedure
EAN	European Article Number
EMA	European Medicines Agency
EU	European Union
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
FAS	Federal Antimonopoly Service of the Russian Federation
FDA	Food and Drug Administration
HPLC	High-performance liquid chromatography
HCP	Healthcare Professionals
HTA	Health Technology Assessment bodies
ICH	International Conference on Harmonisation
IMP	Investigational Medicinal Product
INN	International Nonproprietary Name

MAA	Marketing Authorisation Application
MAH	Marketing Authorisation Holder
MHRA	Medicines and Healthcare Products Regulatory Agency (UK)
MoH	Ministry of Health
MRP	Mutual Recognition Procedure
ND	Normative Documentation (documentation on quality of finished product, approved within registration procedure in Russia)
PIC/S	Pharmaceutical Inspection Co-operation Scheme
PIL	Patient (Product) Information Leaflet
PIP	Paediatric Investigation Plan
PSUR	Periodic Safety Update Report
QP	Qualified Person
OTC	Over-the-counter, medicines without medical prescription
R&D	Research and development
RMS	Reference Member State
Rx	Recipe, subject to medical prescription; also known as prescription-only medicine (POM)
SMF	Site Master File
SmPC	Summary of Product Characteristics
THMP	Traditional Herbal Medicinal Products
TLC	Thin-layer chromatography
UK	United Kingdom
USSR	Union of Soviet Socialist Republics, or Soviet Union
WEU	Well-established use
WTO	World Trade Organization

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1. Introduction: rationales for the choice of subject for the scientific thesis and case studies

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. Especially the European pharmaceutical industry, driven by geographical proximity and historical import/export relationships between regions, has tended to penetrate more into the attractive emerging markets in the near East-European neighbourhood. 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.

Two distinct trends can be identified in the development of the regulatory legislation in the CIS countries: some countries, like Ukraine, try to adopt as much as possible of the European/ International Conference on Harmonisation (ICH) perspective (although some unexpected consequences have occurred during local implementation, as will be demonstrated by the Ukrainian case study below), whereas others, like Russia, continue to go their own way, partly because of their USSR heritage. Since Russia and Ukraine are the two biggest and most attractive CIS markets and have two very different regulatory approaches, this work will be focused mostly on the comparison of the legislation in those two countries with the European Union (EU) regulatory practice. Such a comparison demonstrating similarities and differences of two worlds is definitely interesting, not only for the Regulatory Affairs manager working in an EU-based pharmaceutical companies or the authorities, but also for their regulatory counterpart in the CIS countries.

This work is based on case studies of the development of Russian and Ukrainian regulatory legislation and marketing authorisation of a herbal medicinal product in these countries as compared to the EU regulatory frame-

work. The following support the choice of topic and qualify the author for preparing this thesis:

- The rules for the marketing authorisation in Russia and Ukraine are broadly similar, if not identical, for both herbal and chemical medicinal products, as will be demonstrated in the case studies;
- The choice of a herbal product for the marketing authorisation application (MAA) facilitates illustration of the present situation in the case study;
- The author is a native Russian speaker born and raised in the Ukraine, having broad regulatory experience gained in different countries and in pharmaceutical companies specialising in the phytopharmaceutical sector.

All of the terms used in the thesis should be interpreted in sense of the current European regulatory terminology for human medicinal products. Due to the different tendencies and stages of the development of regulatory legislation in the selected countries, the structure of the presented case studies may be not absolutely identical. Furthermore, 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 authorisation of orphan products, rules for biological products/biosimilars, homeopathics and veterinary products have not been covered in detail but are touched upon where relevant.

The data-lock point for the information included in this work was 1 March 2013. 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.

2. Case study: Regulatory legislation in Russia

2.1 History of development

During the Soviet period, the entire pharmaceutical industry, all hospitals, clinics, scientific institutes and pharmacies belonged to the state monopoly. No system of marketing authorisation for the medicinal products as established in the early 1960s or “post-thalidomide”¹ in EU countries existed in Soviet Union. Despite this, as early as 30 April 1964, Ministry of Health (MoH) of the Union of Soviet Socialist Republics (USSR) has issued a Decree establishing a formal registration procedure for medicinal products including registration certificate, which contained such data as registration number, manufacturer, name of the product, composition, posology and price. This Decree also set up the first list of registered medicinal products allowed to be manufactured and used in the Soviet Union, which contained only 331 names of the active pharmaceutical ingredients. The list was successively amended, e.g. in the year 1967, with a further 290 substances, primarily various phytopharmaceuticals².

From 1971 onwards, the MoH of the USSR collected information about registered medicinal products in the so-called State Register of Medicinal Products. The register included the name and registration number of the product, registration certificate, specification and analytical procedure, product information (e.g. Patient Information Leaflet (PIL)), pharmacological properties, clinical studies conducted, but also the volume needed to be produced to supply a demand of the health system planned by the Soviet government during the next 2 years. By 1 January 1987, the register included 2612 medicinal products in different pharmaceutical forms, 439 herbal drugs and preparations, 61 radiopharmaceuticals, 70 excipients and reagents and, 129 reference standards³.

¹ URL 1 (de.wikipedia.org), 2013

² Decree MoH USSR No.228, 1964, as amended per 1967

³ Mironov, 2011

After the fall of the Soviet Union in 1991, each of the new independent republics started to establish its own registration procedure. In Russia, medicinal products were regulated for more than one decade by the "old" Federal law "on medicines" of 22 June 1998. During this period this law was revised and amended at least 8 times⁴, resulting in not especially fast and transparent, but at least functioning procedures for MAAs. The law was to be amended once again, but during the preparation of the revision it became apparent that the changes were much too grave⁵. It was therefore abolished and replaced in 2010 by completely new legislation, which will be described in the next chapter.

2.2 Recent changes in legislation

2.2.1 Background of the new legislation

The Russian Federal law No. 61-FZ "on the regulation of the medicines" was introduced on 12 April 2010. It came into force on 1 September 2010 and is still valid⁶. Despite some positive changes, like fixed timelines, the new law was criticised heavily from the very beginning by different groups operating on the pharmaceutical market, which has resulted in six amendments up to now. The first was on 27 July 2010, even before the law came into force; the last amendment was passed on 25 December 2012. None of the amendments introduced critical changes, but did correct serious errors which might lead to the stagnation of the regulation of the medicines and import of the medicinal product into Russia, or failure of clinical trials.

The problem with the legislation was that the law was written by the lawyers of the MoH, without any real consultation with the stakeholders like the pharmaceutical industry or professional associations, or with doctors or patients' organizations. In 2009, a year before the new law was passed, the strategy of development of the pharmaceutical industry of the Russian Federation up to 2020 – the so-called programme "Pharma 2020" – was adopted

⁴ Russian Federal law No. 86-FZ, 1998, as amended

⁵ Pharmaceutical bulletin, 2010.

⁶ Russian Federal law No. 61-FZ "on the regulation of the medicines" 2010, as amended.

by the Russian government. Amongst other things, this programme introduced an ambitious goal to increase the market share of domestic medicinal products up to 50% in value⁷. It can be concluded from the content of the new federal law on medicines that some new rules were designed to create additional obstacles for international companies and to support domestic manufacturers simultaneously, to enable the programme Pharma 2020 to be completed on time.

Among significant changes introduced by the new law, especially two aspects should be underlined:

1. The formal processing of the MAA and the assessment of submitted dossiers are split between two different authorities.
2. Requirement for local clinical trials, regardless of the quality and quantity of the existing clinical data submitted by the applicant or application type, e.g. proprietary versus generic.

2.2.2 Separation of procedures of application and assessment of dossiers

According to the previous law and formerly valid rules, all the procedures of the marketing authorisation were under the sole supervision of the Federal service on surveillance in healthcare (Roszdravnadzor). Pursuant to the provisions of Article 13 of the new law No. 61-FZ, direct regulatory functions fall under the supervision of the State executive body (represented by the Drug Regulatory Affairs department of the Ministry of Health, the former Ministry of Health and Social Development, as per Decree No. 608 of the Government of the Russian Federation⁸). The assessment, however, is performed by the completely separate state expert authority established by the MoH, as per Article 15 of the law. In accordance with the Article 16, sections 4 to 6, an expert is not allowed to communicate with the applicant directly, but has to provide deficiency letters using the formal pathway via the MoH, which has

⁷ Ministry of Industry and Trade of Russian Federation, 2009

⁸ Russia: Decree No.608 Government of Russian Federation, 2012

delegated the assessment to the expert body⁹. Such an approach results in non-transparency of the assessment of benefit/risk and quality of the medicinal products and means that scientific advice meetings with the assessors are not possible.

2.2.3 Prerequisite of local clinical testing

According to Article 14.2 of the Russian drug law, the assessment of the MAA starts with the assessment of the request for clinical trial authorisation (CTA). It means that local clinical data are prerequisite for dossier assessment. This practice obviously has its roots in the approach taken by domestic, mostly generic, companies, who normally start the registration procedure by applying to perform a bioequivalence trial. Pursuant to the Article 18.4, any further clinical or bioequivalence data generated in the country of origin or any other country outside of the Russia can be provided by the applicant *optionally* (although such data would be highly appreciated by the clinical assessor), but regardless of quantity or quality, approval cannot be based on such “foreign” data. If local clinical data already exists at the time of application because some Russian centres were included in international multicenter clinical trials, a separate local clinical trial is not required. The only exception to the rule that local data has to be supplied are for medicinal product registered more than 20 years in Russia (mostly old medicinal product from the Soviet Union period), for which bioequivalence assessments are not feasible, as per Article 14.2.1).a) of the law¹⁰. This requirement to provide local clinical data cannot be justified by any ethnic reasons, since the vast majority of the Russian population are Caucasian like all the other European populations. European regulatory authorities and the US Food and Drug Administration (FDA) usually accept clinical data generated in Russia during clinical development, provided the trials are conducted under Good Clinical Practice (GCP)^{11,12}. Usually, clinical data generated on not more than a few hundred

⁹ Russian Federal law No. 61-FZ "On the regulation of the medicines" 2010, as amended.

¹⁰ Russian Federal law No. 61-FZ "On the regulation of the medicines" 2010, as amended.

¹¹ Van Andel, 2012

¹² Caldron, 2012

patients is considered to be sufficient to fulfil the requirements of the law for the assessment of the safety and efficacy in the Russian population, see e.g. a database on the local clinical trials¹³. Hence, the new legislation pursues economical and political goals to boost the number of clinical trials conducted in the Russian Federation, although such increase has not yet been achieved as will be demonstrated further (see a chapter 2.3 on the new legal initiatives).

2.2.4 Subject of the MAAs

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

- 1) Original medicinal products;
- 2) Generics;
- 3) New combinations of already registered medicinal products;
- 4) New pharmaceutical forms and strengths of already registered medicinal products.

This means that any line extensions are subject to a completely new registration procedure, which also entails all the requirements, including that for local clinical trials¹⁴.

2.2.5 Steps of the MAA and corresponding timelines.

The introduction of fixed timelines is a definite advantage of the new legislation, although current practical experience demonstrates considerable discrepancies: time limits have been overrun as a rule, and it has not been uncommon for the milestone decisions to be backdated.

The whole application procedure, from day of application to the issuing of the registration certificate, should not exceed 210 working days (generics are subject to an accelerated procedure of 60 days). A clock-off period is possible for conduct of a local clinical trial. Article 14 of the law describes a two step approach. In the first step, the request for the Clinical Trial Authorisation

¹³ URL 2: Registry of the CTAs (grls.rosminzdrav.ru), 2013

¹⁴ Russian Federal law No. 61-FZ "On the regulation of the medicines" 2010, as amended.

(CTA) along with the dossier on the product has to be submitted and assessed by the corresponding authorities. Approval of the clinical trial is obtained after the positive decisions of the both the clinical expert and an ethics committee. Then the applicant should conduct the clinical trial and submit the final report. In the second assessment step, an assessment of the quality part of dossier, quality control of the samples provided by the applicant and a benefit/risk assessment of the results of the clinical trial are performed by the corresponding authorities. If Russian centres were included in an international multicenter clinical trials already conducted (this means that the applicant can be not only a domestic company), the assessment goes directly to step II. Table 1 describes the procedural steps with the applicant's activities are shaded in grey¹⁵.

Table 1. Marketing authorisation procedure in Russia.

No.	Timelines	Procedural steps
Assessment step I		
1.	day 0 (Article 18)	Submission of the application dossier to the MoH, containing application form, quality part, non-clinical assessment and (preliminary) request for CTA including draft clinical protocol, investigator's brochure, patient information leaflet, intended payment and compensations to the patients, and proof of payment of the fees for CTA assessment. If Russian centres were included in international multicenter clinical trials, results have to be provided. Any further clinical data generated outside Russia can be voluntarily provided. The entire dossier and additional data must be in Russian.
2.	5 working days after application (Article 19)	Validation of application by the drug regulatory affairs department of the MoH, in case of positive validation to make a decision on: - Assignment of the review of the (preliminary) request for CTA by the expert body and ethics committee, or

¹⁵ based on Russian Federal law No. 61-FZ "On the regulation of the medicines" 2010, as amended

No.	Timelines	Procedural steps
		<p>- In case local clinical data were generated within the scope of international multicenter clinical trials or the medicinal product was registered more than 20 years before in Russia, assignment of the benefit/risk assessment, see Assessment step II.</p> <p>The applicant is notified of the results of the validation; in case of the negative opinion also of the reasons for rejection of the application.</p>
3.	30 working days after receipt of assignment (Article 20)	<p>- Assessment of the (preliminary) request for CTA by the expert body, issuing of the assessment report on the application;</p> <p>- Conclusion of the ethics committee, approval/disapproval of clinical trial.</p>
4.	5 working days after receipt of decisions (Article 21)	<p>Evaluation of the experts' decision by the MoH, in case of positive evaluation (if negative, see section 15):</p> <p>- Notification of the applicant on the decision on the (preliminary) request for CTA;</p> <p>- In case of positive decision on (preliminary) request for CTA: clock-stop until the applicant's request for the (formal) initiation of the clinical trial;</p> <p>- In case of the negative decision on (preliminary) request for CTA: rejection of the MAA.</p>
5.	clock-off period	Preparation of the (formal) request for CTA by the applicant.
6.	clock restart (Article 22.1)	Submission by the applicant of the (formal) request for CTA containing, amongst other things, details of investigators and sites where the trial is intended to be conducted, contract on patient health insurance with the notification of the maximal number of study participants, timelines of the study.
7.	5 working days after receipt of	<p>- Validation of (formal) request for CTA by the MoH;</p> <p>- MoH decision on the (formal) request for CTA;</p>

No.	Timelines	Procedural steps
	(formal) CTA (Article 22)	<ul style="list-style-type: none"> - Notification of the applicant of the decision, in case of negative opinion, of the reasons of rejection; - Issuing of approval of CTA.
<i>Maximum of 45 working days in total for Step I (timelines for the assignment of the expert body is not explicitly scheduled by the law)</i>		
8.	clock-off period	Conduct of the clinical trial by the applicant.
Assessment step II		
9.	clock restart (Article 23.2)	Submission by the applicant of the following documents: <ul style="list-style-type: none"> - Application to restart of the MAA; - Final clinical study report; - Proof of payment of fees for the quality and risk/benefit assessment.
10.	5 working days after application for MAA restart (Article 23.3)	<ul style="list-style-type: none"> - Validation of clinical study report; - Decision on restarting the MAA; - Notification of the applicant of the decision, in case of negative opinion, of the reasons of rejection.
11.	110 working days after receipt of samples, clinical study report and re-assignment from MoH (Article 23.1)	Assessment of the application by the expert body: <ul style="list-style-type: none"> - Assessment of the quality of the medicinal product by the quality experts; - Benefit/risk assessment based on the results of the clinical trial by the clinical experts; - Provision of quality and clinical assessment reports to the MoH.
12.	15 working days after receiving positive decision on MAA restart	The Applicant has to supply an adequate number of samples of the following to the qualified analytical laboratory for the assessment of the quality of the medicinal product: <ul style="list-style-type: none"> - Samples of the medicinal product under assessment, produced in accordance with the manufacturing document-

No.	Timelines	Procedural steps
	(Article 23.5)	tation submitted; - All reference samples and samples of the active substance, if required for quality control.
13.	3 working days after receiving samples (Article 23.6)	The qualified analytical laboratory has to acknowledge receipt of samples to the applicant and MoH
14.	5 working days after receiving the assessment reports (Article 27)	- Evaluation of the quality and clinical assessment reports by the MoH; - Decision on approval or non-approval of the marketing authorisation; notification of the applicant of the decision; - In case of positive decision, issuing of the registration certificate and entry of the approved medicinal product in the State Registry of Medicinal Products; - New registration certificate is valid for the period of 5 years; after renewal the period of validity is unlimited (Article 28).
15.	(optional for MoH) (Article 25) 40 working days 15 working days	In case of negative evaluation of the experts' decision by the MoH (e.g. incomplete assessment report, information of the influence of the assessment by the applicant or third party), repeated assessment can be initiated by MoH: - Reassessment by the expert body assigned by MoH; - Re-evaluation by the ethics committee.
<i>Maximum of 160 working days in total for Step II (timeline for the re-assignment of the expert body is not explicit scheduled by the law).</i>		
<i>Theoretically possible to reach the deadline of 210 working days as defined by Article 13.4 of the law, because some steps run simultaneously (e.g. 11 and 12-13): 45 working days Step I + 160 working days Step II = 205 working days in total</i>		

For a flow-chart of the marketing authorisation procedure in Russia see Annex II

2.2.6 Transitional provisions

Although complications occurring during the transition period from old to the new legislation are now a thing of the past, a brief review of recent obstacles that pharmaceutical companies were faced with in 2010 and 2011 is important in understanding the forces at play in the Russian regulatory environment:

Labelling issues

The new law introduced higher standards for product information affecting mainly the outer and immediate packaging. Originally, the requirements had to be observed immediately after the law came in to force on 1 September 2010, despite the fact that the law had not been published until April 2010. After it became obvious that labelling cannot be changed at such short notice, an amendment to the law was passed on 11 October 2010. Amongst other things, the amendment introduced a transitional period until 1 March 2011, less than five Months. Products with the "old" labelling were to be banned from the market after this date. This information triggered many uncertainties in manufacturing plans and worries for the products under manufacture within the pharmaceutical companies. Fortunately, this rule was changed once again later, so at the end of the transitional period, products already produced were able to stay on the market until the end of their shelf-life, upon written commitment from the marketing authorisation holder (MAH) to recall the product and to compensate the costs if required by the government.

Clinical studies issues

A whole range of sensible modifications in the field of clinical trials in Russia were implemented by the new law:

- Clinical trials can be conducted only at sites accredited by the MoH (Art. 38.7);

- The principal investigator has to have at least 5 years of experience in the field of clinical trials (Art. 40.1);
- Compulsory insurance with an unusual breadth of cover was introduced: it has to cover the life and health of each study participant (Art. 44), but not the liability of the investigator/sponsor in case of injury or death of a trial subject according to the usual EU practice¹⁶;
- As from September 2010, an ethics committee has been installed and is organised and managed exclusively by the governmental body, i.e. MoH (Art. 17);
- Phase I studies on healthy subjects (except bioequivalence studies) are prohibited for non-domestic medicinal products (Art. 38.1.1).

The consequences of this were the following problems¹⁷:

- From September 2010 up to the beginning of 2011: collapse of the approval system due to the introduction of the new rules under supervision of new governmental bodies;
- From September 2010 up to May 2011: infeasibility the insurance of study subjects;
- From September 2010 up to June 2011: impossible to import approved medicinal products required for comparative clinical trials;
- Up to September 2011: administrative obstacles with the accreditation of investigational sites by the MoH.

The result was a decline in the number of approved clinical trials and undue delay in review times of the requests for CTAs during the first transitional year. For example, in 2011, only 1.8% of requests for CTAs were approved within the time frame required by the legislation¹⁸.

¹⁶ Directive 2001/20/EC, 2001.

¹⁷ Zavidova, 2012

¹⁸ ACTO, 2012

Issues with pending applications

At the time the new legislation came into force, about 9,000 applications were under assessment by the "old" authority. After 1 September 2010, assessments of those pending applications were stopped; partly assessed applications along with the preliminary assessment report (depending on the stage of evaluation) were to be forwarded to the MoH, but the exact mechanism of such transfer was not clear at that time. A transitional period up to 1 March 2011 was not established until the third amendment to the law on 29 November 2010 (Art. 71.3.3) was passed¹⁹. During those 4 months, not only the experts at the authorities, but primarily the regulatory affairs managers at the companies affected were faced with an enormous workload by transferring of pending applications from "old" to "new" authority: the applications should be received, reformatted and supplemented according to the new rules, and then submitted not later than the end of February 2011 to the MoH. Otherwise, new rules would apply to application already submitted, with all the consequences, i.e. preparation of a completely new submission according to the new requirements, including local clinical trials and re-payment of fees.

Not surprisingly, Russian regulatory colleagues were working in winter 2010/2011 day and night, including weekends, to prepare and resubmit pending applications up to the deadline. Neither electronic nor postal submissions were possible, but only individual attendance without any designated appointments according to the standard procedure. How it was is demonstrated perfectly by a short video (about 13.5 min) entitled "Chaos in drug regulatory affairs"²⁰ placed on YouTube by one of the participants. The recording was made on 26 February 2011, a Saturday, the last two working days before the deadline on 1 March. The regulatory people gathered in front of the MoH starting at 04:00 and waited on the wintry, snowy and cold Moscow streets until 09:15, when the doors of the ministry were opened. All hallways were overcrowded; long queues of the regulatory managers with the application dossiers were standing in the submissions' offices of MoH. All

¹⁹ Russian Federal law No. 61-FZ "On the regulation of the medicines" 2010, as amended

²⁰ URL 3 (www.youtube.com), 2011

these problems in the transitional period culminated in the publication of an open letter to the President of the Russian Federation published on the professional site of the Russian regulatory affairs managers²¹ amongst others, but no official reaction to the letter followed.

2.2.7 Main features of the new legislation

The following brief overview describes some of the principal features of current regulatory legislation in Russia:

- Marketing authorisation is valid for five years. Once renewed, the market authorisation is valid for an unlimited period (Art. 28), corresponding to current EU practice;
- The same brand name for different medicinal products as well as multiple or duplicate applications with different brand names are forbidden (Art. 13.6);
- Despite the fact that herbal medicinal products are precisely defined (Art. 4.14), there are no special provisions for the registration. This means that applications have to be made according to common practice, including the requirement for local clinical testing;
- Orphan medicinal products are not specifically defined by the law, so common practice rules apply to such products;
- Although generics are eligible for the special "accelerated" registration procedure of only 60 working days as described in Article 26, providing results of local bioequivalence studies are submitted, the safety aspect of the product is regarded as independent of its generic status, which means that the appropriate nonclinical data are still required (Art. 26.4). If an applicant is not able to provide essential non-clinical data due to the nature of the application (e.g. an originator has not published such data), locally generated non-clinical data can be required. According to the experts' view, such data should contain, amongst other things, acute toxicity (not required in the EU since 2010²²). Beyond this, the data should be obtained in tests using the pharmaceutical form under application, including all excipients (not solely

²¹ URL 4 (regprof.com), 2011

²² EMA/CHMP/SWP/81714/2010

on active substance)²³. Consequently, generic applications in Russia are similar to hybrid applications as per Art. 10(3) Dir. 2001/83/EC;

- The data exclusivity period of 6 years after the date of registration of the original medicinal products (Art. 18.6) has only applied since 22 August 2012, after the Russian Federation joined the World Trade Organization (WTO);
- The new Russian law regulates both marketing authorisation and clinical studies. Since clinical trials are regarded as a part of the registration procedure, the same rules for the CTA applying to all four phases of clinical research (Art. 38.4). This means that double requests for CTAs (preliminary and formal) are necessary as described in Table 1 "Marketing authorisation procedure in Russia". The requirement of an investigator's brochure for bio-equivalence studies instead of the Summary of Product Characteristics (SmPC) corresponding to the usual EU practice²⁴ is also further evidence of such "inconvenient" approach.

2.3 Most recent regulatory initiatives

The information provided above demonstrates that the new legislation has vast room for improvement. Indeed, suggestions by the different stakeholders regarding the substantial changes in rules laid down by the law No. 61-FZ have been circulating since the publication of its first version. Also, the Federal Antimonopoly Service (FAS) of the Russian Federation has already published a second version of the amendments on 6 November 2012 (the first was published on 11 March 2012)²⁵. Some professional associations, e.g. Association of International Pharmaceutical Manufacturers (AIPM)²⁶ and Association of Clinical Trials Organizations (ACTO)²⁷, have repeatedly made representation to try to influence legislation to harmonise the pharmaceutical legislation of Russia with established EU practice.

²³ Mironov, 2012

²⁴ Pečená, 2012

²⁵ FAS Russia, 2012

²⁶ URL 5 (www.aipm.org), 2013

²⁷ URL 6 (acto-russia.org), 2012

Most of the criticism is directed at the requirement for conducting redundant local clinical trials. Russian officials have announced that clinical trials from other countries will be accepted in Russia only if there is mutual recognition of clinical trials between countries. The former Health Minister, Ms. Tatyana Golikova, after her visit on the 24 February 2011 to the European Commission even said that "Russia and the European Union are prepared to move fast to finalize all issues leading up to an agreement which will set rules for mutual recognition of clinical trial results"²⁸. However, the results of clinical studies are not the subject of agreements between the governments of different countries. The European Commission issued the following answer to the question whether it is legally possible to initiate agreements for mutual recognition of the results of clinical studies between the European Union and the Russian Federation: "There are no mutual recognition agreements on clinical trials. The European Union accepts the clinical trials performed in accordance with Good Clinical Practices"²⁹. Interestingly, according to statistics comparing 2004-2009 and later developments, there has been no substantial increase in the number of both local and international multicentre clinical trials initiated by non-domestic pharmaceutical companies in Russia. Only the number of applications for bioequivalence trials by international sponsors has shown a substantial increase. So, legislation requirements have obviously reverse effect causing in the reserve position of the innovative companies concerning redundant local clinical trials³⁰.

On 17 December 2012, a report concerning a recent meeting with the DG Sanco of the European Commission was published on the website of the Russian MoH. According to the head of the Drug Regulatory Affairs Department, Ms. Elena Maximkina, the new amendment of the law No 61-FZ was under preparation. Based on the information from this meeting³¹ and other

²⁸ ACTO Press Release, 2011

²⁹ European Commission, 2011

³⁰ Zavidova, 2012

³¹ MoH of Russia, 2012

consultations³² and proposals from the stakeholders (i.e. FAS, AIPM and ACTO, see above), among others, the following forthcoming amendments were to be expected (all information subject to change):

- The requirement for nonclinical studies on generics would be abolished;
- The requirement for comparative clinical trials for generics in pharmaceutical forms not a subject of bioequivalence (e.g. parenteral injections) might be abolished;
- The possibility of not submitting local clinical trial data if clinical studies submitted were conducted under GCP is under controversial discussion;
- The documentation for CTAs is to be changed to avoid double (preliminary and formal) request for authorisations, although at present no split between the procedures to request a CTA and submit an MAA is planned;
- Abolishment of the accreditation of clinical sites by the MoH and/or changes to the requirements of the principal investigators are under consideration;
- A new procedure for the quality control of investigational medicinal products may be introduced. If this happens, it would seriously complicate and delayed the procedure for request for a CTA;
- Simplification of the procedures for importing of samples for quality control investigations for the MAA;
- It may be possible to consult experts on the application of the law, but not in the form of scientific advisory boards, only by written communication;
- Appeals against non-approval of the request for CTA or MAA may be introduced.

On 25 January 2013, latest draft of the amendments to the law No. 61-FZ was published on the website of the Russian MoH. According to the draft amendment, the following substantial changes will be implemented by the law³³:

- Some legal definitions will be introduced into the Russian legislation, e.g. for the MAH, orphan drugs, biosimilars, reference products for generics (if the original product is not registered in Russia);

³² URL 7 (www.aptekaexpo.com), 2012

³³ Russia: Draft law on the amendment of the Federal law No 61-FZ, 2013

- It will be possible to obtain regulatory and scientific advice from the experts at the MoH – probably in written form only, especially in case of scientific advice;
- The ethics committee will decide on "orphan designation". There are no specific criteria for orphan drugs, but if a medicinal product is recognised as an orphan drug, i.e. the product can influence the pathogenesis of a disease relevant for the local population and the prevalence of the condition in Russia is rare enough, local clinical data will not be required;
- Clock-stop periods for the preparation of the answers to deficiency letters have been introduced;
- Several changes in the requirement for the PIL will be adopted: quantitative composition of the excipients will not be required in the PIL any more; pharmacodynamic and pharmacokinetic data will not be required for homeopathic medicinal products (although local clinical trial data will still be required); a contact address for complaints will have to be listed in the PIL;
- Implementation of the ICH Common Technical Document (CTD) format on the quality part of the dossier in accordance with Module 3 including S and P-parts (independent of the requirement for the Russian language and Normative Documentation (ND) as a separate document);
- Clinical study reports must be submitted according to the new structure of the dossier, in addition to local clinical trial data;
- The accelerated procedure will be eligible only for the first generic application in Russia, and for orphan drugs;
- Introduction of a 180 day transitional period for the implementation of approved variations after the date of approval (at present it must be implemented on the day of approval);
- Since the scope of the dossier will be widened, a higher volume of variations is anticipated by the authorities. A new fee structure and different requirements for variations, e.g. full quality control in the case of different types of variation, have been introduced;
- New quality control procedures for medicinal products destined for local clinical trials will be required. There are still many questions open here, for example: how will the investigational medicinal product be defined in this case (only the product under authorisation, or placebo/comparator as well);

should it be the same batch as intended for use in the trial; should all batches be investigated or only one in the case of several batches; should ND be prepared, or can the applicant's original documentation be used.

The draft amendments to the law have come under heavy criticism from the different stakeholders³⁴. It is obvious that such changes will bring even more obstacles to market access for the new medicinal products³⁵. Although the current draft amendment contains some positive changes, i.e. the possibility of scientific advice, clock-stop periods, no quantitative composition in the PIL, CTD format and a 180-day transitional period for variations, the crucial negative requirements of the Russian law, such as local clinical trial data, non-acceptance of English documentation in the dossier and new quality control procedure for the clinic samples, will continue to hamper registration procedures in Russia. It will not be clear exactly which changes will be implemented until the third quarter of 2013 (estimated date).

2.4 Regulatory Authorities

As discussed above, the MoH of the Russian Federation plays a crucial role in the granting of marketing authorisations for medicinal products as the State executive body according to Article 13 of the law No. 61-FZ. Since clinical studies are part of this procedure, the MoH is also responsible for CTAs. The Russian MoH in its current structure was established on 19 June 2012 per Decree No. 608 of the Government³⁶ and resulted from splitting the former Ministry of Health and Social Development into 2 separate ministries: the MoH and the Ministry of Labour. A new Minister of Health, Ms. Veronika Skvortsova, physician by training, was appointed. This news was received enthusiastically by the medical and pharmacological communities, since the former Minister of Health and Social Development, Ms. Tatyana Golikova, a labour economist by education, was connected with the mostly unpopular decisions taken in previous regulatory legislation. A key responsibility for

³⁴ Mekshun, 2013

³⁵ ACTO Press release, 2013

³⁶ Russia: Decree No.608 of the Government of the Russian Federation, 2012

marketing and clinical trial authorisations within the new structure of the MoH was assigned to the Drug Regulatory Affairs Department with its head, Ms. Elena Maximkina, a pharmacist by education³⁷.

In accordance with Article 33 of the Russian law the MoH continuously updates the State Registry of Medicinal Products, web-based database of the clinical trials and medicinal products under authorisation³⁸. Amongst other things, the following information is publically available in the registry:

1. Database covering all authorised medicinal products, including name, international nonproprietary name (INN) of the active substance, pharmaceutical form, MAH, country of origin, date and number of the registration, approved PIL;
2. Register of CTAs, including date, name of the sponsor and CRO, dates of the start and (planned) end of the trial, some details of the clinical study protocol such as name, strength and pharmaceutical form of the product, design and objectives of the study, medical sites involved in the trial, number of the study participants and status of the trial;
3. Index of registered maximum ex-factory prices for the products included in the List of essential medicinal products, as per Article 60 of the law;
4. Catalogue of medical sites accredited by the MoH to conduct clinical trials, including name and address of the authorised clinics.

This website is the key instrument in communication between applicants and the MoH, in addition to the still unavoidable individual visits and paper submissions to the Drug Regulatory Department. With official authorisation by the MoH, the applicant can be granted access to a greater body of information, including the "digital office of the applicant" within the scope of the MAA procedure and for maintenance purposes after approval.

According to Article 15 of the law, the MoH has to establish a separate Federal State Expert Authority. Currently, the corresponding expert body operat-

³⁷ URL 8: MoH structure (www.rosminzdrav.ru), 2013

³⁸ URL 9: State registry of medicinal products (grls.rosminzdrav.ru), 2013

ed the so-called "Scientific Centre of Expertise of Medicinal Products" (FGBY NCESMP; ФГБУ НЦЭСМП in Russian). The principal duties of the expert authority are as follows:

- To conduct regulatory assessments of the clinical trial applications and application dossiers provided by the MoH;
- Writing of assessment reports on the quality, non-clinical/clinical and risk/benefit assessments;
- Quality control of the samples provided by applicants;
- Issuing of guidelines and educational activities³⁹.

As per Article 16 of the law, applicants are not permitted to communicate with the experts directly, only with the MoH. This means that there are no scientific advice meetings with the assessors and that the assessment processes of the submitted applications are not transparent.

Previously, according to the old law and formerly valid guidelines, all the procedures for MAAs were governed by the Federal service on surveillance in healthcare (Roszdravnadzor). Currently, this authority performs its direct duties such as domestic GMP, GCP and GLP inspections, certification and state quality control of medicinal products put onto the market, pharmacovigilance, licensing of medical and pharmaceutical activities, certification of medical devices, and surveillance of the functions of hospitals and pharmacies. There are 79 regional surveillance inspectorates spread over the territory of the Russian Federation⁴⁰.

3. Case study: regulatory legislation in the Ukraine

3.1 Historical overview

Like all ex-Soviet Union Republics, the Ukraine started to develop its own regulatory legislation in the early 1990s after gaining independence. The first provisional rules for MAAs for medicinal products were formulated as early as

³⁹ URL 10: "Scientific centre of expertise of medicinal products" (www.regmed.ru), 2013

⁴⁰ URL 11: Federal service on surveillance in healthcare (www.roszdravnadzor.ru), 2013

in 1992. After proper preparation, the first Ukrainian Drug Law came into force in 1996. Despite the unstable political situation of the last decade, frequent changes in government and in the responsibility of different authorities, as opposed to Russia, the Ukraine has a more stable situation with regard to core regulatory legislation. Although the Drug law from year 1996 has been amended many times, it is still in force⁴¹. From the early 2000s onwards, the Ukraine began to harmonise its regulatory legislation with the European laws: procedures for MAAs, non-clinical and clinical trial authorisations, format of the dossiers for initial applications and for variations, pharmacovigilance and Good Manufacturing Practice (GMP) rules have been adopted to a great extent in line with ICH/EU Guidelines and European legislation. There are, however, some domestic peculiarities. In 2005, the currently valid procedures for MAAs were passed by the Cabinet of Ministers of Ukraine in the form of the Decree No. 376⁴². The procedures for the assessment of new submissions, renewals and variations were formulated in the same year by the Ukrainian MoH⁴³. This so-called Decree No. 426, along with the Decree No. 376 and the Ukrainian Drug Law (all three as amended) are what mainly determine regulatory activities in the Ukraine.

3.2 Current regulatory legislation

The Ukrainian Drug Law lays down the provisions on the marketing authorisation, development, manufacturing, quality control and marketing of medicinal products. Other legislation and guidelines regulating the above mentioned aspects have to be in accordance with the law. Corresponding to the definition of a "drug" in Article 2, the following categories of products are regulated by the law: active substances, products "in bulk", finished medicinal products, homeopathic drugs, diagnostic and antiseptic remedies, cosmetic medicines and medicinal food supplements. Article 9 of the law stipulates the scope of the procedure of marketing authorisation for the medicinal products: MAAs containing the required information on quality and manufacture including

⁴¹ URL 12: History (www.dec.gov.ua), 2013

⁴² Ukraine: Decree No. 376 Cabinet of Ministers Ukraine, 2005, as amended

⁴³ Ukraine: Decree No. 426 MoH Ukraine, 2005, as amended

GMP-certificate, non-clinical and clinical data have to be submitted to the competent authority as defined by the MoH. The following documentation is subject to separate approval: product information (labelling and PIL), quality control methods (specifications and analytical procedures), and manufacturing methods. If approved, the registered documentation with the corresponding registration number is included in the State Register of Medicinal Products of the Ukraine. The registration certificates are valid for 5 years; one year before the end of this period, the registration can be renewed upon corresponding application (not later than 90 days before expiry date⁴⁴). According to current practice, a medicinal product for which the registration certificate has expired cannot be marketed in the Ukraine even if renewal application is pending. An unlimited registration period has not yet been established by law. The data exclusivity period for original medicinal products amounts to 5 years, if the application is submitted in the Ukraine during the two years after the first authorisation in the world. The 5-year period of data exclusivity can be extended to a maximum of 6 years if, during the first 3 years, a new therapeutic indication which brings significant clinical benefit in comparison with existing therapies, is authorised. The exact procedure governing the marketing authorisation of medicinal products is determined by the Ukrainian government⁴⁵.

The Decrees No. 376 and No. 426, as amended (including 18 annexes) lay down the procedure for the assessment of new submissions, renewals and variations in accordance with the Art. 9 of the Drug law. Decree No. 426 covers all medicinal products except immunobiologicals (immunobiological medicinal products were included in the scope of Decree No. 376 in August 2012, but exact procedures for assessment have still not been formulated). Most of the provisions of the Decree have been harmonised with the EU Directive 2001/83/EC as amended and this is in line with current Ukrainian legislation on harmonisation with the EU laws⁴⁶.

⁴⁴ Ukraine: Decree No. 376 Cabinet of Ministers Ukraine, 2005, as amended

⁴⁵ Ukrainian Drug Law, 1996, as amended

⁴⁶ Ukraine: Law of Ukraine No. 1629, 2004, as amended

As per Article 2 of Decree No. 426, an applicant (MAH) is a legal entity or individual person responsible for the quality, efficacy and safety of the medicinal product under application. The MAH has to assure the pharmacovigilance measures in the Ukraine; it means that not only domestic companies can act as MAHs. The manufacturer of the medicinal product is defined as a legal entity that performs at least one stage of the technological process, including, amongst other things, packaging, labelling, and quality control.

Article 3 of the Decree No. 426 describes the procedures for the assessment of initial applications (and renewals) by the expert body⁴⁷, as shown in Table 2; the applicant's activities are shaded in grey.

Table 2. Dossier assessment by the Ukrainian expert body.

No.	Timelines	Procedural steps
0.		Pre-submission meeting (optional)
Step I:		Validation of the application
1.	day 0	Submission of the application form according to Annex 1 of Decree No. 426 and dossier, containing quality part, non-clinical and clinical data, draft SmPC/PIL, mock-ups of labelling, samples of the product, letter of guarantee assuring that Ukrainian patent rights of any third party are not violated by the application, as required by Article 9 of the Drug Law. According to Article 6.11 of Decree No. 426, the dossier can be submitted in Ukrainian, Russian or English. Ukrainian is only obligatory for some parts of the dossier, e.g. the application form, labelling, methods of quality control. Two hardcopies of the dossier must be submitted, although electronic submission is possible (according to the established practice it is acceptable for CTD Modules 2 to 5).

⁴⁷ based on "Ukraine: Decree No. 426 MoH Ukraine, 2005, as amended"

No.	Timelines	Procedural steps
2.	not de- fined*	Validation: application type, verification of categorisation as a medicinal product, borderline issues. In case of positive validation: - Confirmation of validation; - Written contract with the applicant on the assessment.
3.	not de- fined*	Applicant pays state fees for the MAA and for the assessment.
Step II:		Preliminary assessment
4.	15 days	Preliminary assessment of the origin of the active substance/finished product, manufacturing processes, completeness of the dossier submitted so that the application can be subjected to the appropriate procedure for specialised assessment. Written answer to the applicant: positive decision (see Step III) or deficiency letter.
5.	clock-off period 90 days	Answer to the deficiency letter, if any. If no answer, the application is rejected. After the answer, the procedure starts again at point 4.
Step III:		Specialised assessment
6.	not de- fined*	Specialised assessment of the efficacy, safety and quality including additional tests of the medicinal product under submission, if necessary. If the documentation is inadequate, deficiency letter to the applicant.
7.	clock-off period 90 days	Answer to the deficiency letter, if any. Clock-off period can be extended for the preparation of the additional data upon written request by the applicant. If no answer, the application is rejected.
8.	clock-off	Additional tests/assessment of the medicinal product, if necessary. Extra contract/fees with the separate expert organisation (e.g. analytical laboratory for the quality control) may be required.

No.	Timelines	Procedural steps
9.	not de-fined*	Assessment report on the quality, safety and efficacy of the medicinal product under submission, including recommendation on approval of PIL, mock-ups of labelling, methods of the quality controls and manufacturing.
* <i>Maximum of 210 days in total for Steps I to III for a full application; maximum of 90 days for generic, WEU, informed consent or fixed combination applications. The deadlines are often exceeded.</i>		

3.3 Topical issues in the regulatory environment

The following topics, partly determined by the declared policy of the Ukraine to be in harmonisation with European legislation, have been widely discussed and are the focus of the attention of all stakeholders operating on the Ukrainian pharmaceuticals market.

3.3.1 Confirmation of GMP certificates

The Ukraine joined to the Pharmaceutical Inspection Co-operation Scheme (PIC/S), a network of the leading GMP-competent authorities of the world, on January 2011⁴⁸. On 14 November 2011, Decree No. 1165 of the Cabinet of Ministers of Ukraine "On changes in the marketing authorisation procedures" went into force. According to the Decree, conformity between the manufacturing processes used for the medicinal product under submission with current GMP rules has to be ensured during the assessment of initial applications, renewals and variations. This has to be confirmed by the Ukrainian GMP-competent authority in the form of a manufacturing license for domestic pharmaceutical companies or as "Certificate of Compliance" for foreign manufacturers. A Ukrainian Certificate of Compliance with GMP has to be provided for all marketing authorisations issued before the Decree becomes effective (1 July 2013) after an amendment made in June 2012 (originally, this deadline was 1 July 2012)⁴⁹. For currently pending applications (initial MAAs,

⁴⁸ URL 13: PIC/S Accession dates (www.picscheme.org), 2013

⁴⁹ Ukraine: Decree No 1165 of the Cabinet of Ministers of Ukraine, 2011, as amended

renewals and variations), a Ukrainian GMP certificate has to be provided not later than by the end of the assessment period. Originally, and until late Spring 2012, this was a critical issue, because the Ukrainian certificate based on the then version of the Decree had to be submitted before assessment, or for pending applications up to November 2011 directly after the publication of Decree No 1165 without any transitional period. Applications that did not comply with this were to be rejected⁵⁰. The result was that assessments practically came to a standstill in this period. Pending renewal applications with deadlines between the end of 2011 and June 2013 are especially affected by this Decree, since the marketing of medicinal products after the expiry date of registration is prohibited, regardless of whether the renewal application is pending, whereas renewal without the Ukrainian Certificate of Compliance with GMP is not possible.

The present MoH Ukraine Decree No. 1130 of 27 December 2012 (valid from 8 February 2013) "On the procedure of confirmation of compliance to the GMP" provides for a simplified procedure of the confirmation of GMP certificates issued by the competent authorities of the member-countries of PIC/S, as in EU countries. Despite being simplified, the procedure still required a series of documents, including a special application form, a certified translation of the GMP-certificate and manufacturing license into Ukrainian, Site Master File (SMF), list of medicinal products registered in the Ukraine and intended to be submitted including data on marketing authorisation in other countries and on the quality of products, such as complaints, recalls etc. Additional documentation is required if all or part of the manufacturing process is performed by a contract manufacturer. The Certificate of Compliance with GMP issued by the Ukrainian authority is product-specific⁵¹. It means all authorised medicinal products and products intended for submissions have to be included in the Annex to the certificate.

⁵⁰ Prihod'ko, 2012

⁵¹ Ukraine: Decree No. 1130 MoH Ukraine, 2012

The validity of such "confirmed" GMP certificates corresponds with the validity of the original certificate issued by the authority of a PIC/S country, and is valid for not more than 3 years as a rule. As per Decree, the whole procedure should take not more than 25 working days (with a possible clock-off period for answers to deficiency letters), although experience shows that the deadlines are often exceeded. Taking into account the time need to prepare all the required documentation by the pharmaceutical company and the relatively short validity of the certificates, the whole procedure of GMP confirmation requires tough time-schedules to maintain efficient regulatory life-cycle activities and operations on the Ukrainian market.

The actual situation with regard to GMP confirmation has been made more difficult with the issuing of Decree No 793 of the Cabinet of Ministers on 8 August 2012 "On changes to the procedure of the control of imported medicinal products". According to the Decree, the MAH or importer of the medicinal products has to provide a Certificate of Compliance with GMP issued by the Ukrainian competent authority containing the name of the imported products, as from 15 February 2013 (originally from 1 January 2013)⁵². Due to the very short transitional period (the first version of the Decree was officially published on 5 September 2012) and the complicated and unfinalised procedure of the GMP confirmation, a whole range of medicinal products cannot be imported into Ukraine after the deadline on 15 February 2013, regardless of whether they have valid marketing authorisations or not. The MoH of the Ukraine and numerous professional organisations of pharmaceutical manufacturers have suggested extending the deadline to 1 July 2013⁵³, but this suggestion was not adopted by the Ukrainian government.

3.3.2 Import licence

The next non-monetary hurdle for the import of medicinal products was introduced by the Ukrainian Law No. 5038-VI of 4 July 2012 "On licensing of the import of the medicinal products". According to its provisions, an authorised

⁵² Ukraine: Decree No. 793 Cabinet of Ministers Ukraine, 2012, as amended

⁵³ Association of Pharmaceutical Research and Development (APRaD), 24.12.2012

medicinal product can be imported into the Ukraine only by an importer (the manufacturer or representative in the Ukraine) with a corresponding import licence. The licence is product-specific, which means that the name of the medicinal product must be included in the annex to the licence. To obtain a licence, the importer has to prove that appropriate premises, technical equipment, qualified personnel and control facilities are available. The competent authority has to perform a corresponding audit before issuing the import licence. The provisions of the law come into force on 1 March 2013 ⁵⁴.

In the draft of the law, the following reasons were given for adopting this approach⁵⁵:

- EU regulatory rules concerning imports from third countries are to be adopted in Ukrainian legislation;
- 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;
- Qualified personal, especially a qualified person (QP) for GMP, have to be involved and declared;
- The importer will be responsible for the possible complaints or recalls of batches from the market, if necessary.

According to the explanations of the Head of the Ukrainian GMP authority, Mr. Solovjov, with the Law, the Ukraine has harmonised its legislation with Article 40 of the Directive 2001/83/EC (on the manufacturing authorisation for imports coming from third countries as per Art. 40.3⁵⁶).

Currently, licensing procedures for the manufacture, wholesale and retail sales of medicinal products already exist in the Ukraine. The import licence can be obtained by the manufacturer/MAH or their distributor independent of

⁵⁴ Ukraine: Law of the Ukraine No. 5038-VI, 4 July 2012

⁵⁵ Ukraine: Draft Law "On licensing of the import of the medicinal products", 06.06.2012

⁵⁶ Directive 2001/83/EC, as amended

existing licences. One importer can even represent several manufacturers. The importer is responsible for the quality, efficacy and safety of the medicinal product including pharmacovigilance and compliance with the approved dossier⁵⁷. The importer must be a resident of the Ukraine. If the MAH, manufacturer and importer are different persons or legal entities, a clear three-party contract is required. The implementation of the import license procedure in the Ukraine was prompted by experience made in other countries, especially Poland⁵⁸. To obtain authorisation, Poland's current requirements for third country imports are as follows⁵⁹:

- The following documents must be submitted to the Polish competent authority: application form, SMF, information on QP;
- A GMP audit of the manufacturer has to be conducted before the contract is signed;
- The manufacturer must have their own facilities for storage, transport of medicinal products and conducting batch release, or must have an appropriate contract with the accredited laboratory;
- A QP for GMP is responsible for batch release;
- Comply with the current GMP standards documented by GMP inspection;
- To issue their own certificates of analysis after quality control of the each imported batch;
- Responsibility for quality, efficacy and safety of the imported products;
- To organise batch recalls, if necessary.

It is obvious that such requirements go far beyond the usual capabilities of representative offices of the most pharmaceutical companies or their distributors in the Ukraine. It seems that the Law was initiated by a strong lobby by domestic, mostly generic, pharmaceutical companies. A range of the professional organisations have tried to prevent the Law from coming into force, without any noticeable effect⁶⁰. By the end of 2012, there were rumours that

⁵⁷ Sinicyna, 2012

⁵⁸ State Administration of Ukraine on medicinal products, Information from 31.10.2012

⁵⁹ State Administration of Ukraine on medicinal products, Information from 17.10.2012

⁶⁰ Spivak, 2012

the legislation might be postponed⁶¹, although such decision cannot be made by the MoH, but only by the Parliament of the Ukraine, which was blocked at that time due to the difficult political situation in the country. A draft law "On withdrawal of the law «On licensing of the import of the medicinal products»" was tabled on 5 February 2013 in the Ukrainian Parliament⁶², but so far had had no impact. Due to the difficulties with the implementation of the new legislation, the Ukraine could face considerable deficits of imported medications, including some essential medicinal products from 1 March 2013 onwards⁶³.

As of 1 March 2013, valid secondary legislation establishing the full procedure of import licensing has not been legally implemented. The first draft legislation for licensing was published on 14 January 2013. The rules were revised several times, and a fourth version of the draft procedures for import licensing was published on 20 February 2013 on the Ukrainian MoH website⁶⁴. Since such draft rules have to be open for public consultation for at least a month, as per current Ukrainian legislation, it is obvious that a full procedure for import licensing cannot be implemented by 1 March 2013.

It was not until 11 February 2013 that the Ukrainian government issued Decree No. 103 which designated the State Administration of Ukraine on Medicinal Products (GMP body) as the authority responsible for import licensing procedures⁶⁵. On 13 February 2013, the Ukrainian Government issued Decree No. 112 on the addition of import licensing to the general Ukrainian licensing rules, which will be valid from 1 December 2013 onwards⁶⁶. As per press-release of the Ukrainian MoH, between 1 March and 1 December 2013, the "formal" import license can be issued on the basis of a simplified

⁶¹ Prohorenko, 2012

⁶² Journal "Apteka", Press office, 11.02.2013

⁶³ Journal "Apteka", Press office, 19.11.2012

⁶⁴ Journal "Apteka", Press office, 20.02.2013

⁶⁵ Ukraine: Decree No. 103 Cabinet of Ministers Ukraine, 11.02.2013

⁶⁶ Ukraine: Decree No. 112 of the Cabinet of Ministers Ukraine, 13.02.2013

application by the importer. The exact procedures for import licensing should have been established during this period⁶⁷.

On 20 February 2013, the Ukrainian MoH issued Decree No. 143 establishing a simplified procedure for application for an import licence, which comes into force on 1 March 2013. The company (resident of Ukraine) is eligible to apply for import licensing using the simplified procedure if it already has a local license for the manufacture or wholesale trading of medicinal products. If there is no local licence, the premises involved have to be audited by the competent authority⁶⁸.

According to a press-release of the State Administration of Ukraine on medicinal products, 72 applications for the simplified procedure for import licensing were approved on the first day of licensing, i.e. 1 March 2013⁶⁹. These licenses, however, are valid only during the transitional period up to 1 December 2013 only. After 1 December, the rules described above in this section should apply, although the entire scope of the legislation had still not been established by 1 March 2013.

3.3.3 Extension of the procedure for marketing authorisation

In February 2012, the Ukrainian MoH introduced new rules on the interactions between the pharmaceutical department of the MoH and the Ukrainian 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:

- A. Service centre "Single point of contact" for direct communication with applicants within the structure of the expert body;

⁶⁷ MoH Ukraine, press office, 20.02.2013

⁶⁸ Ukraine: Decree MoH Ukraine No. 143 from 20.02.2012

⁶⁹ State Administration of Ukraine on medicinal products, Information from 01.03.2013

- B. Standing Committee for Marketing Authorisation of Medicinal Products for the approval of the assessment reports of the expert body and to take decisions on applications within the structure of the MoH Ukraine.

According to the Decree No 98, the procedure of dossier assessment (see Table 2) has been supplemented with the following steps⁷⁰. (A) and (B) in the first column of the Table 3 indicate the responsibilities of both new structures.

Table 3. Additional steps in the MAA as per Decree No 98 MoH Ukraine

No.	Timelines	Procedural steps
1.	day 0	Submission of the application (see Table 2)
1(A)		Applications have to be submitted via the Service Centre "Single point of contact" of the National expert body.
Points 2 to 9 as per Table 2		Assessment of the application by the Ukrainian National expert body.
10 (B)	not defined*	After assessment, the expert body sends assessment report with the accompanying documentation to the Pharmaceutical Department of the MoH (Committee for Marketing Authorisation of Medicinal Products).
11 (B)	1 month ⁷¹	The Committee reviews the assessment report of the expert body. In case of a positive decision, a draft registration certificate for the MAA (or renewal/variation) is prepared and sent to the expert body. Otherwise the Committee can send a deficiency letter to the expert body (or reject the application). The expert body has to justify its position and provide additional supportive documentation if necessary.
12 (B)	6 working days	The expert body reviews and confirms the draft reg-

⁷⁰ Ukraine: Decree MoH Ukraine No. 98 from 09.02.2012, as amended

⁷¹ Ukraine: Decree No. 376 Cabinet of Ministers Ukraine, 2005, as amended

No.	Timelines	Procedural steps
		istration certificate and sends it to the Pharmaceutical Department of the MoH for signature.
13 (B)	2 working days	The signed registration certificate is sent back to the expert body.
14(A)	2 working days	The expert body provides to the Service centre "Single point of contact" the following documentation for forwarding to the applicant: <ul style="list-style-type: none"> - Original signed registration certificate (or amendment to it in the case of a variation); - PIL/SmPC (optional); - Approved methods of quality control (or changes in case of variations).
* see Table 2		

Annex III shows a flow-chart with the entire marketing authorisation procedure in the Ukraine.

Immediately after publication, Decree No 98, nicknamed the "Mini-revolution in regulatory affairs" by the regulatory affairs community, triggered controversial discussion between all stakeholders. The greatest criticism was directed towards the increase in bureaucratic hurdles and the fact that now the Committee for Marketing Authorisation of Medicinal Products of the Ukrainian MoH takes decisions on the basis of the assessment reports of the expert body. The Committee may send a deficiency letter to the expert body or even reject the application (point 11 (B) of Table 3). Criteria for the review of the assessment reports by the Committee were not defined, nor were possible reasons for rejection of the MAA. The final decision on the applications is now therefore dependent on new, unknown factors⁷².

Representatives of the authorities claim that their aims are to harmonise with the European regulatory practice and to optimise registration procedures. It is

⁷² Snegirev, 2012

also worth mentioning that a new electronic database for applications called "Pharma-solution" has been introduced, and that a single contact expert within National expert body for the each application submitted will be appointed⁷³.

3.3.4 Upgrading of legislation on CTAs

An amendment to the Decree MoH Ukraine No 690 on CTAs⁷⁴ come into force on 6 August 2012 to harmonise Ukrainian legislation on clinical trials with the European GCP rules as per Directives 2001/20/EC and 2005/28/EC. Amongst other changes, the following modifications to Ukrainian GCP were recently introduced by the amendment^{75,76}:

- New requirements in the contracts between sponsor, Clinical Research Organization (CRO) and clinical sites (as well as medical university, if necessary);
- The terms of the insurance contracts with regard to the responsibilities of the sponsor towards study participants were expanded and clarified;
- The process of ethical assessment was transferred from the central ethics committee to the local ethics committees at the clinical sites;
- Parallel submission of the requests for a CTA to the MoH and the local ethics committees is now possible;
- The new structure of the Development Safety Update Report (DSUR) was introduced;
- Updated requirements for investigators and clinical sites participating in the trial;
- Some changes in the language of documents to be submitted, e.g. the protocol synopsis has to be in Ukrainian;
- Updated rules on the labelling of the investigational medicinal products (IMP);
- If clinical trials are conducted in the Ukraine only (with the aim of obtaining marketing authorisation in the Ukraine), each batch of the IMP has to un-

⁷³ Schegol, 2012

⁷⁴ Ukraine: Decree MoH Ukraine No. 690 from 23.09.2009, as amended

⁷⁵ Ukraine: Decree No. 523 MoH Ukraine from 12.07.2012

⁷⁶ Mihajlov, 2012

dergo full quality control testing at the analytical laboratory certified by the Ukrainian competent authority.

For the most part, the further adaptation of the GCP rules by the Ukrainian legislation was well received by all those involved in clinical studies. Further recent changes in the procedure of requests for CTAs and substantial amendments to the protocol (analogously to the procedures for MAAs and variations) as implemented per Decree No 98⁷⁷ are briefly described in Section 3.3.3 "Extension of the procedure for marketing authorisation" above.

3.3.5 New regulatory initiatives

Decree No. 426, as amended (including 18 valid annexes) lays down the procedure for assessment of new submissions, renewals and variations⁷⁸ 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 products⁷⁹:

- Upgraded classification of the various categories of variations to the terms of marketing authorisations for medicinal products as introduced by the "new" Variation Regulation No 1234/2008 and corresponding Guideline of the European Commission 2010/C 17/01 (currently the Ukraine has nationally implemented "old" categorisation of the variations corresponding to the Regulation (EC) No 1084/2003, see Annex 5 to 7 of the Decree No. 426);
- New annex for orphan medicinal products describing special aspects of marketing authorisation;
- New annex with criteria for additional studies on quality control, non-clinical trials, clinical efficacy and safety studies for some categories of medicinal products;
- Updated rules on bioavailability and bioequivalence testing for the authorisation of generics, requirement for different pharmaceutical forms, the pos-

⁷⁷ Ukraine: Decree No. 98 MoH Ukraine from 09.02.2012, as amended

⁷⁸ Ukraine: Decree No. 426 MoH Ukraine, 2005, as amended

⁷⁹ Schegol, 2012

- sibility of a "biowaiver" procedure involving in vitro dissolution tests (e.g. for new strengths) as introduced by Guideline on bioequivalence updated in year 2010 (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr);
- New requirements for immunobiological medicinal products.

Further trends in the Ukrainian regulatory legislation worthy of mention are:

- The State Administration of Ukraine on Medicinal Products suggests amending Decree No. 376 on the procedures for marketing authorisation of medicinal products with the following text: "if a medicinal product is authorised by European Medicines Agency (EMA)⁸⁰, marketing authorisation (renewal) in the Ukraine will be performed under the application without expert review of the dossier and quality control of the samples"⁸¹;
- It is interesting to note that the planned changes in legislation are made at a time when the Ukrainian government plans to implement non-voluntary licensing of patented medicinal products in year 2013⁸². The establishment of such an approach would allow domestic generic companies to manufacture and apply for marketing authorisation of innovative medicinal products legally and without any substantial payment to the owners of patented inventions⁸³.

3.4 Regulatory Authorities

The MoH of the Ukraine is a central executive body for the development and implementation of national policies in the pharmaceutical field as per Article 4 of the Ukrainian Drug Law⁸⁴. Within the structure of the MoH, the Department of Medicinal Product and Medical Devices is responsible for the strategic preparation of pharmaceutical legislation and for the formal processing of registration procedures. To find solutions for the controversial regulatory issues raised recently, a special advisory committee was established by De-

⁸⁰ correct would be the "European Commission"

⁸¹ State Administration of Ukraine on Medicinal Products, information from 18.02.2013

⁸² Uljanickij, 2013

⁸³ Popova, 2013

⁸⁴ Ukrainian Drug Law, 1996, as amended

cree No. 178 MoH Ukraine of 20 March 2012. The committee includes key specialists from different fields, such as clinical pharmacology, pharmacy, internal medicine, paediatrics, cardiology, and oncology⁸⁵.

The following key competent regulatory authorities are formally subordinated to the MoH, despite the fact that they are organised as separate legal entities.

The State Expert Centre MoH Ukraine (National expert body) acts as the key regulatory authority by performing the following tasks, amongst others⁸⁶:

- Expert assessment of dossiers submitted within the scope of initial marketing authorisations, 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;
- Maintenance of the State Registry of Medicinal Products;
- "Single point of contact" service for applicants;
- Participation in the development of new laws and scientific guidelines.

The procedure for the assessment of documentation submitted is regulated by the Decree No. 426⁸⁷, as described above.

The State Administration of Ukraine on Medicinal Products (former: State Inspectorate for Quality Control) acting as the GMP-competent authority performs its principal activities in the surveillance of quality control of the medicinal products on the Ukrainian market. The authority is responsible for GMP inspections, authorisation of domestic manufacturers, confirmation of the

⁸⁵ Ukraine: Decree No. 178 MoH Ukraine from 20.03.2012, as amended

⁸⁶ URL 14: State expert centre MoH Ukraine (www.dec.gov.ua), 2013

⁸⁷ Ukraine: Decree No. 426 MoH Ukraine, 2005, as amended

GMP certificates issued by the other countries, and, since 1 March 2013, for import licensing. The Ukraine, represented by the State Administration, has been a member of the PIC/S since January 2011. Nowadays the Authority plays a prominent part in the development of legislation in the field of the quality of medicinal products⁸⁸, which are especially relevant to the regulatory activities of international pharmaceutical companies.

4. Case study: herbal medicinal product - actual regulatory requirements for marketing authorisation in Russia and the Ukraine in comparison to the EU

4.1 Scenario for the case study

Justification for choice of case study

A special scenario is described to customise the case study of the MAA of a medicinal product in the CIS countries. Since the rules for the marketing authorisation of herbal and chemical medicinal products are similar in Russia and the Ukraine, a herbal product was chosen.

Status-quo

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 authorisations 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". The substance is not patent-protected; the pharmaceutical form is a syrup. Wunderherb is authorised under the well-established use (WEU) application with the legal status of an over-the-counter (OTC) drug. The WEU indication is mostly based on the data of German Commission E⁸⁹ Monograph on Phyto herbalis. The Tradi-

⁸⁸ URL 15: State Administration of Ukraine on Medicinal Products (www.diklz.gov.ua), 2013

⁸⁹ German Commission E for herbal medicinal products, special expert commission as per German Medicines Act (AMG); see URL 16: Expert commissions (www.bfarm.de), 2013

tional Herbal Medicinal Product (THMP) indication is established in the EU by the final Community herbal monograph for Phyto herballis issued by the Committee for Herbal Medicinal Products (HMPC) as described in Article 16a of amended Dir. 2001/83/EC. A Community list entry as per Art. 16f has not been made since no data on genotoxicity has yet been published.

Projects in progress at Phytopharmaka GmbH

A development programme for the new semi-ethical indication for Wunderherb was started by the research and development (R&D) department of Phytopharmaka GmbH some years ago. The programme includes all additional studies necessary to make a full application according to Article 8(3) Dir. 2001/83/EC, including non-clinical trials on genotoxicity and reprotoxicity, and two pivotal clinical trials. The first pivotal trial delivered very promising results and the second study is under preparation. In addition, the new pharmaceutical form film-coated tablets was developed by the pharmaceutical production and analytical departments of Phytopharmaka GmbH, and already included in the clinical development.

A dedicated project team was initiated by business development, including representatives from R&D, marketing and Regulatory Affairs to evaluate the different possibilities for marketing authorisations/registrations of the Wunderherb in the EU and worldwide.

Outlook for business development in the EU

Taking into account all the complex factors, the following – not necessarily contradictory – approaches to seeking approval in the EU were considered by the Project Team Wunderherb:

1. MAA based on WEU Indication via mutual recognition procedure (MRP) in key, "herbal-driven" EU markets.

Since Wunderherb is already authorised in Germany in accordance with Art. 10a Dir. 2001/83/EC as amended (WEU), an MRP with Germany as Reference Member State (RMS) could be initiated as per Art. 28 Dir. 2001/83/EC to obtain marketing authorisations in other EU countries. Taking into consideration that the WEU Monograph has not yet been estab-

lished by the HMPC (only THMP, see above) when choosing the Concerned Member States (CMS), careful attention would have to be paid to the selection of “herbal-driven” countries. Since HMPC monographs are not legally binding in the EU as per current legislation, approval of the WEU indication submitted via MRP application is considered to be realistic in some “herbal-driven” Member States. A scientific and procedural advice with German Authority (BfArM) acting as RMS and pre-submission meetings with the CMS would have to be scheduled.

2. Application for simplified registration of the THMP-Indication via the decentralised procedure (DCP) in the selected EU countries.

According to Art. 16d Dir. 2001/83/EC as amended, THMP registrations can be performed in the EU via DCP provided that the Community herbal monograph (or the Community list entry as per Art. 16f) has been established. Since the final HMPC monograph for Phyto herbalis has already been published, Wunderherb is eligible for application for registration via DCP with the THMP indication in accordance with Art. 16a Dir. 2001/83/EC. Proper selection of the RMS (highly probable excluding Germany because Wunderherb is already authorised here as WEU product) and CMS will be necessary and scientific and procedural advice meetings with the relevant authorities, including BfArM, must be arranged.

3. Full MAA according to Art. 8(3) Dir. 2001/83/EC for the new semi-ethical indication (new pharmaceutical form film-coated tablets has to be considered as well) via centralised procedure at the EMA.

According to Art. 3 Reg. (EC) No 726/2004 as amended, any medicinal product is eligible for the centralised procedure if the applicant can demonstrate that the medicinal product constitutes a significant therapeutic or scientific innovation or that the granting of the central marketing authorisation is in the interests of patients at Community level⁹⁰. The herbal preparations of Phyto herbalis are considered to be safe, especially in contrast with the authorised chemical entities used to treat patient with the semi-ethical indication so far.

⁹⁰ Regulation (EC) No 726/2004 as amended

In the opinion of the project team, the new, effective and safe herbal medicinal product Wunderherb can be considered as a significant therapeutic innovation and in the interests of patients at the EU level. A corresponding eligibility request should be submitted to the EMA in advance. Beyond simultaneous marketing authorisation in all 27 EU countries, authorisation of this type has the advantage of the same legal status throughout the EU. OTC status of the product is very important for marketing success since Phytopharmaka GmbH usually does not develop and market prescription-only medications (Rx). The company up to now has also had only very limited experience with reimbursement or communication with the Health Technology Assessment bodies (HTA) within the market access procedures in the EU. Due to the semi-ethical character of the indication on the borderline between OTC and Rx from country to country, a decision by some national competent authorities to assign Rx status is considered highly probable, even within an optional DCP procedure. A central decision on the legal status would overrule any national decisions and would be binding in the all member states. Additionally, a paediatric investigation plan (PIP) would not be obligatory with an application according to the Art. 8(3) Dir. 2001/83/EC for the following reasons:

- Wunderherb has already been authorised by the national procedure in Germany (WEU indication);
- Art. 7 of the Paediatric Regulation (EC) No 1901/2006 on new applications will not apply due to the concept of global marketing authorisation: if another marketing authorisation for that substance exists in the EU, regardless of the procedure for authorisation, the medicinal product in question will be considered as already "authorised"⁹¹;
- Art. 8 of the Paediatric Regulation on line extension applications such as authorisation of a new pharmaceutical form or a new indication (e.g. via variation type II)⁹² will not apply since the active substance – herbal drug preparation of Phyto herballis – is not patent-protected.

⁹¹ EMA, 2013. Questions and answers: Paediatric-investigation-plan guidance, Question 16

⁹² Regulation (EC) No 1901/2006

Current tasks of the Drug Regulatory Affairs Manager responsible for the CIS countries

The following key tasks were assigned by the Project Team to the Regulatory Affairs Manager of the Phytopharmaka GmbH relating to the future development of Wunderherb worldwide, especially in the CIS:

- To assess different possibilities of gaining approval in the region and to choose the best method based on procedures in Russia and Ukraine;
- To prepare information on the MAA/dossiers required for submissions;
- To estimate the possible impact of the different EU approaches;
- To assess requirements for registration in Russia and Ukraine;
- To evaluate the specific local requirements for successful access of Wunderherb to the Russian and Ukrainian markets;
- To anticipate the regulatory workload for at least the next 5 years after authorisation.

4.2 Basic conditions for the MAAs in the CIS countries

4.2.1 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)⁹³.

Russian legislation does not differentiate in this way. According to Art. 4 of the Russian Federal Law, medicinal products are drug substances in the defined pharmaceutical form used for the prevention, diagnosis and treatment of diseases, and for rehabilitation, or for maintenance, termination of pregnancy or for contraception. A drug substance is any substance or combination coming into contact with the human body, penetrating into the organs

⁹³ Dir. 2001/83/EC as amended, Art. 1(2)

and tissues for the purposes as described for the medicinal products, and originating from blood, blood derivatives, organs, human or animal tissues, plants, or chemicals obtained by synthesis or biotechnology⁹⁴.

In contrast to Russia, the Ukrainian legislation has practically adopted European concept of the definition of medicinal product, although pregnancy prevention is mentioned separately. As per Art. 2 of the Ukrainian Drug Law, a medicinal product is any substance or combination (used in defined pharmaceutical forms) which has properties for treating or preventing diseases in human beings (by presence), or which can be intended for contraception, recovery, correcting or modification of physiological functions in human beings by exerting a pharmacological, immunological or metabolic action, or for making a medical diagnosis (by functions)⁹⁵.

No medicinal product may be placed on the market without marketing authorisation in any of the countries concerned, pursuant to Art. 6 of Dir. 2001/83/EC as amended as well as Art. 13 of the Russian law No. 61-FZ and Art. 9 of the Ukrainian Drug Law.

Herbal medicinal products

Corresponding to Art. 1.30 to 1.32 Dir. 2001/83/EC as amended, a herbal medicinal product contains exclusively herbal substance(s) or preparation(s) or their combination (although acc. to Art. 16a.2 THMPs can contain some vitamins or minerals, or both). Herbal substances are mainly whole, fragmented or cut plants, plant parts, algae, fungi, lichen in an unprocessed – usually dried – form, which are defined by the plant part used and the botanical name. Herbal preparations are obtained from herbal substances by extraction, distillation, expression, fractionation, purification, concentration or fermentation, i.e. are comminuted or powdered herbal substances, tinctures, extracts, essential oils, expressed juices and processed exudates.

⁹⁴ Russian Federal law No. 61-FZ "On the regulation of the medicines" 2010, as amended

⁹⁵ Ukrainian Drug Law, 1996, as amended

As per Art. 4 of the Russian law No. 61-FZ, herbal medicinal products are products manufactured from herbal substances or combinations. Herbal substances are the plants or their parts used for the manufacture of the herbal medicinal products. In contrast with the terse Russian definitions, the Ukraine has completely adopted the wording of the European Directive 2001/83/EC in Art. 2.11 to 2.13 of Decree No. 426, as amended⁹⁶. In the CIS countries, herbal medicinal products are usually subject to the same regulatory legislation as chemical entities, although some particularities are possible.

4.2.2 Type of the applications

Full MAA

Art. 8(3) Dir. 2001/83/EC as amended lays down the scope of the full application for all types of medicinal products. Besides administrative documentation, all pharmaceutical data accompanied by the entire range of non-clinical and clinical studies have to be provided for the assessment. In contrast to full applications, there are some specific rules and exceptions for different types of the products, e.g. WEU applications, THMPs, homeopathics. The current Russian regulatory framework does not make such differences. According to the Russian law, all types of the medicinal products, including herbals, are subject to the same requirements as for chemical entities, so an application dossier containing a request for a local CTA or results from local clinical studies already performed have to be submitted. The Ukraine, however, basically follows European legislation, although with some local peculiarities. The scope of the full application is regulated by Art. 9 of the Ukrainian Drug law.

WEU application

If the active substance has had a well-established medicinal use with recognised efficacy and an acceptable level of safety for at least ten years, a WEU application can be submitted in the EU according to the Art. 10a of Dir. 2001/83/EC. In this case, non-clinical and clinical trials are replaced by the appropriate scientific literature. Bibliographic dossiers of this sort cover all aspects of safety and efficacy, as per Annex 1 of the EU Directive. This type

⁹⁶ Ukraine: Decree No. 426 MoH Ukraine, 2005, as amended

of MAA is primarily used for herbal medicinal products. A WEU monograph from HMPC, once available, can provide additional support for such applications.

WEU applications in this form do not exist in Russia, although bibliographic non-clinical and clinical data provided supportively in a dossier are usually well accepted by the assessors. However, a similar concept to "well-established use" is provided by Article 14.2.1).a) of law No. 61-FZ for "old" medicinal products registered more than 20 years in Russia, for which bioequivalence studies are not feasible⁹⁷. Such products, mostly originating from Soviet times (including herbals), are exempt from the requirement to provide results of a local clinical trial. For such applications, the Ukraine once again has word-to-word adopted the European legal texts on the WEU applications in Art. 2.15 and 6.3.2 of the Decree No. 426⁹⁸. This type of application is widely used for herbal medicinal products analogously to European practice.

THMP application

In 2004, a new way of licensing herbal medicinal products was introduced by Dir. 2004/24/EC, amending Dir. 2001/83/EC. The directive allows a new type of simplified registration procedure, so called traditional-use registration as per Art. 16a. The requirements for the quality part of the application dossier are the same as for all other herbal medicinal product; safety must also be established, while for efficacy, plausible medicinal use for at least 30 years including a minimum of 15 years in the EU have to be demonstrated bibliographically or by expert evidence⁹⁹. So far, more than one hundred final monographs suitable for THMP applications have been established by the HMPC¹⁰⁰. The weak point of the HMPC monographs is that they are not legally binding as per current EU legislation. Not only THMP, but especially WEU monographs find different levels of acceptance in different Member

⁹⁷ Russian Federal law No. 61-FZ "On the regulation of the medicines" 2010, as amended

⁹⁸ Ukraine: Decree No. 426 MoH Ukraine, 2005, as amended

⁹⁹ Dir. 2001/83/EC as amended, Chapter 2a.

¹⁰⁰ URL 17: Herbal medicines for human use (www.ema.europa.eu), 2013

States, e.g. acceptance is generally higher in Germany and Austria than in the UK¹⁰¹.

Simplified registration corresponding to the European THMP rules currently is not possible in Russia. This means that despite the status of the original registration in the EU, the applicant has to provide a full application including the results of a local clinical trial. By contrast, the Ukraine has adopted most of the THMP rules with some peculiarities. The applicant has to provide evidence of traditional use of the herbal medicinal product for at least 30 years in the world and at least 10 years in the Ukraine, pursuant to Art. 2.14 of the Decree No. 426 (or 15 years, according to annex 12 of the same Decree)¹⁰². Not least because of this requirement, the use of THMP applications plays a minor part in current registrations practices in the Ukraine.

The HMPC monographs have rather negligible influence on the registration procedure in all CIS countries. Mutual recognition of the European monographs is not possible at present due to the lack of a legal basis, although some information – particularly safety data – is taken into account by the regulatory authorities of Russia and Ukraine.

4.2.3 Presentation and format of the dossier for initial submission

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". The guidance for the compilation of the dossier is applicable to all types of EU marketing authorisation procedures, i.e. central, MRP, DCP and national applications. The application is presented in the format of CTD as agreed within the

¹⁰¹ MHRA, 2007

¹⁰² Ukraine: Decree No. 426 MoH Ukraine, 2005, as amended

framework of ICH. CTD format composed of Modules 1 to 5 of the dossier applies to all categories of the medicinal products, although there are some special requirements for different types of application or products types, e.g. for generics, herbals or WEU applications¹⁰³. Submission of an electronic version of the CTD (eCTD) is eligible, although not mandatory for most European procedures and countries¹⁰⁴, except central submissions to the EMA.

Russia still has its own format for the application dossier. The Russian language is mandatory for all documents, including bibliographic references. A European dossier in CTD format is not accepted by the Russian authorities, and its content has to be reorganised according to local requirements¹⁰⁵, as described below. Article 18 of law No. 61-FZ lays down the complete basic structure of the application dossier. Table 4 compares the Russian requirements to the EU CTD format. The numbers in the first column corresponds to the articles of the law¹⁰⁶; the numbers in the second column correspond to the CTD numbering as per Volume 2B "Presentation and content of the dossier: Notice to Applicants" of Eudralex¹⁰⁷, indicating where the required information can be found.

Table 4. Russian application dossier versus CTD format

Russian Dossier	CTD Module
Art. 18.2 Application form containing following information: 1) Name and address of applicant and/or manufacturer; 2) Name of the medicinal product (INN and brand name); 3) Qualitative and quantitative composition; 4) Pharmaceutical form, strength, posology, method of administration and proposed shelf-life;	1.2 Application Form (AF)

¹⁰³ Eudralex Volume 2B, 2008

¹⁰⁴ CMDh, CMDh/085/2008/Rev9, November 2012

¹⁰⁵ Hessenauer-Illicheva, 2012

¹⁰⁶ Russian Federal law No. 61-FZ "On the regulation of the medicines" 2010, as amended

¹⁰⁷ Eudralex Volume 2B, 2008

Russian Dossier	CTD Module
5) Overview of pharmacologic, pharmacodynamic or immunobiological properties of the medicinal product;	1.3.1 SmPC (Section 5)
6) Highest price (if subject of special list of the essential medicinal products);	
7) Justification for not conducting clinical trials for the product authorised more than 20 years, if applied.	
Art. 18.5 Annexes to application form: - Proof of payment of fees depending on the type of application (request for local CTA, or assessment for the product authorised for Russian market more than 20 years, or in case Russia was included in the international multicenter studies)	
Art. 18.3 Dossier for submission containing:	
1) Mock-ups of the outer and immediate packaging;	1.3.2 Mock-up
2) GMP certificate of manufacturer of finished product, notarised copy;	Annex 5.9 AF
3) Draft Methods of quality control of the finished product (so called Normative Documentation (ND)), including composition of finished product, specifications, analytical procedures, mock-ups, description of labelling, container-closure system, shelf-life etc. (for details see section 4.2.4/Table 5);	3.2.P.1 Composition 3.2.P.5.1 3.2.P.5.2 1.3.1 SmPC (sections 6.3 to 6.6)
4) Description and flow diagram of manufacturing process of active substance and finished product;	3.2.S.2.2 - 3.2.S.2.4 3.2.P.3.2 - 3.2.P.3.4
5) GMP certificate of manufacturer of active substance, notarised copy, containing name of substance, address of manufacturer, shelf-life;	Annex 5.9 AF (if available), alternatively Annex 5.22, additionally CoA
6) Specification for the active substance;	3.2.S.4.1
7) Methods of quality control of the active substance (ND) or reference to the monograph in pharmacopoeia, if available;	3.2.S.4.1 3.2.S.4.2
8) Information on storage and shipment conditions of finished product;	3.2.P.8.1 1.3.1 SmPC (6.4)

Russian Dossier	CTD Module
9) Reports on results of non-clinical studies ¹⁰⁸ ;	2.4 Nonclinical Overview / 4 Non-clinical Study Reports
11) Draft clinical trial protocol; 12) Investigator's Brochure; 13) Patient information sheet including informed consent; 14) Information on compensations for participants of the clinical trial;	Request for CTA
15) Report on results of international multicenter clinical trial partly conducted at the local Russian sites, if available;	2.5 Clinical Overview / 5 Clinical Study Reports
16) Draft SmPC/PIL including composition of finished product (for details see section 4.2.4)	1.3.1 SmPC/PIL 3.2.P.1 Composition
17) Certificate of a Pharmaceutical Product (CPP), for the imported medicinal product;	
18) Request for CTA as required per Art. 19 - 22 of law, including application form, Curriculum Vitae (CV) of investigators, copy of contract on the compulsory insurance (detailed maximum quantity of study participants), information on clinical sites, and timeframes of the study.	Request for CTA
Art. 23.2 Examination of quality of medicinal product and risk/benefit assessment after conducting local clinical trial: 1) Application to restart of the registration procedure; 2) Final clinical study report; 3) Fees for quality control and risk/benefit assessment.	
Art. 23.5 Samples of the medicinal product and corresponding reference substances in amounts sufficient for the quality control.	

¹⁰⁸ 10) the same as 9), but for the veterinary products only

MAA in the Ukraine

In contrast to the special requirements in Russia, the Ukraine accepts the CTD format as described in the current version of Volume 2B "Presentation and content of the dossier: Notice to Applicants" of Eudralex¹⁰⁹. In addition to this, corresponding to Art. 6.8 and Annexes 2 and 3 of the Decree No. 426, the former European NTA format as described in the 1998 edition of Volume 2B of Eudralex is acceptable as well¹¹⁰. As per Art. 6.11 of the Decree, Ukrainian, Russian or English languages are eligible for the documentation submitted. Ukrainian is mandatory only for the application form and SmPC/labelling. Translations of some documentation from Module 1 and 2 can be requested by the authority. Methods of quality control (analogous to the Russian ND) and description of the manufacturing process of finished product should be prepared in Russian or Ukrainian (for details see next section).

4.2.4 Preparation of the documentation with special requirements

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;
- Colour mock-ups of the outer and immediate packaging have to be approved. The finished packaging has to comply 100% with the approved mock-ups, whereas some placeholder are normally acceptable, e.g. for pack-size, registration number, European Article Number (EAN)-code etc;
- Braille is optional, except Ukraine.

¹⁰⁹ Eudralex Volume 2B, 2008

¹¹⁰ Ukraine: Decree No. 426 MoH Ukraine, 2005, as amended

According to Article 18.16 of Russian law, the PIL must contain following information¹¹¹:

- Name of the medicinal product (INN and brand name);
- Pharmaceutical form including qualitative and quantitative composition of active substance(s) and excipients;
- Indications;
- Contraindications;
- Posology, method of administration, time of application/intake (if relevant), duration of treatment (including paediatric population subsets before and after one year)
- Special warnings and precautions for use;
- Symptoms and methods of the initial treatment of an overdose;
- Special considerations concerning starting or withdrawal of treatment, if applicable;
- Actions in case of dose omission(s);
- Possible side effects;
- Interactions with other medicinal products and food;
- Considerations for special populations: pregnancy, lactation, children, patients with chronic diseases;
- Effects on ability to drive and use machines;
- Shelf-life and instruction not to use medicinal product after the expiry date;
- Storage conditions;
- Special precautions for storage the medicinal product out of the sight and reach of children;
- Special precautions for disposal of unused medicinal product, if applicable;
- Name and address of the manufacturer and manufacturing site(s);
- Legal status (Rx or OTC).

According to Article 46.1. of Russian law, the following information must be provided on the labelling¹¹²:

¹¹¹ Russian Federal law No. 61-FZ "On the regulation of the medicines" 2010, as amended

¹¹² Russian Federal law No. 61-FZ "On the regulation of the medicines" 2010, as amended

- On the immediate packaging: name (INN or brand name), batch, expiry date, strength or concentration/volume;
- On the outer packaging: name (INN and brand name), manufacturer, batch, number of registration certificate, expiry date, method of administration, strength or concentration/volume, pack size, pharmaceutical form, legal status, storage conditions, special precautions.

Russian language is obligatory for the PIL and labelling. There are some special considerations for herbal medicinal products, i. e. no printing on the immediate packaging and a "Radiologically tested" label on the outer packaging, but these requirements apply to herbal teas only¹¹³.

As per Art. 12 of the Ukrainian Drug Law, the following are required for the product information in the Ukraine¹¹⁴:

- For labelling: name of the medicinal product, name and address of the manufacturer, registration number, batch, method of administration, strength, pack size, expiry date, storage conditions, special precautions, information in Braille (name, strength, pharmaceutical form) on the outer package;
- For the PIL: name of the medicinal product, INN, physico-chemical characteristics, composition, pharmacological properties, indications, contraindications, interactions, method of administration and posology, possible side effects, special warnings and precautions for use, pharmaceutical form, shelf life, storage conditions and legal status.

Ukrainian language is mandatory for the PIL and labelling, although additional information in other languages is possible. The SmPC may be approved, otherwise the PIL only is the subject to approval. Further details, mostly in accordance with current European practice, including requirements

¹¹³ Balandina, 2011

¹¹⁴ Ukrainian Drug Law, 1996, as amended

for the labelling of THMPs are provided in Annexes 8 to 10 of the Decree No. 426¹¹⁵.

Approved PIL and mock-ups of the outer and immediate packaging are considered to be part of the marketing authorisation in both Russia and Ukraine; therefore they are forwarded to the MAH as annexes to the registration certificate.

Documentation on quality control

Preparation of the special documentation on quality of the finished product is typical for the CIS countries. This approach originated from the so-called "Temporary pharmacopoeal monographs" of the Soviet Union times. This documentation was used for the quality control of the finished product within the marketing authorisation procedure and in the postmarketing quality control, currently called "Normative Documentation" (ND) in Russia and "Methods of the Quality Control" in the Ukraine (hereinafter called also ND, for the sake of convenience). ND is the subject of the special approval by the competent authorities.

Structure and basic content of the current Russian ND is laid down by Decree No. 82 MoH Russia of 2000 "On the industry-specific standard (OCT 91500.05.001-00) "Standards of quality of medicines". There are different requirements for different pharmaceutical forms and different type of products, e.g. immunobiologicals or homeopathic products. Table 5 shows the ND sections^{116,117} indicating the location of the corresponding information from the CTD dossier¹¹⁸.

¹¹⁵ Ukraine: Decree No. 426 MoH Ukraine, 2005, as amended

¹¹⁶ Russia: Decree No. 82 MoH Russia, 2000

¹¹⁷ Mitkina, 2011

¹¹⁸ Eudralex Volume 2B, 2008

Table 5. ND Structure versus CTD-format

ND Structure	CTD Module
1. Name of the medicinal product (brand name in Russian); 2. INN (in Russian), structural formula and molecular weight of active substance, if applicable	1.2 Application form 3.2.S.1, 3.2.S.3
3. Quantitative composition of the finished product, e.g. for tablets separately for core and coating of tablet, including references to quality standards for all components.	3.2.P.1 Description and composition
4. Specification ¹¹⁹ : - Appearance (e.g. colour, shape of the tablets); - Identity (physical and chemical methods, e.g. TLC); - Average mass and uniformity of mass; - Dissolution or disintegration (e.g. for herbals); - Impurities (related substances), (not relevant for herbals, as a rule); - Microbiological purity; - Uniformity of dosage units (optionally, depending on active substance; alternatively to the uniformity of mass); - Assay (e.g. HPLC, spectroscopy, titrimetry).	3.2.P.5.1 Quality specification
5. Analytical Procedures (corresponding to the specification): - Appearance (e.g. organoleptically); - Identity (e.g. description of TLC method); - Average mass and uniformity of mass; - Dissolution or disintegration; - Impurities (related substances); - Microbiological purity;	3.2.P.5.2 Analytical Procedures

¹¹⁹ as required for the tablets (for the sake of demonstration)

ND Structure	CTD Module
- Assay (e.g. for HPLC including chromatographic conditions, system suitability tests; description of reagents and reference standards with references to their quality standards).	
6. Container closure system.	1.3.1 SmPC (6.5) 3.2.P.7
7. Labelling (mock-ups of outer and immediate packaging).	1.3.2 Mock-up
8. Shipment conditions of finished product; 9. Storage conditions; 10. Shelf-life.	1.3.1 SmPC (sections 6.3, 6.4) 3.2.P.8.1
11. Pharmacological group (ATC-code).	1.3.1 SmPC (5.1)

According to the Guideline of the State Expert Centre MoH Ukraine No. 41 as amended, Ukrainian "Methods of the quality controls" contains similar sections for the structure to those in the Russian ND, i.e. composition, specifications, analytical procedures, container closure system, labelling, storage conditions and shelf-life¹²⁰.

Approved NDs are considered to be part of the marketing authorisation in both Russia and Ukraine; therefore they are forwarded to the MAH after approval as annexes to the registration certificate. Certificates of analysis issued by manufacturer of the imported finished products have to correspond completely with the specification from ND.

4.2.5 Preliminary conclusions and advice for the case study

The preceding chapters describe the requirements for the MAAs and dossiers for initial submission in Russia and Ukraine. 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 and Ukraine:

¹²⁰ Ukraine: Guideline of State expert centre MoH Ukraine No. 41, as amended, 2011

Choice of the registration procedure

- In both countries Wunderherb will be considered as a medicinal product and a herbal medicinal product (especially if the German CPP will be submitted with the application);
- The current Russian legislation makes no significant differences between different types of applications. The MAA for Wunderherb should be submitted according to the standard procedure for chemical entities, whereby additional bibliographic data will be acceptable;
- Since Ukraine has mostly adopted EU rules on herbal medicinal products, both WEU and THMP applications are possible. WEU application is the most practicable method for the authorisation of herbals in the Ukraine. THMP registration is not recommended because the Ukrainian authorities have little experience with this type of application and there are some restrictions on marketing and special requirements of the data on traditional use in the Ukraine for at least 10 years (15 years as per other source, see above).

Possible impact of the different EU-approaches on the CIS-applications

1. Application for the WEU-Indication via MRP.

Since Wunderherb is already authorised in Germany, CPP for the applications in CIS can be provided by the competent authorities. Any further development should not jeopardise initial authorisation, since most of the ex-EU authorisations and further renewals will be based on the German CPPs. European procedure like the MRP can involve some risks for the initial marketing authorisation due the probable referral procedures designated by Art. 29 Dir. 2001/83/EC, for example. Since HMPC has not yet established monograph for the WEU Indication of Phyto herbalis, the risk of referral with an MRP for the WEU indication should be considered.

For these reasons, the so-called "duplicate" application¹²¹ via DCP procedure¹²² with Germany as RMS is advisable. In this way, the basis German national marketing authorisation of Wunderherb would not be jeopardised by the risk of referral. Since any harmonisation or mutual recognition of the HMPC monographs in Russia or Ukraine is established by now, only the fact of the marketing authorisation of Wunderherb in Germany (reflected by CPP) will be considered by the local regulatory authorities.

2. Application for the THMP Indication via DCP

Must probably, such an application would have no or negligible impact on any ex-EU authorisation procedures, since a final Community herbal monograph for Phyto herbalis has already been published by HMPC. The risk of referral or a negative outcome is therefore considered to be very low since the EU legislation on THMPs does not provide for referral to Committee for Medicinal Products for Human Use (CHMP). According to Art. 16h.1.(c) Dir. 2001/83/EC as amended, HMPC is responsible for performing the tasks set out in Article 32 (opinion on referrals) as regards referrals to the EMA under Chapter 4 (MRP/DCP), in relation to herbal medicinal products, as described in Article 16a (traditional use). So, if the Co-ordination Group for Mutual Recognition and Decentralised Procedures - Human (CMDh) fails to reach an agreement regarding THMP application, the matter would be referred to the HMPC¹²³. Because the HMPC has already reviewed the data available on Phyto herbalis during the preparation of the Community monograph, there should be no objections unless any new crucial safety data has emerged. As a matter of fact, if only the THMP registration exists in the EU, the applicant can usually use the CPP issued on the basis of this for full (or WEU) applications in all CIS countries, despite the legal basis in the country of origin according to Dir. 2001/83/EC as amended.

¹²¹ CMDh, Procedural Guidance, 2007

¹²² CMDh, Questions & answers, 2013, Question 1

¹²³ CMDh, Standard operating procedure, 2011

3. Full MAA on the new semi-ethical indication (possibly with additional pharmaceutical form film-coated tablet) via centralised procedure.

Since the clinical programme for the new semi-ethical indication of Wunderherb is still in progress, there is no point in waiting for the results of this project. The applications in the CIS countries can be done based on the existing marketing authorisation in Germany. If the centralised procedure in the EU has a positive outcome, the corresponding line extension applications can be submitted in the ex-EU countries, most probably as new applications (especially if the new pharmaceutical form film-coated tablet is to be introduced). To ensure compliance with local requirements at the outset of the project, inclusion of Russian clinical sites in the second pivotal study should be considered by the Project Team. The other possibility could be a local comparative study between syrup (especially if it will be already registered in Russia by that time) and the film-coated tablet demonstrating therapeutic equivalence, since bioequivalence is generally not applicable to herbal medicinal products. In addition to this, a local clinical trial in one indication can be sufficient to gain approval for all the other indications, as per current interpretation of the Russian legislation by the competent authorities.

Fulfilment of requirements for the initial MAA

The following steps should be taken to prepare the initial MAA of Wunderherb for Russia and Ukraine:

- Availability of a reliable liaison person communicating between the headquarters' Regulatory Affairs Department and the Russian and Ukrainian authorities, since most of the activities should be done locally and personally;
- Consider the local brand names in both countries and start the trademark registrations;
- Apply to the German authorities for the CPPs for Russia and Ukraine;
- Prepare application dossiers as described above. For the Russian dossier, this must be in Russian;
- Prepare draft NDs, PILs and mock-ups for both countries correspondingly;
- Prepare samples of the finished product with the Certificates of Analysis (CoA) as per specifications described in the NDs, accompanied by reference substances for full quality control;

- Check current requirements with regard to fees and bank details and provide proof of payment.

Valid for Russia only:

- Check availability of Phyto herbalis preparations authorised on the Russian market for more than 20 years in case there are any. Consider the same pharmaceutical form as in CPP and the appropriate indication, if not
- Check availability of the any clinical trials on Wunderherb/Phyto herbalis in Russia, if not
- Discuss within the project team the necessity for a local clinical trial for marketing authorisation. As soon it is decided to conduct a study,
- Select a reliable CRO for the Russian local trial;
- Together with the CRO, choose the appropriate design for the clinical trial (e.g. therapeutic equivalence with the comparator, superiority to placebo, open-label vs. double-blind);
- Prepare request for a CTA according to the current requirements.

Valid for the Ukraine only:

- Consider the availability of the Ukrainian authorities' recognition of the German GMP certificates, if not to apply for them;
- Initiate inclusion of the new product in the list of the products annexed to the Ukrainian GMP recognition;
- Consider the availability of the local legal entity for import licensing.

4.3 Maintenance of marketing authorisation

4.3.1 Special considerations for local postmarketing

To ensure smooth access of Wunderherb to the Russian and Ukrainian markets after obtaining marketing authorisations, the following special local aspects must be borne in mind:

- Approved mock-ups should be customised, i.e. to put the registration number on the package, replace placeholders for pack size and EAN-code with the final versions, if applicable;

- The same applies to the approved PIL, i.e. the registration number and date of approval have to be entered, and the layout adopted in accordance with the packaging;
- To establish a template for the CoA of the imported finished product in accordance with the requirements of the approved specification from the ND, with some additional local requirements, for instance registration number, date and validity period, manufacturing and expiry dates, for the Ukraine additionally batch size, data on GMP certificate and manufacturing licence, and name of manufacturer with address of manufacturing sites.

Furthermore, according to Art. 46.10 of Russian law, transport packaging (boxes for wholesale activities) have to be marked with the following information: name of the medicinal product, batch number, manufacturing and expiry dates, quantity of finished packages in the transport package, manufacturer with address, information on storage and shipment conditions of the finished product and a warning text and signs, so that corresponding labelling should have been established before the first supplies are dispatched.

Before the putting the product on the market, the current local requirements of the state supervision bodies on the quality control of batches imported in both Russia^{124;125} and Ukraine¹²⁶ have to be fulfilled during the custom clearance. This process might be especially crucial for the first batches delivered; Launch activities should be scheduled correspondingly.

As stated in Section 3.3 (above), the approved medicinal product has to be listed in the annex of the Ukrainian Certificate of Compliance with GMP issued by the local competent authority. The validity of the Ukrainian GMP certificate should be checked before launching and maintained during the whole postmarketing period¹²⁷. Also, as from 1 March 2013, the authorised medicinal product can be imported into the Ukraine only by an importer (the manu-

¹²⁴ URL 18: Quality control of medicines (www.roszdravnadzor.ru)

¹²⁵ URL 19: Documents for the applicants (86.62.95.226)

¹²⁶ State Administration of Ukraine on Medicinal Products, 12.01.2012

¹²⁷ Ukraine: Decree No. 1165 Cabinet of Ministers Ukraine, 2011, as amended

facturer or a representative in the Ukraine) with the corresponding import licence, as per current law¹²⁸.

A further point to consider is that from summer 2012 onwards, the possibility of public advertising of medicinal products in the Ukraine has to be approved during the marketing authorisation procedure, as per Art. 5 Decrees No. 376¹²⁹. This rule is especially crucial for OTC products like Wunderherb, since some herbal products (such as those indicated for the symptomatic treatment of benign prostatic hyperplasia) are already affected by the advertising restrictions in the Ukraine. The current "List of OTC products for which Public Advertising is Banned" was established by Decree No. 876 MoH Ukraine and has been in force since 10 December 2012¹³⁰.

Furthermore, a type of sunset clause was introduced in the Ukraine with the last amendment of the law in summer 2012. According to Art. 8 Decree No. 376, the MoH has the right to reject or suspend marketing authorisation if the medicinal product was not launched during the first two years after initial marketing authorisation or renewal (provided it was not justified by the manufacturing procedure)¹³¹.

In contrast to the European definition of the sunset clause, which can be invoked if the medicinal product is not marketed for three consecutive years corresponding to Art. 24 (4-5) Dir. 2001/83/EC as amended, the Ukrainian legislation specifies 2 years after registration or renewal. This might be explained by the local requirement for renewals every 5 years (see Section 4.3.4 Renewals), which would mean that a medicinal product, once launched, allowed to be not marketed up to 2 years after the next renewal.

¹²⁸ Law of the Ukraine No. 5038-VI, 4 July 2012

¹²⁹ Ukraine: Decree No. 376 Cabinet of Ministers Ukraine, 2005, as amended

¹³⁰ Ukraine: Decree No. 876 MoH Ukraine from 06.11.2012

¹³¹ Ukraine: Decree No. 376 Cabinet of Ministers Ukraine, 2005, as amended

4.3.2 Variations to the terms of marketing authorisations

Current situation with the variations in Russia

The application form for a variation can be submitted to the MoH of Russia along with the supportive documentation as provided by Art. 30 of the Russian law. The whole procedure is the same as that for the initial marketing authorisation as described in Section 2.2.5 above and should take not more than 90 working days. Full quality control of the medicinal product and/or risk/benefit reassessment have to be performed in the following cases:

- Changes to the PIL: indications, contraindications, posology, method of administration, time of application/intake, duration of treatment, special warnings and precautions for use, symptoms and methods of the initial treatment of an overdose, specialities concerning starting or withdrawal of treatment, possible side effects, interactions with other medicinal products or food, special populations (pregnancy, lactation, children, patients with chronic diseases), effects on ability to drive and use machines, shelf-life or legal status (Rx/OTC);
- Change in the qualitative or quantitative composition of the finished product;
- Change of manufacturing site;
- Changes into specification parameters or limits;
- Changes in test procedures for the finished product;
- Change in the shelf-life of the finished product.

No risk/benefit reassessment or quality control measures are required for other changes to the PIL. After approval of the variation stocks of medicinal products produced before approval can be marketed within the Russian Federation¹³².

No transitional periods are provided for at present, so every variation in Russia requires thorough planning of manufacturing, especially if packaging materials or specifications are affected. Regarding the procedure itself, all Rus-

¹³² Russian Federal law No. 61-FZ "On the regulation of the medicines" 2010, as amended

sian variations are processed similarly to the major variations of type II as per Regulation (EC) 1234/2008¹³³.

On 29 December 2012, the Russian Expert Body published a draft Guideline on the documentation required for variations for medicinal products, which can be used now as guidance for the preparation of variations¹³⁴.

Variations in the Ukraine

From year 2006 onwards, Decree No. 426 has been valid in the Ukraine. This introduced new rules for variations. The decree mostly adopted the "old" European Variation Regulation (EC) No 1084/2003¹³⁵. For the time being, these rules are still valid, although several updates are currently under consideration, as mentioned in Section 3.3.5 above.

Art. 4 of Decree No. 426 distinguishes between different types of variations: minor variations of type IA and IB as classified by Annex 5 of decree and major variations of Type II. Annex 6 of the Decree lists the changes to a marketing authorisation that result in a new MAA, in the same way as in Annex II of Regulation (EC) No 1084/2003. The application form for the variations is provided as Annex 7 to Decree No. 426. Several different variations can be grouped. Type I and II variations have to be assessed in 60 days. The clock is stopped for up to 60 days to answer deficiency letters¹³⁶. Approved variations can be implemented from the next production run, which is usually the approach taken.

4.3.3 Renewals

Pursuant to Art. 28 of the Russian law, the initial marketing authorisation certificate is valid for five years. The first authorisation may be renewed. Once renewed, the marketing authorisation becomes valid for an unlimited period,

¹³³ Commission Regulation (EC) No 1234/2008, 2008

¹³⁴ Russia: draft Guideline on the application dossier for the variations, FGBY NCESMP, 2012

¹³⁵ Commission Regulation (EC) No 1084/2003, 2003

¹³⁶ Ukraine: Decree No. 426 MoH Ukraine, 2005, as amended

analogously to the European practice as per Art. 24 Dir. 2001/83/EC as amended. According to Art. 29 of the Russian law, the renewal procedure should not exceed 90 working days, and marketing of the product under review is permitted by law. The exact timeframes for submission are not specified in the law, although it is anticipated that the renewal application should be submitted during the validity period of the first authorisation (usually half a year before the expiry date). The same application form as for the initial MAA is used for renewal (Art. 18.2 of the law, see Table 4 of the paper), re-evaluation of the risk-benefit and complete quality control of the medicinal product in the case of variations to the ND accompanying the renewal application. A Periodic Safety Update Report (PSUR) in special Russian format has to be submitted additionally to regular EU format of PSUR as an annex to the application form (see Annex IV of this thesis). The ND, draft PIL and mock-ups of the labelling have to be submitted with the renewal if subject to the variations¹³⁷. So, the Russian law suggests that some variations can be implemented within the renewal procedure, which is not provided for by the EU legislation, although it may be usual practice by some European national competent authorities.

Currently, rather different rules from those in the EU and Russian legislation have been implemented in the Ukraine. Registrations of medicinal products are generally valid for 5 years, even after a number of renewals, pursuant to Art. 9 of the Ukrainian Drug Law¹³⁸. There legislation for initial authorisations and renewals is the same, i.e. Decrees Nos. 376 and 426, as amended. According to Art. 10 of Decree No. 376, the renewal application may not be submitted more than 1 year but at least 90 days before expiry of the marketing authorisation (although Art. 6.10 of Decree No. 426 provides the possibility of submitting a renewal application later than 90 days before the expiry date). It is not permitted to market medicinal products without the valid authorisation¹³⁹, even while a renewal application is pending, so medicinal

¹³⁷ Russian Federal law No. 61-FZ "On the regulation of the medicines" 2010, as amended

¹³⁸ Ukrainian Drug Law, 1996, as amended

¹³⁹ Ukraine: Decree No. 376 Cabinet of Ministers Ukraine, 2005, as amended

product with expired registration certificates can neither be imported into the Ukraine or sold via wholesalers or pharmacies during the approval period. Assessment of the renewal formally should not exceed 90 days, with the clock stopped to respond to deficiency letters. The application form for renewal is provided as Annex 14 of Decree No. 426. According to Art. 6.10 and Annex 15 of the Decree No. 426, the documentation described in Table 6 has to be provided along with the renewal application form ¹⁴⁰:

Table 6. Application dossier for the renewal in the Ukraine

CTD Module	Description
1.0	Cover Letter.
1.1	Comprehensive table of content.
1.2	Renewal application form with the following annexes:
	Details on contact persons (Qualified Person for Pharmacovigilance in the Ukraine).
	Valid GMP certificate (cave: subject to the confirmation by the Ukrainian competent authorities, see Chapter 3.3.1 of the thesis).
	Copy of the manufacturing licence.
	List of countries where the product is on the market indicating the date of the first registration for each country.
	Chronological detailed list of complaints on the medicinal product, received during the last 5 years in the Ukraine, with measures taken by the applicant.
	Chronological list of post-authorisation commitments and follow-up measures since the grant of marketing authorisation or last renewal indicating scope, status, date of submission and date when the issue was been resolved.
	Revised list of all outstanding follow-up measures/post-authorisation commitments and signed letters of commitment (where applicable).

¹⁴⁰ Ukraine: Decree No. 426 MoH Ukraine, 2005, as amended

CTD Module	Description
1.3 1.3.1 1.3.5	Product information: Currently approved and updated SmPC/PIL and labelling, with tracked changes, if any.
3.2.P.5.1 3.2.P.5.2	Currently approved methods of quality control (ND) and updated quality specifications and analytical procedures on the finished product.
3.2.P.3.2 – 3.2.P.3.4	Currently approved and updated description of the manufacturing process of finished product.
5.3.6	PSUR and summary on the safety status of the medicinal product in the Ukraine since the grant of marketing authorisation or last renewal.

If any variations are to be implemented simultaneously with renewal, the applications for the variations should be submitted via the separate variation procedure described above in Section 4.3.2. It is obvious, that application dossiers for renewals in the Ukraine are similar to those in the EU, but are not identical. As opposed to EU practice, however, renewals in the Ukraine are regularly recurring procedures in the life cycle of a medicinal product.

4.3.4 Pharmacovigilance

Pharmacovigilance is rather a new topic for the healthcare systems of the CIS countries. For social or historical reasons, patients and even HCP often prefer not to report adverse events occurring under the treatment with medicinal products, although some progress with this issue has been registered during the past few years.

Nonetheless, Art. 64 to 66 of the Russian law and Decree No. 757n of the MoH of Russia describe a national pharmacovigilance system. Safety monitoring is currently performed by the Federal Service on Surveillance in Healthcare (Roszdravnadzor). All HCP are obliged by law to report all unexpected or serious adverse drug reactions (within 15 days after becoming aware of them at the latest) to this body. There is a special procedure for the

suspension of the marketing authorisation should it appear necessary due to new information on the safety of a medicinal product. The pharmacovigilance authority can issue decision on the variations to the PIL, suspend or revoke marketing authorisation, or recall the product from the market¹⁴¹.

According to Decree No. 757n, the MAH has to submit the PSURs within the following timeframe beginning from the first marketing authorisation in the world:

- Every six months during the first two years after the first authorisation;
- Once a year for the following two years (third and fourth years);
- Thereafter (beginning from the fifth year) at three-yearly intervals.

The PSURs have to be submitted not later than 30 days after the data lock point of the report¹⁴². Since, therefore, the Russian legislation recognises the European/world birth date of the product and requires the same time frames of the reporting, the submission of PSURs to the Russian and European competent authorities could be at least currently harmonised, although the last developments in European legislation on pharmacovigilance would have to be considered by the MAH.

Decree No. 749n of the MoH of Russia in accordance with Art. 29 of the Russian law determines the special template for the PSUR for renewal of the medicinal product¹⁴³. Since the terminology used in any pharmacovigilance documentation is crucial for its correct preparation, an English translation of the template using European regulatory terms is provided in Annex IV.

With regard to the Ukraine, Decree No. 898 MoH Ukraine of 27 December 2006 as amended regulates the pharmacovigilance system for authorised medicinal products¹⁴⁴. The Ukrainian legislation on pharmacovigilance has been largely harmonised with the corresponding current European legislation (including Dir. 2010/84/EU amending, as regards pharmacovigilance, Dir.

¹⁴¹ Russian Federal law No. 61-FZ "On the regulation of the medicines" 2010, as amended

¹⁴² Russia: Decree No. 757n MoH Russia from 26.08.2010

¹⁴³ Russia: Decree No. 749n MoH Russia from 26.08.2010

¹⁴⁴ Ukraine: Decree No. 898 MoH Ukraine from 27.12.2006, as amended

2001/83/EC). The Ukraine intends to adopt the EMA's Good Pharmacovigilance Practices during 2013¹⁴⁵. A local Qualified Person for Pharmacovigilance (resident of the Ukraine) is required, even for the imported medicinal products. PSURs written in English are acceptable, although some parts (update on actions taken by regulatory authority or MAH for safety reasons, changes to reference safety information and conclusions) should be translated into Russian or Ukrainian.

4.3.5 Consequences for the case study

Based on the information provided above, last two questions raised by the project team "Wunderherb" should be answered as follows:

Special local considerations regarding access to the Russian and Ukrainian markets:

Since herbal products are not usually the subject of reimbursement and price regulations, these issues are of little relevance to the launch of Wunderherb and therefore are beyond of the scope of the analysis. Nevertheless, due to recent developments in legislation, launching the product, especially on the Ukrainian market, might involve some tough challenges:

- Wunderherb will have to be listed in the annex of the Ukrainian Certificate of Compliance with the GMP issued by the local competent authority and the validity of the certificate will have to be maintained during the whole post-marketing period, as per current law;
- the MAH or distributor of Wunderherb will have to obtain an import license from the Ukrainian competent authority (as of 1 March 2013), and Wunderherb will have to be listed in the annex to the import license;
- since advertising is crucial to the business model of Phytopharmaka GmbH for OTC products, possibility of publically advertising Wunderherb has to be explicitly stated in the approval documentation, and at it must be ensured that Wunderherb is not listed in the current Ukrainian "List of OTC Products for which Public Advertising is Banned";

¹⁴⁵ Barmina, 2013

- Wunderherb must be launched in the first two years after marketing authorisation, otherwise the terms of the Ukrainian sunset clause will come into force.

Scope of regulatory activities for the 5 years after authorisation

Directly after marketing authorisation but before launch of the product:

- The approved product information (PIL, labelling) has to be customised to ensure ready-to-print packaging materials are available;
- Template for the CoA for the finished product must be created, based on the approved specification and local requirements;
- Special labelling has to be created for transport packaging into Russia (for wholesale trading);
- Batch certification and quality control approval from the local authorities must be obtained.

After launching of the medicinal product:

- any variations have to be carefully scheduled and the manufacturing processes for the product should be planned in compliance with the timelines of submission and approval of variations, to provide a continuous supply of the product to the market. This applies especially to variations of the information approved in the ND or product information (PIL, labelling) in Russia, and also to some extent in the Ukraine;
- Renewals have to be submitted during the fifth year after marketing authorisation in the both countries. In Russia it would be the only renewal (after that the authorisation has unlimited validity), whereas the Ukrainian legislation requires submission of renewals every 5 years. It is highly recommendable to submit the renewals as soon as possible, especially in the Ukraine, i.e. one year before expiry, since marketing of the product on the Ukrainian market is not permitted after the expiry date, regardless of whether a renewal is pending or not;
- PSURs for Wunderherb can be submitted in both countries within the same time frame as for the German authority, but with some special considerations, especially at the time of renewals. Moreover, for renewal applications, the Russian authority requires the special format of the PSUR given in An-

nex IV. However, according to Article 107b.3 of Dir. 2010/84/EU 146, submission of the PSURs for WEU products will not be required in the EU any more, except when specially requested by the competent authority. Furthermore, by implementing Article 107c paragraphs (4) and (7) Dir. 2010/84/EU, on 1 October 2012, the EMA published the list of EU reference dates and frequency of submission of PSURs known as the "EURD list". The EURD list becomes legally binding on 1 April 2013 (6 months after publication), and replaces the existing schedule for PSURs submissions and any earlier conditions related to the frequency of submission of PSURs in the EU member states¹⁴⁷. It is highly possible that Phyto herbalis, similar to many other herbal preparations, is (or will be) included in the EURD list as subject to a PSUR submission frequency of 5 years, with the next data lock point on 1 January 2018 and no requirement for PSUR submission for WEU authorisations (Art. 10a Dir. 2001/83/EC as amended) or THMP registrations (Art. 16a Dir. 2001/83/EC as amended)¹⁴⁸, especially since the HMPC has already issued the final Community herbal monograph for Phyto herbalis. At present, it is not clear how far the Ukraine will adopt the current European pharmacovigilance legislation, especially regarding PSUR's submission for medicinal products authorised using WEU applications. In other words, although regular PSUR submissions for WEU authorisations (and potentially for THMP registrations) in Germany and other EU member states will not be necessary in the future as per current European pharmacovigilance legislation, PSURs still have to be prepared by the pharmacovigilance department of Phytopharmaka GmbH for the other ex-EU countries based on local requirements, especially for Russia.

¹⁴⁶ Directive 2010/84/EU, 2010

¹⁴⁷ URL 20: EMA publishes EURD list (www.ema.europa.eu), 01.10.2012

¹⁴⁸ EMA/630645/2012 Rev.5. List of European Union reference dates, .2013

5. Overall conclusions and recommendations

As has been demonstrated above by 3 case studies, the Russian Federation and Ukraine both have 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 scheduled for 2013. Russia appears to be more conservative and intent upon paving its own way as far as legislation is concerned, although they are considering European and non-European elements of regulatory legislation more and more. In marked contrast to Russia, the Ukraine is pursuing clear, Europe-driven policies in the field of authorisation and marketing of medicinal products, although some distortion does occur on a local level. The above should not be considered blanket statements, however, as there are some marked exceptions, e.g. the rules on renewals in Russia are much closer to the European approach than the Ukrainian rules. It seems more likely that the Ukraine will attempt to introduce further harmonisation with the EU regulatory framework, although both the Ukraine and Russia are concerned about protecting and improving the state of their domestic pharmaceutical industries by introducing regional differences in legislation.

The following recommendations can be given to EU-based pharmaceutical companies with points of interest in the CIS region:

- From start of the planning of marketing authorisations outside the EU it is important to accept the idea that some special aspects – which often do not seem to be logical from the European point of view – must be considered in the different ex-EU countries. The CIS countries, represented here by Russia and Ukraine, are no exceptions to this observation;
- Planning and preparation of initial applications should be done taking into account the regional requirements discussed in this paper, e.g. the need for local clinical trials in Russia. Inclusion of Russian centres in international clinical trials should be considered in the early stages of clinical development programs to satisfy this requirement later;

- Highly qualified people with experience in the region are required as the liaison persons responsible for communication with the Russian and Ukrainian authorities, and preparation of local dossiers is crucial for the success of the marketing authorisation procedure in these countries;
- Regional postmarketing requirements like GMP-recognition, import licensing or pharmacovigilance rules must be taken into account early enough;
- Life-cycle of the medicinal product – thorough planning of the timing of renewals and variations is crucial, as the situation with transitional periods is inconsistent and volatile, e.g. for renewals in the Ukraine, marketing of a product for which an application is pending is not allowed after the expiry date of the registration certificate, whilst variations in Russia have to be implemented immediately;
- It is important to establish regulatory intelligence with the native, bilingual colleagues, since most of the new trends important for strategic decisions or pending applications are discussed mostly in Russian or Ukrainian. Moreover, even if some information is translated into English, this is often done by translators not used to European regulatory terminology, so the meaning can be distorted and difficult to interpret;
- Local colleagues should be regularly informed about new developments on the EU regulatory scene to raise acceptance of forthcoming changes and increase commitment to current and scheduled regulatory projects.

Applying for marketing authorisation in Russia and the Ukraine can be efficient and successful, but only if the special aspects discussed here are taken into account in good time.

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¹⁴⁹ The information in brackets like (RU:...) or (UA:...) indicates that the reference exists in original language only.

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Zavidova S. Legislative initiatives by regulatory bodies and their influence on the sector's development, from the material of Adam Smith Conferences' 3rd annual Forum Innovative Drug Research and Development in Russia, SPECIAL FOCUS DAY. CLINICAL TRIALS IN RUSSIA: How to design, plan & run efficient clinical trials. 21 November 2012. (RU: Завидова С. Законодательные инициативы РА и их влияние на развитие сектора, 2012), available from www.drug-research-russia.com (under proper authorisation)

Annex I. Useful links.

Russia, official links

grls.rosminzdrav.ru (Russian only)

State Registry of Medicinal Products, electronically recorded databases of the submitted dossiers and clinical trials, access to the "digital office of the applicant" within the scope of MAA procedure and after the approval for the maintenance purposes (official authorisation by the MoH is required)

www.regmed.ru (Russian only)

"Scientific Centre of Expertise of Medicinal Products" FGBY NCESMP (ФГБУ ИЦЭЦМП) MoH of Russia, regulatory assessment authority/expert body.

www.rosminzdrav.ru (Russian only)

The MoH of Russia

www.roszdravnadzor.ru (Russian only)

Federal Service on Surveillance in Healthcare (Roszdravnadzor), surveillance authority of Russia, former regulatory affairs authority/expert body.

Russia, regulatory intelligence

www.regprof.com (Russian only)

Professional forum of the Russian Regulatory Affairs Managers.

www.pharmvestnik.ru (Russian only)

Pharmaceutical bulletin (periodical publication)

gmpnews.ru (Russian only)

GMP news (periodical publication)

acto-russia.org (Russian, partly English)

Association of Clinical Trials Organisations (overview of the clinical trials in Russia, periodical statistics and analytical materials)

Ukraine, official links

<http://www.dec.gov.ua/> (Ukrainian only)

new web site of the State Expert Centre MoH Ukraine, Regulatory Authority, MAA for medicinal products and requests for CTAs, expert body, scientific advices, pharmacovigilance.

<http://www.pharma-center.kiev.ua/view/en/index> (Ukrainian, partly on English and Russian, no update after 11 Oktober 2012)

old web site of the State Expert Centre MoH Ukraine.

<http://www.drlz.kiev.ua/> (Ukrainian only)

State Registry of Medicinal Products, website supported by the State Expert Centre MoH Ukraine.

<http://www.diklz.gov.ua/en> (Ukrainian, partly English)

State Administration of Ukraine on Medicinal Products, surveillance of the quality control of products on the market, GMP competent authority.

<http://www.moz.gov.ua/ua/portal/> (Ukrainian only)

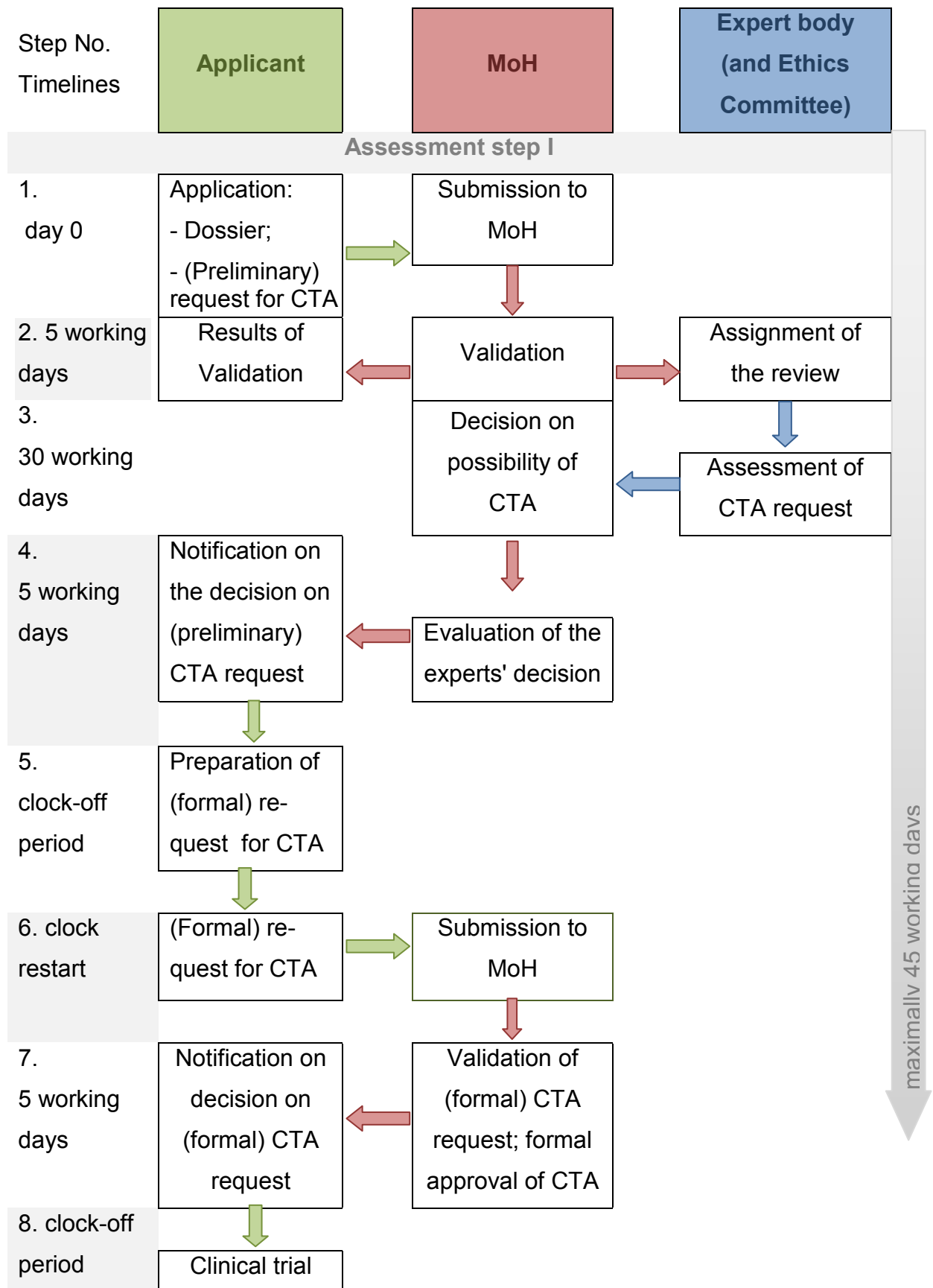
The MoH of the Ukraine

Ukraine, regulatory intelligence

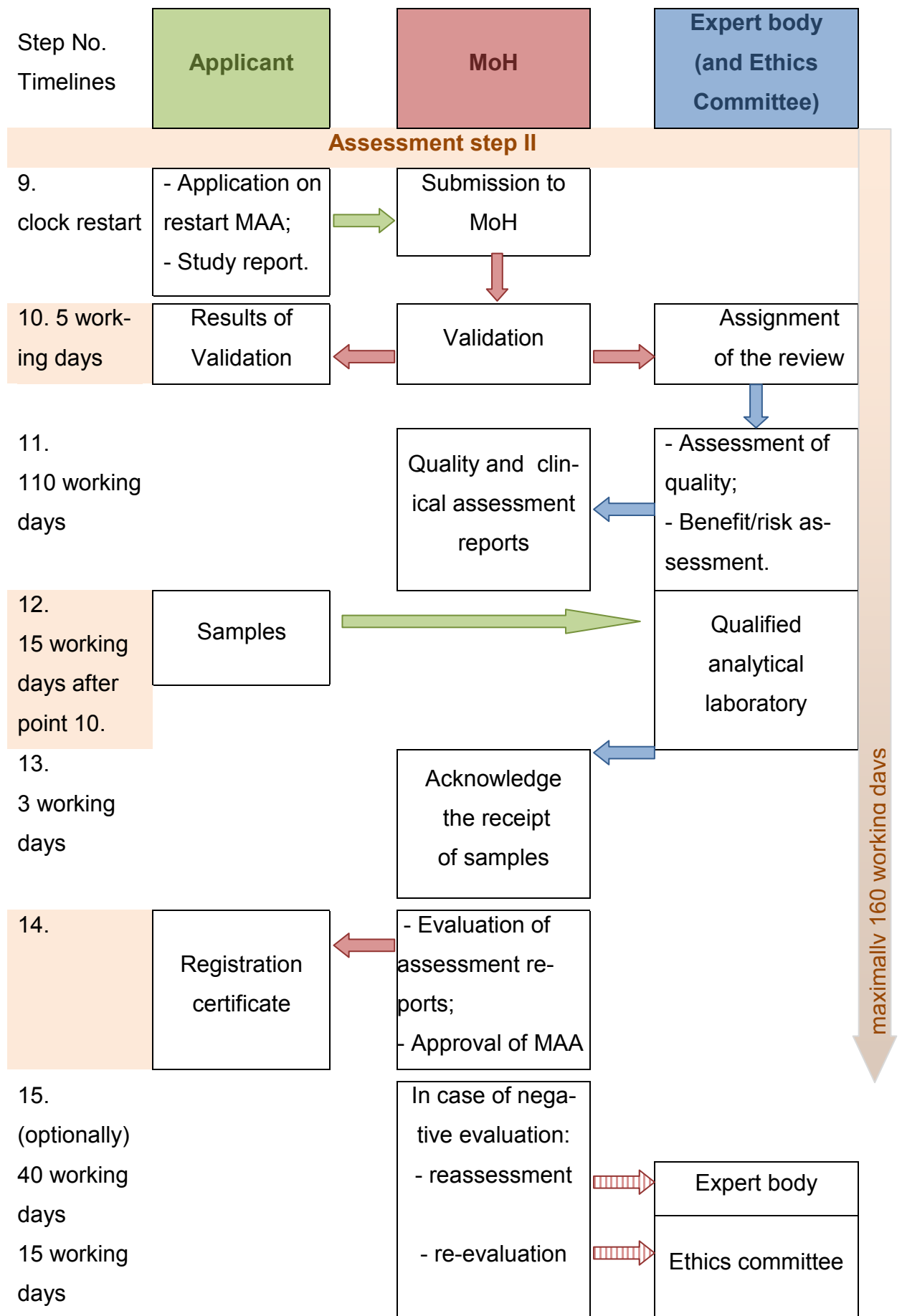
<http://www.apteka.ua> (Russian/Ukrainian only)

Apteka.ua, specialised pharmaceutical online publication.

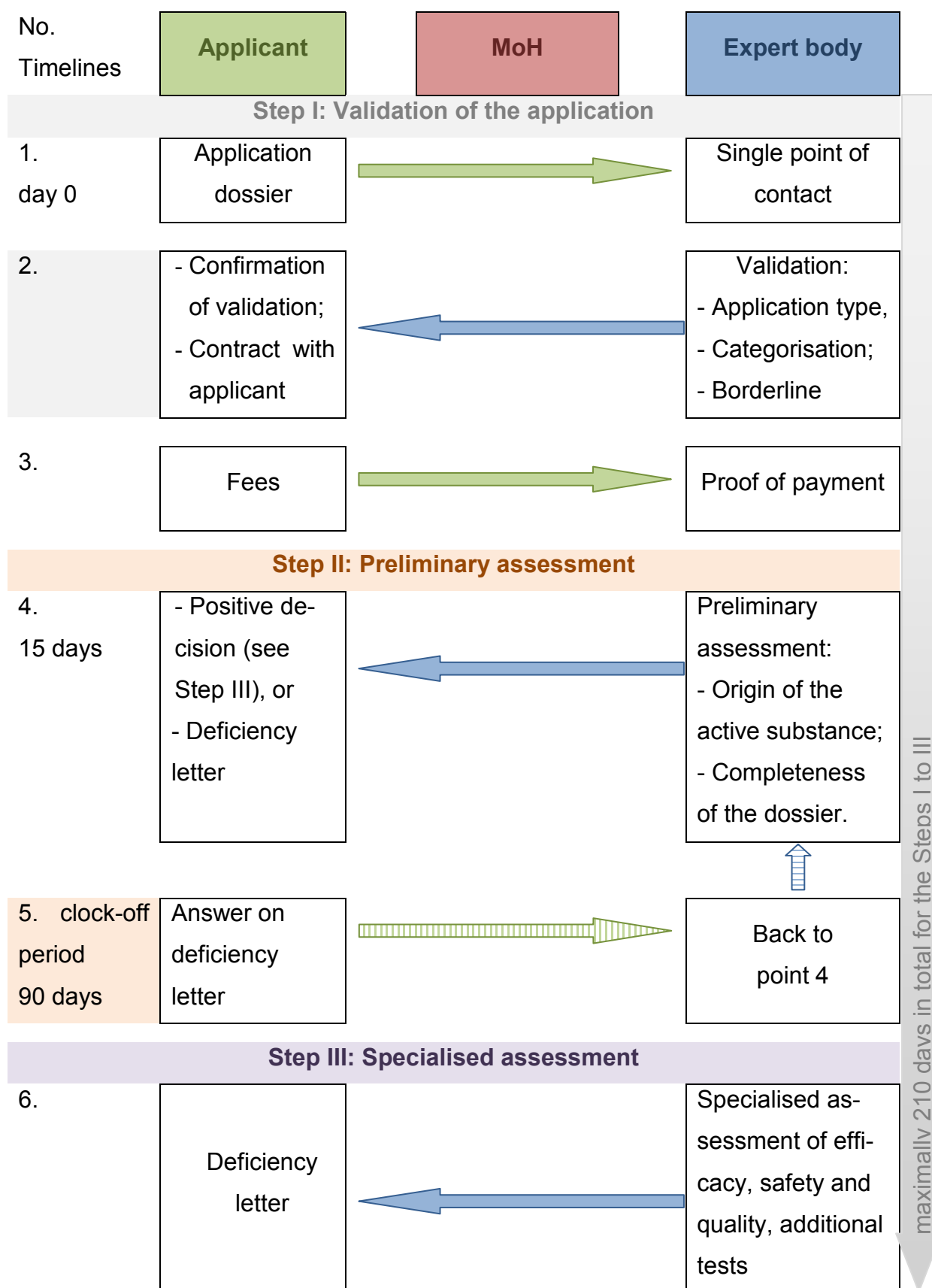
Annex II. Flow-chart of MAA procedure in Russia ¹⁵⁰



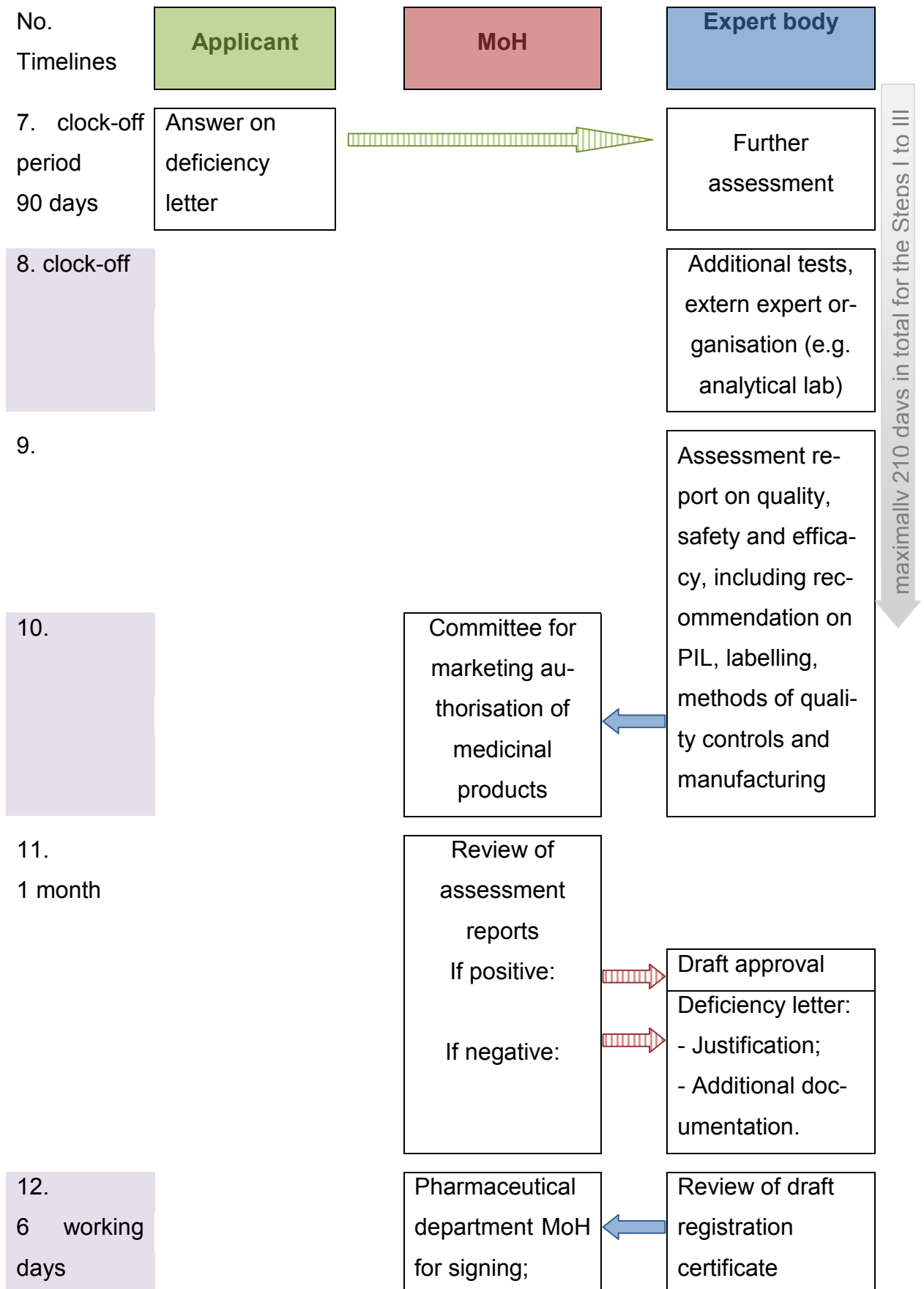
¹⁵⁰ based on Russian Federal law No. 61-FZ, 2010, as amended

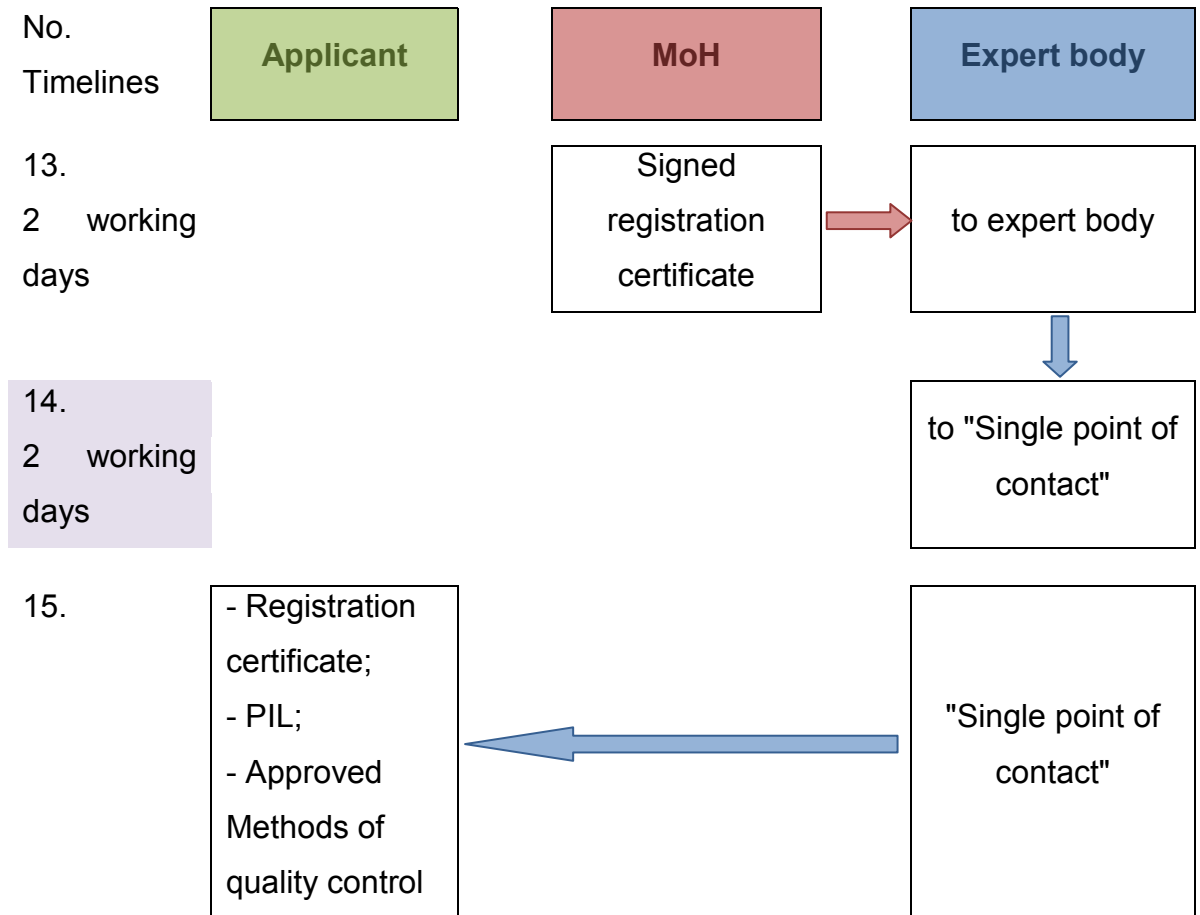


Annex III. Flow-chart of MAA procedure in the Ukraine¹⁵¹



¹⁵¹ based on Decree No426 MoH Ukraine, 2005 and No98 from 09.02.2012, both as amended





Annex IV. Russian template for the PSUR for renewal¹⁵²

Annex to Decree No. 749n MoH of Russia from
26.08.2010 "On template of the PSUR for the
renewal of medicinal product"

Template

Results of safety monitoring of medicinal product for the renewal**1. General provisions**

- 1.1. Legal entity name and address _____
- 1.2. Number of medicinal product registration certificate _____
- 1.3. Date of registration: _____
- 1.4. Product name:
International non-proprietary or chemical name _____
Trade name _____
- 1.5. Dosage form, doses, routes and methods of administration, shelf life of the product:

- 1.6. Medicinal product composition (list of active ingredients and excipients, indicating the quantity of each):

- 1.7. Period of safety monitoring of the medicinal product - from “...” till “...”.
- 1.8. Date of submitting the results of medicinal product safety monitoring: “...”
- 1.9. Medicinal product safety monitoring results are submitted by: _____

(Position)

(Name)

(Signature)

¹⁵² Russia: Decree No. 749n MoH of Russia from 26.08.2010

2. Results of safety monitoring of medicinal product:

2.1. Information about foreign countries where the medicinal product has been authorised:

Country	Trade name of medicinal product	Date of marketing authorisation	Date of renewal	Differences in the patients' information leaflet (indications, contraindications, route of administration etc.)

2.2. Information about any cases of suspension or prohibition of marketing authorisation in foreign countries where the medicinal product is authorised

Country	Trade name of medicinal product	Date of suspension or prohibition of marketing authorisation	Reasons for suspension or prohibition	Date (timeframes) of suspension or prohibition	Reasons for suspension or prohibition

2.3. Information about any cases of refusal to authorise the medicinal product in foreign countries

Country	Trade name of medicinal product	Date of refusal	Reasons for refusal

2.4. Information containing results of safety monitoring of clinical studies being carried out during the timeframes covered by the report in the Russian Federation or in any other countries

Country	Trade name of medicinal product	Aim of clinical study	Information concerning the stage of progress of clinical trial or its finalisation	Number of patients participating in clinical study	Assessment of clinical study results

2.5. Information reflecting quantity of patients who received the medicinal product within the Russian Federation and in other countries where the product is authorised

Country	Number of patients	Total number of medicinal product packages received by the patients
Russia		
Other countries		

2.6. Information reflecting quantity of the medicinal product supplied for marketing within the Russian Federation and in other countries where the product is authorised

Country	Number of medicinal product packages supplied for marketing
Russia	
Other countries	

2.7. Information reflecting (unexpected) adverse drug reactions not mentioned in the patient information leaflet that occurred after the authorisation in the Russian Federation

Number of adverse drug reactions reports	Adverse drug reactions description	Source of adverse drug reactions report	Patient's sex and age	Adverse drug reactions outcome (no complications, with complications, death, unknown)

2.8. Information reflecting serious adverse drug reactions obtained after authorisation in the Russian Federation

Number of serious adverse drug reactions reports	Description of serious adverse drug reactions	Source of serious adverse drug reactions report	Patient's sex and age	Serious adverse drug reactions outcome (death, congenital abnormalities, developmental failures, hospitalisation, patient's health impairment (worsening) accompanied by persistent failure of body functions, persistent loss of ability to work, disability)

2.9. Number of serious adverse drug reactions obtained after authorisation in the Russian Federation

Disorders as per system organ class	Number of serious adverse drug reactions	Percentage of serious adverse drug reactions of the total number, %
Cardiovascular system disorders		
Congenital, familial and genetic disorders		
Eye disorders		
Musculoskeletal and connective tissue disorders		
Neoplasms benign, malignant and unspecified (including cysts and polyps)		
Reproductive system and breast disorders		
Skin and subcutaneous tissue disorders		
Surgical and medical procedures		
Overall		

2.10. Information about single serious adverse drug reaction reports obtained after authorisation in the Russian Federation

Disorders as per system organ class	Single adverse drug reactions reports
Cardiovascular system disorders	
Congenital, familial and genetic disorders	

Eye disorders	
Musculoskeletal and connective tissue disorders	
Neoplasms benign, malignant and unspecified (including cysts and polyps)	
Reproductive system and breast disorders	
Skin and subcutaneous tissue disorders	
Surgical and medical procedures	
Overall	

2.11. Information reflecting unexpected adverse drug reactions obtained after authorisation in the Russian Federation

Number of unexpected adverse drug reactions reports	Description of unexpected adverse drug reactions	Source of unexpected adverse drug reactions report	Patient's sex and age	Unexpected adverse drug reactions outcome (death, congenital abnormalities, developmental failures, hospitalization, patient's health impairment (worsening) accompanied by persistent failure of body functions, persistent loss of ability to work, disability)

2.12. Number of unexpected adverse drug reactions obtained after authorisation in the Russian Federation

Disorders as per system organ class	Number of unexpected adverse drug reactions	Percentage of unexpected adverse drug reactions of the total number, %
Cardiovascular system disorders		
Congenital, familial and genetic disorders		
Eye disorders		
Musculoskeletal and connective tissue disorders		
Neoplasms benign, malignant and unspecified (including cysts and polyps)		
Reproductive system and breast disorders		
Skin and subcutaneous tissue disorders		
Surgical and medical procedures		
Overall		

2.13. Information about single unexpected adverse drug reactions obtained after authorisation in the Russian Federation

Disorders as per system organ class	Single unexpected adverse drug reactions reports
Cardiovascular system disorders	
Congenital, familial and genetic disorders	
Eye disorders	

Musculoskeletal and connective tissue disorders	
Neoplasms benign, malignant and unspecified (including cysts and polyps)	
Reproductive system and breast disorders	
Skin and subcutaneous tissue disorders	
Surgical and medical procedures	
Overall	

2.14. Information about suspension of marketing authorisation in the Russian Federation due to safety considerations

Date of suspension	Reason of suspension	Comments

2.15. Information about medicinal product withdrawal from the market due to its safety consideration

Date of withdrawal from the market	Reason for withdrawal from the market	Comments

2.16. Information regarding any decisions to revise PIL of the medicinal product, including the data as follows:

- a) Dosage form, including composition of active substance(s) and excipients;
- b) Indications;
- d) Contraindications;

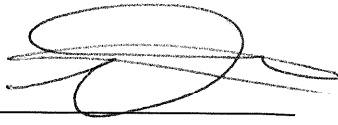
- e) Posology, route of administration, time of administration (if applied), duration of treatment (distinguishing between paediatric patients aged under one year and above);
- g) Precautions for use;
- h) Symptoms of overdose, measures in case of overdose;
- i) Specific effects at first take of the product or withdrawal, if applied;
- j) Description of measures in case of missing of one or several doses of the drug;
- k) Possible adverse drug reactions;
- l) Interaction with other medicinal products or food;
- m) Special considerations of use during pregnancy, lactation, by children and adults with chronic diseases.
- n) Data concerning the effects on ability to drive and use machines.

Date of revision of PIL	Details reflecting revisions of PIL	Reasons for revisions of PIL
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Eidesstattliche Erklärung

Hiermit erkläre ich an Eides statt, die Arbeit selbständig verfasst und keine anderen als die angegebenen Hilfsmittel verwendet zu haben.

24.04.2013
Datum


Unterschrift