Analytical center “New Social and Economic Policy”

Regulation of the market for medicinal products in Ukraine: problems and solutions
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TERMS USED AND ABBREVIATIONS

Abbreviations

AIDS    See HIV/AIDS
API     Active pharmaceutical ingredient
ATC Code Anatomical Therapeutic Chemical Classification System Code
CAS     Administrative Services Center
CIS     Commonwealth of Independent States
CMU     Cabinet of Ministers of Ukraine
EBA     European Business Association
EC      European Commission
EDQM    European Directorate for the Quality of Medicines
EEC     European Economic Community
EMA     European Medicines Agency
EU      European Union
FDA     Food and Drug Administration
FDI     foreign direct investments
GCP     Principles of good clinical practice
GDP     Gross domestic product
GLP     Standards of good laboratory practice
GMP     Standards of good manufacturing practice
GPP     Standards of good pharmacy practice
HIV/AIDS Human immunodeficiency virus infection and acquired immune deficiency syndrome
MOH     Ministry of Health
NGO     Non-governmental organisation
SAUMP   State Administration of Ukraine on Medicinal Products
SEC     State Expert Center of the MoH of Ukraine
SSUMP   State Service of Ukraine on Medicinal Products
UNICEF  United Nations Children’s Fund
WHO     World Health Organization

Terms Used

<table>
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<tr>
<th>Term Used in Report</th>
<th>Ukrainian</th>
<th>Transliterated</th>
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<tr>
<td>SAUMP (State Service of Ukraine on Medicinal Products)</td>
<td>Державна служба України з лікарських засобів</td>
<td>Derzhavna služba Ukrainy z likarskykh zasobiv</td>
</tr>
<tr>
<td>SEC (State Expert Center of the MoH of Ukraine)</td>
<td>Державний експертний центр МОЗ України</td>
<td>Derzhavnyi ekspertnyi tsentr MOZ Ukrainy</td>
</tr>
<tr>
<td>MOH (Ministry of Health)</td>
<td>Міністерство охорони здоров’я України</td>
<td>Ministerstvo okhorony zdrav’ia Ukrainy</td>
</tr>
<tr>
<td>SSUMP (State Service of Ukraine on Medicinal Products)</td>
<td>Державна служба України з лікарських засобів</td>
<td>Derzhavna služba Ukrainy z likarskykh zasobiv</td>
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Executive summary

The pharmaceutical sector plays a vital social role, providing people with medicinal products and medical supplies and is one of the key elements in ensuring efficient functioning of the healthcare system. Taking into account that about 90% of expenditures on pharmaceuticals are paid out-of-pockets\(^1\) any fluctuations in the pharmaceutical market have an immediate and noticeable impact on Ukrainian households and spur up heated political discussions. The affordability and physical availability of medicinal products depends, among other important factors, on the structure and regulation of pharmaceutical market.

Thus, the pharmaceutical sector is a subject of strict state regulation. The regulation of pharmaceutical market is aimed at ensuring safety, quality and efficacy of medicinal products manufactured and sold to the final consumer. To that end, the state sets out marketing authorization rules, the framework for quality control of medicinal products during their production and circulation, and qualification requirements for manufacturers and traders of the medicinal products. The state regulation impacts physical availability of the medicinal products by setting public procurement procedures for medicinal products, and regulatory rules for wholesale and retail pharmaceutical market. The regulatory system impacts affordability of the medicinal products for the consumer by setting direct and indirect price controls and providing cost reimbursement schemes for medicinal products.

The regulatory system of pharmaceutical market is considered to be efficient when it ensures affordability and physical availability of safe, high quality and efficacious medicinal products for the patients while minimizing regulatory costs both for the state and business.

The purpose of this study was to analyze the regulatory system of pharmaceutical market in Ukraine (related to the manufacturing and circulation of medicinal products) and its influence on the physical availability and affordability of medicinal products for public. We addressed several research questions, in particular:
- Is the regulatory system of pharmaceutical market in Ukraine efficient?
- Does it ensure safety and quality of medicinal products and their availability for the final consumers?
- Is the regulatory system transparent and friendly for business?
- How was it changing?
- Is it possible to evaluate its performance in an unbiased and fair way?

We attempted to assess the main changes in the regulatory system over the last 5 years pointing out at the positive and problematic developments, highlight the most important remaining problems, and develop recommendations. For the preparation of this Report, we conducted a survey of 32 the manufacturers and distributors of medicinal products which operated in Ukraine. The survey studied business perceptions of the recent changes in the regulation of pharmaceutical market and its main challenges.

A workshop was carried out to discuss potential recommendations with key stakeholders. The objective of the workshop was to validate key findings and assist the authors in clarifying and ranking in terms of priority the key issues and the policy recommendations.

Changes in regulations of the market for medicinal products of Ukraine over the last five years

Over the recent years, the pharmaceutical regulatory system of Ukraine has undergone significant changes. The declared objectives of such changes were harmonizing the national legislation with the EU acquis, implementation of the international standards in marketing authorization procedures for medicinal products, improvement of the control mechanisms, simplification of the regulatory procedures, and enhancing the safety of medicinal products. Ukraine made considerable steps forward, including joining the Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme (PIC/S) in 2011, implementing the GMP standards as a tool for ensuring safety of medicinal products, introducing permanent re-registration, and simplifying registration procedures for certain groups of medicinal products, etc.

However, sometimes these changes were implemented in a controversial way and did not yield expected results:

- **Practical implementation of legal changes remained slow.** The changes in legislation were often not supported by adoption of relevant by-laws. This slowed down their implementation (like in case of permanent registration) or even contributed to uncertainty of business rules (like the delay in adopting new licensing terms for manufacturing and trading of medicinal products);
- **Weak organization caused problems in efficient implementation.** For example, the introduction of GMP standards in Ukraine required mandatory confirmation of compliance of manufacturing of medicinal products with GMP requirements effective in Ukraine, even for the foreign manufacturers and certified by a European competent agency or located in the territory of PIC/S member states with manufacturing facilities in the EU. Such double confirmation was unnecessary, it put up additional barriers for business.
- **Some steps were controversial.** A short introduction of import licensing for an active pharmaceutical ingredient (API) contradicted the European practices and exposed Ukrainian pharmaceutical manufacturers to the risk of halting their business. The introduction of licensing for importing of medicinal products failed to enhance the responsibility of foreign manufacturers for the quality of imported drugs, however increased the regulatory burden.
- **Some positive developments were reversed.** A drawbacks in the implementation of a reference price mechanism led to its abolition (instead of correcting). It reduced the efficiency of state control of producers’ prices. In early 2015, a successful pilot project on reimbursement of anti-hypertension was stopped for fiscal reasons.
- **Frequent restructuring of regulatory institutions contributed to the unpredictability of the regulatory environment,** because every merger/association/split destabilized the activity of regulatory agencies for 6-9 months.

Main regulatory problems in the market for medicinal products

In spite of many positive developments, the regulation of the pharmaceutical market remains complicated and lacks transparency. The institutional capacity of the regulators needs an improvement in order to speed up the implementation of modern regulatory changes. The main regulatory drawbacks in the market for medicinal products include the following:

- **Delays in the adoption of the relevant by-laws prevent putting into force recent provisions of the permanent re-registration and simplified registration for some medicinal products** (registered by the European Medicines Agency and intended
only for treatment of several diseases, registered in the USA, Switzerland, Japan, Australia, Canada or the European Union).

- **Delay in putting the newly established regulatory agency – State Service of Ukraine on Medicinal Products and Drug Controls- causes disruptions in the licensing procedures.**
- **Administration of the regulatory procedures remains complicated and burdensome for business.**
  
  a) One-stop-shop approach is not fully implemented. There is no on-line application possibilities for business and no functioning electronic document flow between the regulatory agencies. Thus, following the regulatory procedures imposes high administrative costs on business and creates risks of corruption.
  
  b) **Confirming compliance of manufacturing of medicinal products with GMP requirements in Ukraine remains complicated for foreign manufacturers.** It makes both the registration of medicinal products and licensing of the market agents long and difficult. No agreement on mutual recognition of GMP certificates between Ukraine and the PIC/S members has been signed so far.

- **Lack of clarity and transparency in regulatory procedures reduces the accountability of regulatory authorities and increase the regulatory costs for business.**
  
  a) Lack of transparency of the registration procedures provides grounds for their unjustified prolongation. Any public official or expert may at his/her own discretion "extend" any regulatory procedure by requesting additional examinations and tests. There is no clear list of grounds for requesting such additional, and this allows their arbitrary application extending and complicating the registration of drugs.

  b) Additional confirmation of the individual expert assessments on the registration and clinical trials dossier by the of SEC’s advisory bodies (Scientific Expert and Science and Technology Councils) does not contribute to the quality of decision making, but increases the length of the regulatory procedures.

  c) Present distribution of responsibilities between the regulatory institutions (Ministry of Health of Ukraine, State Service of Ukraine on Medicinal Products and State Expert Center) in conducting the registration procedures (as well as allowing clinical trials) leads to duplication of functions and complicates regulatory procedures for business.

  d) In practice, government bodies bear no responsibility for the delayed decisions or unreasonable additional examinations during the regulatory procedures.

- **The organization of quality control of medicinal products is costly (both for the state and for business), but not highly efficient**
  
  a) Duplication of regulatory controls increase the regulatory tax for business. Compliance with licensing terms is often controlled separately from quality inspections of medicinal products. This increase control costs both for the state and business.

  b) The scheduled inspections with a compulsory prior notice are not efficient in revealing medicinal products of poor quality in circulation. The intended extension of moratorium on the inspections of small businesses (including pharmaceutical companies) will not contribute to the efficiency of quality control.

  c) **Efficiency assessment of the activities of state control agencies needs an improvement.** Presently, public information on the quality of medicinal products in circulation is limited (e.g. data on the share of low-quality and counterfeit medicinal products in market is absent). It makes difficult to assess the outputs of control system (e.g. the decline in the share of low-quality and counterfeit drugs) versus inputs (the quantity and costs of inspections). Thus, presently,
the quantity of inspections remains the main success indicator for the control agencies.

- **Incentives for a prompt access of the innovative medicinal products to the Ukrainian market remain limited.** The main reasons include: a) a unified approach to price regulation for the original drugs and generics (as a result, generics sometimes may cost more than the original medicines), b) a weak protection of exclusivity of data in the registration dossiers of innovative medicinal products.

- **Capacity development of the regulatory institutions in the pharmaceutical market is restrained by:**
  a) underfinancing which cannot be resolved without reconsidering the functions of all the regulatory authorities and finding new sources of financing,
  b) a lack of competitive selection procedures and regular rotation of experts which are involved in the examination of applications.

- **The economic regulation of the pharmaceutical market has a limited impact on affordability of medicinal products for public:**
  a) the abolishment of reference price mechanism made effective regulation of the producers’ prices more difficult;
  b) in the absence of cost-reimbursement schemes for medicinal products, the regulation of wholesale and retail mark-ups has a limited impact on the affordability of medicinal products;
  c) volatile VAT mechanisms for medicinal products, and a possibility for customs authorities to manipulate with the classification of medicinal products relevant for VAT rates, causes the risk of increasing drug prices.

As a whole, the regulatory system for the Ukrainian pharmaceutical market can hardly be viewed as an effective one.

These findings are echoed by the results of the survey conducted by the Ukrainian office of the IFAK Institute within the framework of this project in October 2015. The representatives of 32 pharmaceutical companies operating in Ukraine were surveyed. According to the respondents, in the Ukrainian pharmaceutical market companies typically face regulatory problems related to registration procedures, quality control of medicinal products in circulation (81% of the respondents), price regulation (75% of the respondents) and taxation and licensing (72% and 69% accordingly). The most significant problems are associated with taxation (65% of those who responded), price regulation (50%) and registration procedures (58%).

While assessing changes in the regulatory framework of the Ukrainian pharmaceutical market for the last 5 years the respondents reported almost no significant improvements or even worsening of the situation. Primarily, this concerns taxation and price regulation (78% and 63% of the respondents accordingly). The most positive changes are associated with registration procedures (46% of those who responded).

Inadequate implementation of the legislation (due to untimely preparation of regulatory documents for implementation of legislative decisions) presents a significant problem. This is particularly relevant to registration procedures (68% of those who responded), licensing (62%) and quality control of medicinal products in circulation (60%).

**All regulatory gaps have a negative impact on the availability and affordability of the medicinal products in Ukraine.** The range of drugs in the Ukrainian pharmaceutical market is still narrower than in the European countries. Generics prevail on the market, and there are limited incentives for quick introduction of innovative drugs. More than 32 percent of the medicinal products included in the WHO Model List of Essential Medicines
(that are necessary to meet basic healthcare needs in the developing countries) are absent in the Ukrainian market. The problem of low-quality and counterfeit medicinal products remains significant. Frequent failures in public procurements of medicinal products cause disruptions in the drug supply.

**Affordability of the medicinal products went down** due to a drop in real incomes of the households and sharp increase in drug prices (in particular, imported ones) as a consequence of high inflation and evaluation of the national currency over the last two years. The volume of drugs (in physical terms) consumed by the population by the end of 2014 decreased by 12.3%, during the next 9 months of 2015 – by further 12.4%. Till the end of 2015, the total drug consumption (in physical terms) may fall below the 5-year minimum.

**The regulatory framework for manufacturing and circulation of medicinal products in Ukraine needs a significant improvement.** It requires progress in three directions, including the following:

1. Strengthening the institutional capacity of the regulatory system. This requires a clearer distribution of functions between the regulatory agencies and elimination of their duplications;
2. Further simplification of the regulatory procedures, improvement in their administration in order to make them business friendly and cost-efficient both for the state and business;
3. Increase in transparency of the regulatory procedures and activities of the regulatory bodies;
4. Improving economic regulations to ensure accessibility of medicinal products

It will provide a basis for closing the implementation gap (between the adopted regulations and their actual implementation), making progress in the harmonization of national regulations with the international standards, creating a business friendly regulatory environment in the pharmaceutical market, increasing performance efficiency of the regulatory institutions. Therefore, it will contribute to the increase in accessibility and affordability of safe and high-quality medicinal products for the final consumes.

Our main recommendations across four directions are summarized in the following table:

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<thead>
<tr>
<th>Direction/ Actions</th>
<th>Responsible agency</th>
<th>Time-frame</th>
<th>Priority</th>
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<tbody>
<tr>
<td><strong>Institutional Strengthening</strong></td>
<td>CMU, MoH</td>
<td>2016</td>
<td>High</td>
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<tr>
<td>1. Complete the restructuring and ensure full operations of the newly established State Service on Medicinal Products and Drugs Control with clear and transparent functions</td>
<td>CMU, MoH</td>
<td>2016</td>
<td>High</td>
</tr>
<tr>
<td>2. Remove the artificial division of the registration/re-registration functions of medicinal products between two agencies and concentrate them in one place.</td>
<td>MoH</td>
<td>2016</td>
<td>High</td>
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<td>3. Introduce a regular rotation and improve the selection procedure for the experts in SEC who are responsible for the examination of the application dossiers. The selection procedure should become more competitive and focus on professional criteria. Introduce a regular expert rotation.</td>
<td>CMU, MoH</td>
<td>2016-2017</td>
<td>High</td>
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4. Introduce the electronic document flow between the regulatory agencies.
5. Enhance the institutional capacity of regulatory agencies by clear allocation of their functions after conducting a thorough audit of functions; eliminate duplications of functions and provide an adequate functions-related financing. Consider raise in the registration fee and as an additional source of financing.

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<thead>
<tr>
<th>Direction: Simplification of the regulatory procedures, improvement in their administration</th>
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<tr>
<td>6. Sign the agreement on mutual recognition of GMP certificates between Ukraine and PIC/S countries.</td>
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<td>7. Abolish the requirement to have a GMP conformity confirmation from the national regulatory body for the foreign manufacturers that have GMP certificates issued by the competent authority of the PIC/S member.</td>
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<td>8. Adopt new licensing terms with a clear and exhaustive list of requirements for businesses.</td>
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<td>9. Ensure full implementation of the one-stop-shop principle in registration of drugs. The applicant should be able to submit all the requested materials and receive a positive or negative decision in one shop.</td>
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<td>10. Provide a regulatory framework for the interaction between the applicants and the experts during the expert reviewing of the registration dossier.</td>
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<td>11. Introduce a simplified procedure for insignificant amendments of the registration dossier based on the declarative principle: do-tell principle - for minor changes of type IA, and tell-wait-make principle – for minor changes of type IB.</td>
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<td>12. Introduce an exhaustive list of criteria for requesting additional information / making tests from business during the regulatory procedures.</td>
</tr>
<tr>
<td>13. Develop an efficient liability mechanism of the regulatory agencies for missing the deadlines of the regulatory procedures or requesting additional unjustified information/making additional tests for business within the regulatory procedures.</td>
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<td>14. Consider using the declarative principle for some of the regulatory procedures (e.g. re-licensing, expanding business activities subject to licensing).</td>
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<th></th>
<th>CMU, MoH</th>
<th>2017</th>
<th>high</th>
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<td>5.</td>
<td>CMU, MOH</td>
<td>2017</td>
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<td>6.</td>
<td>CMU, MoH</td>
<td>2016-2018</td>
<td>high</td>
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<td>7.</td>
<td>CMU, MOH</td>
<td>2016</td>
<td>high</td>
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<td>8.</td>
<td>MoH SSUMP</td>
<td>2016</td>
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<td>9.</td>
<td>CMU, MOH</td>
<td>2016</td>
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<td>10.</td>
<td>CMU, MoH</td>
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<td>11.</td>
<td>MoH</td>
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<td>12.</td>
<td>CMU, MoH</td>
<td>2016</td>
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<td>13.</td>
<td>CMU, Verhovna Rada</td>
<td>2016</td>
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<td>14.</td>
<td>MoH</td>
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<td>Ensure the electronic submission of applications</td>
<td>MoH</td>
<td>2016</td>
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<td>Adopt by-laws to regulate the termination of marketing authorizations for medicinal products (based on requirements of the Directive 2001/83/EC) for a clearly defined list of cases.</td>
<td>MoH</td>
<td>2016</td>
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<td>Reconsider the “warning” requirement while conducting scheduled inspections of the medicinal products in circulation. The scope and frequency of the inspections should be risk-related, and the mandatory warning of business before the inspection might be cancelled/</td>
<td>MoH, CMU</td>
<td>2016</td>
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<td>Refrain from the moratorium on inspections of manufacturers and traders of medicinal products.</td>
<td>Verhovna Rada, CMU</td>
<td>2016</td>
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<td>Replace the incoming quality control in pharmacies by an introduction of the GPP quality management system</td>
<td>MoH</td>
<td>2016</td>
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**Direction: Increase transparency of the regulatory procedures and activities of the regulatory bodies.**

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<td>Cancel the function of SEC’s advisory bodies (Scientific Expert and Science and Technology Councils) to confirm individual expert assessments of the registration dossiers. Implement best practices of EU countries when decisions on drug registration are based on the individual expert assessments (with a high personal responsibility of an expert for the assessment results).</td>
<td>MoH</td>
<td>2016</td>
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<tr>
<td>Remove the grounds for unmotivated extension and complication of the regulatory procedures. Adopt a clear and exhaustive list of grounds for conducting additional examinations (or submitting additional documents) in the process of obtaining registration and licenses, and during quality control.</td>
<td>CMU, MoH</td>
<td>2016</td>
</tr>
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<td>Provide the applicants with e-monitoring of the progress in completing regulatory procedures</td>
<td>CMU, MoH</td>
<td>2016</td>
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<td>Develop a methodology for calculating the share of the counterfeit and poor-quality medicinal products in the market. Develop an electronic database of counterfeit and poor-quality products.</td>
<td>MoH, SSUMP</td>
<td>2016</td>
</tr>
<tr>
<td>Develop the assessment criteria for public monitoring the efficiency of quality control system for medicinal products. These criteria</td>
<td>MoH, CMU</td>
<td>2016</td>
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should be result-oriented and show among others the results in fighting against the low-quality and counterfeit drugs. Ensure public access to the information on performance indicators of the control agencies.

**Direction: Improve economic regulations**

**Price Regulation**

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<td>25.</td>
<td>Unify rules for regulating prices for medicinal products procured with public funds;</td>
<td>CMU</td>
</tr>
<tr>
<td>26.</td>
<td>Restore the mechanism of reference prices to control the wholesale prices for medicinal. Pay a special attention to the choice of reference countries.</td>
<td>CMU</td>
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<td>27.</td>
<td>Introduce the maximum price for generics with a fixed discount compared to the declared price of the original drug.</td>
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**Reimbursement for Medicinal Products**

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<tr>
<td>28.</td>
<td>Renew the reimbursement project for anti-hypertension medicinal products.</td>
<td>CMU</td>
</tr>
<tr>
<td>29.</td>
<td>Develop a step-by-step plan to extend the list of medicinal products covered by the reimbursement programs</td>
<td>CMU, MoH</td>
</tr>
<tr>
<td>30.</td>
<td>Implement e-technologies for issuing and registering medical prescriptions</td>
<td>CMU</td>
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**Taxation**

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<td>31.</td>
<td>Apply 7% VAT to medicinal products in circulation with the expired market authorizations until the expiration of the consumption date</td>
<td>MoH, CMU</td>
</tr>
<tr>
<td>32.</td>
<td>Clarify the rules for classification of medicinal products for custom clearance concerning the VAT rates. Deprive customs authorities of the possibility to manipulate with different VAT rates for medicinal products.</td>
<td>MoH, CMU</td>
</tr>
<tr>
<td>33.</td>
<td>Refrain from further increases in the VAT rates for medicinal products in the short-run.</td>
<td>Verhovna Rada, KMU</td>
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This report consists of seven chapters. Chapter I reviews the situation in the Ukrainian pharmaceutical market. Chapter II addresses the issues of pre-registration procedures - conducting preclinical and clinical trials. Chapter III examines changes and gaps in the registration procedures for medicinal products. Chapter IV explores procedures for licensing business entities that produce, import or market medicinal products. Chapter V covers the issues of post-registration control of medicinal products’ quality and circulation.
Chapter VI focuses on the regulatory framework of the pharmaceutical market. Chapter VII examines certain issues of economic regulation on the pharmaceutical market (price and tax regulation, reimbursement practices). The analytical note on the findings of the survey of pharmaceutical market representatives, conducted in October of 2015, is attached thereto.

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The report is prepared by Iryna Akimova (Introduction, Chapters II, III, VI and VII), Hanna Husieva (Chapters II and III), Kostiantyn Kosiachenko (Chapter 6), Olena Osinkina (Chapters IV and V), Yuriy Podvysotskyi (Chapters I, V and VII) and Vladyslav Melnyk (Chapter II).

The analytical note on the findings of the survey conducted in October 2015 was drawn up by the Ukrainian office of IFAK Institut research agency.

General editing is done by Iryna Akimova.

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Introduction

The pharmaceutical sector plays a vital social role, providing people with medicinal products and medical supplies and is one of the key elements in ensuring efficient functioning of the healthcare system. Taking into account that about 90% of expenditures on pharmaceuticals are paid out-of-pocket, any fluctuations in the pharmaceutical market have an immediate and noticeable impact on Ukrainian households and spur heated political discussions. The affordability and physical availability of medicinal products depends, among other important factors, on the structure and regulation of pharmaceutical market.

Thus, the pharmaceutical sector is a subject of strict state regulation. The regulation of pharmaceutical market is aimed at ensuring safety, quality and efficacy of medicinal products manufactured and sold to the final consumer. To that end, the state sets out marketing authorization rules, the framework for quality control of medicinal products during their production and circulation, and qualification requirements for manufacturers and traders of the medicinal products. The state regulation impacts physical availability of the medicinal products by setting public procurement procedures for medicinal products, and regulatory rules for wholesale and retail pharmaceutical market. The regulatory system impacts affordability of the medicinal products for the consumer by setting direct and indirect price controls and providing cost reimbursement schemes for medicinal products.

The regulatory system of pharmaceutical market is considered to be efficient when it ensures affordability and physical availability of safe, high quality and efficacious medicinal products for the patients while minimizing regulatory costs both for the state and business.

The purpose of this study was to analyze the regulatory system of pharmaceutical market in Ukraine (related to the manufacturing and circulation of medicinal products) and its influence on the physical availability and affordability of medicinal products for public. We addressed several research questions, in particular:

Is the regulatory system of pharmaceutical market in Ukraine efficient? Does it ensure safety and quality of medicinal products and their availability for the final consumers?

Is the regulatory system transparent and friendly for business? How was it changing?

Is it possible to evaluate its performance in an unbiased and fair way?

We attempted to assess the main changes in the regulatory system over the last 5 years pointing out at the positive and problematic developments; highlight the most important remaining problems; and develop recommendations.

We analyzed the regulations in the market of medicinal products across the following areas: pre-registration procedures (preclinical and clinical trials), registration; licensing business entities that produce, import or market medicinal products; post-registration control of medicinal products’ quality and circulation; regulatory institutions framework of the pharmaceutical market; and some issues of economic regulation (price and tax regulation, reimbursement practices).

For the preparation of this Report we followed the following approach:

- Reviewed available analytical work on the regulation of pharmaceutical market,
- Reviewed the policy, legal, regulatory and institutional framework of regulations in the market for medicinal products in Ukraine,
- Conducted a survey of 32 the manufacturers and distributors of medicinal products which operated in Ukraine. The survey studied business perceptions of the recent changes in the regulation of pharmaceutical market and main regulatory challenges.
- Carried out a workshop to discuss potential recommendations with key stakeholders. The objective of the workshop was to validate key findings and assist the authors in clarifying and ranking in terms of priority the key issues and the policy recommendations.
CHAPTER 1. ECONOMIC REVIEW OF THE PHARMACOLOGICAL MARKET

The pharmaceutical sector plays an important social role since it provides the population with medicinal products necessary for effective treatment and profilactics. The share of pharmaceutical products within the healthcare costs is more than one third, i.e. over 35% of the entire healthcare spending falls on pharmaceuticals\(^3\). Taking into account that Ukrainians pay about 90% of the cost of pharmaceuticals out of their own pockets\(^4\), any fluctuations in the pharmaceutical market have an immediate and noticeable impact on the population and spur up the heated political discussions. The structure of the pharmaceutical market, its development and regulation influence the affordability and physical availability of medicinal products.

Review of the Ukrainian Pharmaceutical Market

The size of pharmaceutical market as a share of the GDP was growing from 1.8% in 2010 to 2.8% in 2014 (Figure 1.1). Economic crisis of 2014-2015 led to the dramatic increase in drug prices and a reduction of real income of Ukrainian households.

Source: Proxima Research, State Statistics Committee.

Figure 1.1. Ukrainian Pharmaceutical Market as a Share of GDP

In 2014, the price index of pharmaceutical products grew by 44.9%, in January-September 2015 – by 23.7% p-o-p. In September 2015, the price of one packing in the pharmaceutical basket goods amounted to UAH 31.6, which represents a 44.7% hike over the same period of last year. The prices of drugs have doubled since the beginning of 2014. The biggest price jump was related to the imported drugs (affected by the sharp devaluation of the national currency from UAH 8 to 22 for USD), which accounts for more than 66.2% of the market in value terms. More than 2/3 of all drugs registered in Ukraine are imported.

A significant rise in prices of medicinal products was accompanied by a decrease in real incomes, which occurred due to a high inflation (consumer price index in 2014 is 124.9%; in January-September 2015 - 141.4%) and a low indexation of living standards (by 13.1% during 2014- September 2015). In real terms, the average salary decreased by 14.7% in 2014 , and by 23.2% in January – September 2015 (period-to-period).


Consequently, by the end of 2014 the physical volume of drugs consumed by the population had decreased by 12.3%, and during the next 9 months of 2015 – by further 12.4% (Figure 1.3). In January-September 2015, the total sales of the pharmaceutical basket in physical terms shrank by 14.5%. Therefore, till the end of 2015, the total drug consumption (in physical terms) may fall below the 5-year minimum. Notably, in Ukraine the consumption of drugs per capita was much lower compared to the developed countries even before the crisis (Figure 1.2).

These developments on the pharmaceutical market reflect an acute social problem – a significant decline in the affordability of medicinal products for the public. This was reflected in sociological surveys. For instance, the survey by the international research group TNS covering about 5,000 respondents showed that in the first quarter 2015 as much as 20% of the people living in large cities (population over 50 thousand people) were forced to save on health services and medicinal products. A year ago this indicator was 15%. There are several social groups for which the availability of drugs is constantly decreasing, including:

- retirees – 11 million persons receiving pensions ranging to 2,000;
- low-paid workers and employees – 0.6 million people whose monthly salary is less than the poverty line according to World Bank and United Nations methodology – UAH 1,335 per month;
- the unemployed – 1.7 million people of which only 407.4 thousand receive unemployment benefits averaging UAH 1,387 per month;
- internally displaced persons (IDPs) – almost 1.6 million people, whose monthly allowance is UAH 842 per month.

Taken altogether, these four groups make up for 14.5 million people or more than 35% of the total population, who faces worsening access to quality healthcare.

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In value terms (UAH bln) | In volume terms (mln packs)
---|---
2010 | 19.7 | 1186
2011 | 23.0 | 1201
2012 | 27.0 | 1267
2013 | 30.4 | 1274
2014 | 43.8 | 1117
2015 | 41.6 | 1012

* The data for 2015 are calculated by doubling the data for the first six months of 2015.

Source: Proxima Research.

Figure 1.3. Developments in the Size of the Ukrainian Pharmaceutical Market

The range of drugs admitted to the Ukrainian market is narrower than in the developed countries. In October 2015, the State Register of Medicinal Products of Ukraine included 12,410 drugs, including 9.9 thousand finished drugs (compared to more than 45 thousand registered finished drugs in Poland, and more than 90 thousand-in Germany). This gap is especially significant in the group of drugs for diseases of the blood circulatory system, though cardiovascular diseases are the problem No. 1 in Ukraine.

Ukraine lacks 32% of the medicinal products included in the recommended WHO Model List of the Essential Medicinal Products for the developing countries. Imported drugs dominate the market in value terms. The range of the imported drugs on the Ukrainian market is much wider than the range of the domestically-produced ones. In the State Register of Medicinal Products, over 70% (8,704) of the registered medicinal products are imported.

The share of foreign medicinal products in quantitative terms on the Ukrainian market, by contrast, is lower than the share of the domestic ones. Due to the rapid devaluation of the hryvnia in 2014-2015, the share of foreign drugs in quantitative terms on the Ukrainian domestic market has decreased. However, in terms of value, foreign drugs still dominate. While in 2011 their share accounted for 35% of the Ukrainian pharmaceutical market in terms of quantity and 72% in terms of value (Figure 1.5), in the first half of 2015, according to the Apteka publishing house, it declined to 23% in quantitative terms and to 60% – in value.
Figure 1.4. The Shares of Domestic and Imported Drugs on the Ukrainian Pharmaceutical Market

Ukrainian pharmaceutical market is dominated by the generic medicinal products. The market share of original medicinal products is not more than 6% in physical terms and 19% in value. It is lower than in most of the European countries (Figure 1.5). The vast majority of the original drugs in circulation in Ukraine are imported.

Figure 1.5. The share of generics in the market in select countries in 2011.

The pharmacy / hospital segment. The two main segments of the domestic pharmaceutical market are the pharmacy (retail) segment and the hospital segment. The hospital segment

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6 "Generics and original drugs: a pharmacologist's view " newspaper "Apteka" (21.7.2014), access: <http://www.apteka.ua/article/298852>

is only about 10% of the pharmaceutical market both in physical and value terms, while with pharmacy (retail) segment covers over 90% of the market (Figure 1.6).

Source: Proxima Research.

Figure 1.6. The Shares of Retail and Hospital Segment of the Ukrainian Pharmaceutical Market

**Competition on the Domestic Pharmaceutical Market**

The level of competition among the market participants affects the prices of medicinal products, the availability of drugs on the market and the quality of medicinal products. The major players of the pharmaceutical market are manufacturers, wholesale distributors and retail distributors (pharmacies).

**Manufacturers.** Presently, 115 companies manufacture drugs in Ukraine. Domestic manufacturers of drugs include a group of top-5 largest producers (Farmak, Darnitsya, Arterium, FK Zdorovya and Kyiv Vitamin Plant) accounting for almost a third of all domestic production of medicinal products\(^8\). Therefore, the production of drugs in Ukraine is not very much concentrated. Ukrainian pharmaceutical manufacturers also export their products. Although pharmaceutical exports are gradually increasing\(^9\) (see Figure 1.7), their share in the total volume of Ukrainian exports is still negligible. In particular, it amounted to 0.47% in 2014, and the CIS countries have been and remain the main consumers of the Ukrainian pharmaceutical products (over 80% of the Ukrainian pharmaceutical exports).

Importantly, Ukraine's pharmaceutical industry is basically low-tech: only three to four companies are engaged in the production of substances, medical gases and non-sterile drugs (including traditional), and 25% companies are licensed to manufacture sterile drugs, i.e. modern generics.

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Foreign direct investments (FDI) in the domestic pharmaceutical industry is low, unlike the other countries. Such countries as Ireland, Singapore and Brazil have gained great experience in enhancing their pharmaceutical sectors. In 2015, 12 countries – the USA, Ireland, China, Singapore, Germany, France, Spain, Italy, United Kingdom, Canada, Brazil and Russia – accounted for 70% of all the FDI in the pharmaceutical industry\(^\text{10}\). Ireland has become the most successful country in attracting investments: in this country the pharmaceutical industry FID to GDP ratio is 3.1% compared with 0.1% for other countries from the Top-12 list.

**Wholesale distributors.** Although 487 companies have the marketing license, the wholesale distribution sector is very concentrated. According to Proxima Research, the 5 largest wholesalers account for almost 88% of the market (Figure 1.8).

In the recent years, the concentration of the wholesale market has gradually expanded with the share of the top-5 distributors growing from 66% in 2009 to 92% in 2013. In 2014,

\(^{10}\) *Vision 2020: Action Plan on Development of the Pharmaceutical Sector in Ukraine*, ACC and APRAD
the share of the top-5 distributors has slightly decreased following the bankruptcy of Alba-Ukraine, the third largest market distributor.

**Pharmacies.** The highest level of competition is observed in the retail market segment. According to Proxima Research, the country has more than 21,659 pharmacy outlets, while the share of retail sales of largest pharmacy chain, LLC "Magnoliya Pharmacy", is only 5.3%.

However, there is a slow and gradual increase in market concentration – the share of 100 largest pharmacy chains grew from 56% in 2011 to 63% in 2014. Furthermore, a hidden monopolization of the market is observed when some pharmacy chains try to monopolize regional markets. It has become a common practice when one owner, in order to avoid antitrust investigation, creates several pharmacy chains which are, in fact, managed from one center and, therefore, have coordinated pricing policies.

**Regulation of the Pharmaceutical Market**

Great social significance of the pharmaceutical sector makes it subject to rigorous government regulation. The main purpose of the regulatory system in the pharmaceutical market is to ensure the safety, quality and efficacy of medicinal products. In order to achieve this goal, the state establishes a regulatory frame for the registration of medicinal products, pharmaceutical supervision, and licensing of business entities engaged in the production and marketing of drugs. Government regulations may affect the physical availability of drugs by setting the rules for public procurement, rules for drugs distribution through the wholesale and retail chains or creating incentives to expand the range of medicinal products, especially innovative ones. The regulatory system impacts the affordability of medicinal products for the final consumer through direct and indirect price controls, cost reimbursement of medicinal products.

An effective regulatory system of pharmaceutical market have to ensure economic and physical availability of the efficient, safe and quality medicinal products for the patients. Its goals include the following:

- Providing market access for the medicinal products that are of high quality, effective and safe for the patients (registration procedures);
- Providing market access for the producers and distributors that meet established standards (licensing requirements);
- Monitoring the efficacy and safety of drugs and controlling the quality of medicinal products supplied to the Ukrainian market both by domestic and foreign producers (pharmacovigilance and drug traffic control);
- Creating incentives for the domestic and foreign producers to supply effective and quality medicinal products to the Ukrainian market (economic regulation);
- Ensuring affordability of medicinal products for population (economic regulation).

These objectives could be met if the pharmaceutical market regulation system is able to perform its key functions, along with imposing a low “regulatory tax” and ensuring sufficient market competition among the business entities. This relationship is depicted in Figure 1.9.
Main components of the regulatory system. State regulates the operations of the major market players: manufacturers (domestic and foreign), wholesale distributors and retail distributors (pharmacies) (see Figure 1.11).

[4] Economic regulation of the drugs market
1) Taxation (VAT, import duty)
2) Limiting wholesale prices
3) Maximum wholesale and retail margins

[1] Introduction of drugs in the market
1) Preclinical trials
2) Clinical trials
3) Registration of drugs
4) Re-registration of drugs
5) Pharmacovigilence

[2] Entity access to the market
1) Licensing of producers
2) Licensing of wholesale distributors
3) Licensing of pharmacies
4) Certification of pharmacists

[3] Post-marketing (pharmacovigilance) and quality control

Figure 1.9. The Role of the Efficient Pharmaceutical Market Regulation System

Figure 1.10. Elements of Regulator System in the Pharmaceutical Market

According to the WHO methodology[^11], the national regulatory system should have the following mandatory components: pre-registration and registration procedures, licensing of economic activities, post-registration quality and drugs trade control. They are complemented with economic regulation of the pharmaceutical market.

Regulatory system imposes costs both on the state and market actors. The risks of high regulatory barriers and corruption arise when regulatory procedures are not transparent and enable conflict of interest, or if there is duplication in supervisory functions. On the other hand, market players try to shift part of their regulatory costs on the final consumers - patients - by including these costs in the final price of medicinal products.

The regulatory system in each country seeks a balance between the regulatory costs and the ultimate results, i.e. provision of safe, effective and affordable medicinal products to the people. The purpose of this report is to analyze how the Ukrainian regulatory system is trying to address these important issues.
CHAPTER 2. PRE-REGISTRATION PROCEDURES

Developing and bringing drugs to the market is a complex, lengthy and multistage process (see Figure 2.1).

<table>
<thead>
<tr>
<th>Invention</th>
<th>Pre-clinic</th>
<th>Phase I: 1 year</th>
<th>Phase II: 2 years</th>
<th>Phase III: 3 years</th>
<th>Registration: 2-3 years</th>
<th>Phase IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Objective</td>
<td>Assessment of safety, biological activity</td>
<td>Determination of safety and doze</td>
<td>Assessment of efficacy, determining side effects</td>
<td>Comparison of efficacy, Monitoring of long-term use</td>
<td>Adoption process/issuance of trade license</td>
<td>Additional post-registration trials</td>
</tr>
</tbody>
</table>

Figure 2.11. New (Innovative) Drug Development Phases

Source: *Food and Drug Administration, 2006.

Pre-registration and registration procedures have a large impact on the availability of the effective and safe medicinal products. First, they have to ensure prompt entrance of the new drugs to the market (both internationally innovative medicinal products and those new to the Ukrainian market). Second, the regulatory procedures should allow a limited and controlled access of the new drugs even before the full registration procedure is completed. Third, it should create a friendly environment for the development of domestic medical research and capacity building.

2.1. Preclinical Trials of Medicinal Products in Ukraine

Preclinical trial is the first stage of the drug life cycle. Preclinical trials are mandatory for the development of original/innovative medicinal products. They represent a set of research procedures/operations to study potential risks and specific effects of the drug, and to ensure its safety and therapeutic efficacy. Preclinical trials determine the safe dosing and possible toxicological properties of the drug.

Conducting preclinical trials in Ukraine is important for:
- the developers of domestic original (innovative) drugs, herbal medicinal products and biosimilars;
- foreign producers that conduct research activities on the new drug in Ukraine (research institutions should hold a GLP certificate in order their findings to be internationally recognized).

Today, the number of preclinical trials in Ukraine is very low. As of 01 August 2015, there were only 7 registered original drugs with preclinical trials carried out in Ukraine. Domestic pharmaceutical manufacturers are not active in developing new medicinal products. Ukraine is a country of generics: over 60% of the drugs registered in Ukraine are generic ones. Preclinical trials are mostly conducted for original medications and fixed combinations, when their application is expanded to include the pediatric group etc. Low

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12 Preclinical Trials on Medicinal Products / Edited by O.V.Stefanova. — Kyiv, 2001
innovation activity of the domestic manufacturers is mainly explained by the economic crisis and lack of incentives for the long-term investment.

Conducting of preclinical trials is regulated by the Law of Ukraine "On Medicinal Products" (Article 6), and the Procedure for Conducting Preclinical Study of Medicinal Products and Expert Review of Preclinical Study Findings and the Guidelines on Good Laboratory Practice.

**Changes in the Organization of Preclinical Trials in Ukraine**

During 2001-2009, about 30 laboratories investigated the properties of drugs at the preclinical stage in Ukraine. The laboratories did the toxicology study of the domestic generics so that medicinal products could be registered in Ukraine. These laboratories received a permission to conduct pre-clinical trials from the State Pharmacological Center of the MoH of Ukraine. Their findings were not recognized abroad.

Since 2009, substantial efforts were made to **approximate preclinical trials in Ukraine with the international standards**. The Guidelines on Good Laboratory Practice was adopted to harmonize Ukrainian practices with EU requirements. **Good Laboratory Practice** (GLP) ensures quality and reproducibility of data. It is a system of quality control with regard to planning, implementation, monitoring, data recording, sharing of findings and storage of materials on preclinical trials of drugs. According to the GLP requirements, both domestic (national) and external (by competent authorities of international organizations) certification is acceptable. The state should ensure the existence of a National GLP Enforcement Agency, a National GLP Program and a National GLP Regulator.

An introduction of GLP rules in preclinical trials was expected to promote the development of research laboratories which results might be recognized internationally. It had to help the domestic producers to avoid duplication of their preclinical tests and promote domestic medicinal products on the international markets.

In 2010, the Ministry of Health of Ukraine approved new rules which allowed conducting preclinical trials by the research institutions irrespective of their ownership and subordination. Previously, such studies were conducted only by the public health institutions. However, domestic certification and inspection procedures for such institutions have not been put in place to date.

In terms of research areas, preclinical trials principles in Ukraine meet EU requirements. An introduction of a detailed regulation of preclinical trials for new (original/innovative) and herbal medicinal products and determining inexpediency of carrying out such studies for generics was another important step in harmonization with EU standards.

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13 Contrary to the European practices, where any institution certified according to the standards of good laboratory practice (GLP) may carry out such studies.
14 Implementation of GLP is regulated by order of the Ministry of Health of Ukraine No. 95 dated 16 February 2009 "On Approval of Documents on Ensuring the Quality of Medicinal Products".
17 Directive 2004/10/EC of the European Parliament and of the Council of 11 February 2004 on the harmonization of laws, regulations and administrative provisions relating to the application of the principles of good laboratory practice and the verification of the applications or tests on chemical substances (codified version)
In 2011, the legal grounds for importing unregistered medicinal products for pharmaceutical development were widened. The law allowed importing limited amounts of unregistered medicinal products by the licensed manufacturers of medicinal products and the scientific institutions that were involved in the development of drugs. It became an impetus for the development of domestic pharmaceutical production and for scaling-up of preclinical and clinical trials.

The next step in the implementation of international standards in the field of preclinical trials was the adoption of the guidelines “Guidelines. Medicinal Products. Preclinical Safety Trials as a Ground for Clinical Trials Involving a Human and Registration of Medicinal Products” based on the principles of EMA/CPMP/ICH/286/1995 (ICH M3(R2)) "Guidance on Non-clinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals”. The above mentioned guidelines establish requirements for planning and conducting preclinical studies of medicinal products, clinical trials and registration of drugs.

**Problems**

The development of regulatory framework for pre-clinical trials moved forward. However, the development of GLP-conformed laboratories is slow. Confirming compliance with GLP requires substantial financing to follow the strict rules concerning vivarium, pure lines of animals, standardized and controlled feeding, logging of each step in the research. Public funds for these purposes are lacking, and private investors often invest in such projects outside Ukraine.

Ukraine has no agency to inspect the laboratories and produce the reports on their GLP conformity. Neither is any procedure for GLP certification of the institutions that conduct the preclinical trials of medicinal products. Therefore, Ukrainian laboratories that seek to operate in accordance with global standards have to apply to foreign accreditation companies (e.g. SNAS) that carry out such inspections and audits, and request a high fee for their services. Presently, Ukraine has only one laboratory that with the GLP certificate – the interdepartmental laboratory of preclinical trial of medicinal products of Ministry of Health and National Academy of Medical Sciences of Ukraine which has been created in 2001 and operates at the Institute of Pharmacology and Toxicology of the NAMS of Ukraine. This laboratory covers the small demand for preclinical trials of Ukrainian pharmaceutical manufacturers. Further development of preclinical trials and research in Ukraine is directly related to change in demand from domestic and foreign pharmaceutical manufacturers.

### 2.2. Clinical Trials of Medicinal Products in Ukraine

Clinical trials are the second stage of the life cycle of a medicinal product and constitute an important step in determining its effectiveness and safety. Clinical trial (research) of the medicinal product is a study that involves a human being as a research subject, and intends to detect/confirm clinical, pharmacokinetic, pharmacodynamic and/or other effects of medicinal products in order to assess their safety and efficacy. The carrying-out of

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20 Order of the Ministry of Health of Ukraine and the National Academy of Medical Science of Ukraine No. 48/262 dated 04 July 2001 “On Establishment of the Interagency Laboratory for the Preclinical Investigation of Medicinal Products between the Academy of Medical Science and the Ministry of Health of Ukraine”.

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clinical trials on medicinal products is regulated by Articles 7 and 8 of the Law of Ukraine "On Medicinal Products".

Clinical trials are an integral part of the development of new medicinal products. Conducting clinical trials is mandatory for the innovative/original medicinal products, generics (bioequivalence study), orphan products (orphan medicinal products), biological, homeopathic and herbal medicinal products etc. No medicinal product can be brought to the market, with the exception of some generics, well-studied, traditional medicinal products and so on, if clinical trials have not been successfully completed.

![Figure 12.3](image-url)

**Figure 12.3. Dynamics of Ukrainian Clinical Trials of Medicinal Products Approved in 2012-2014**

*Source: State Expert Center, MoH of Ukraine (www.dec.gov.ua).*

![Figure 2.4](image-url)

**Figure 2.4. Dynamics of Positive Assessments concerning Clinical Trials of Medicinal Products in Ukraine in 2012-2014.**

*Source: State Expert Center, MoH of Ukraine (www.dec.gov.ua).*
In Ukraine, the main types of clinical trials of medicinal products include:

- multicenter (international) clinical trials requested by the world's leading companies that develop new (innovative) medicinal products;
- pre-registration clinical trials ordered mainly by the domestic manufacturers of medicinal products (after a full or shortened program);
- tests of bioavailability/bioequivalence (generic medicinal products).

Over the last three years, the volume of international multicenter clinical trials has declined (from 213 in 2012 to 188 in 2014, and to 134 during January-October 2015) contrary to the slight increase in pre-registration clinical trials (see Figures 2.2 and 2.3).

The state regulates the whole procedure of clinical trials defining the requirements both for the research entities and objects of clinical trials. The experts point out that the potential of Ukraine for conducting clinical trials is used only by 10-15%. Ukraine has competitive advantages for accommodating new clinical trial projects: namely, the centralized healthcare system, highly professional personnel and the opportunity to engage in research patients with rare diseases. Clinical trials promote the influx of new medicinal products into Ukraine and the substantial improvement of doctors' professional skills.

**Changes in Regulation of Clinical Trials in Ukraine**

Since 2006, clinical trials has been regulated by the order of the MoH of Ukraine\(^1\) which determined both the lists of healthcare institutions and medicinal products for clinical trials. In fact, only institutions of the National Academy of Medical Science of Ukraine were allowed to conduct clinical trials.

*In 2009, Ukraine started to implement the principles of good clinical practice (GCP)\(^2\) which brought national practices closer to the European standards. MoH approved a new procedure for conducting both clinical trials and expert reviewing of clinical trials materials\(^3\).* This Procedure introduced some important changes that positively affected the development of clinical trials in Ukraine:

First, it was developed in accordance with the provisions of Directive of the European Parliament and Council 2001/20/EU\(^4\), and other international documents that define basic principles of conducting clinical trials worldwide. The Procedure secured ethical principles and set the requirements for life and health insurance of the patients (healthy volunteers) during clinical trials of the medicinal products. The State Expert Center of MoH (hereinafter – the SEC) had a mandate to conduct the expert review of materials of clinical trials prepare assessment report.

Second, the document set equal requirements for the researchers and sites of conducting clinical trials. It cancelled the MoH’s approval of the list of the institutions eligible for

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\(^1\) Order of the Ministry of Health of Ukraine No. 66 dated 13 February 2006 “On Approval of the Procedure for Conducting Clinical Trials on Medicinal Products and Expert Review of Clinical Trial Materials and the Standard Ethics Commission Statute”.

\(^2\) Implementation of GCP is regulated by Order of the Ministry of Health of Ukraine No. 95 dated 16 February 2009 “On Approval of Documents on Ensuring the Quality of Medicinal Products”.


\(^4\) DIRECTIVE 2001/20/EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use.
conducting clinical trial allowing any healthcare facility with a license for medical practice and an accreditation certificate from MoH to start these activities. At the same time, clinical trials remain the subject of contract between the legal entities and individuals (who take part in them).

Third, this Procedure ensured the implementation of ethical principles of Helsinki Declaration concerning the assurance and adherence to the basic requirements for protection of persons under study (patients or healthy volunteers).

In the next two years, much attention was paid to improve ethical side of clinical trials.

- In April 2011, the duplication in assessment of protocol of clinical trials by the Central Ethics Committee and local committees on ethics in health institutions was liquidated.
- In May 2011, the involvement of minors in the clinical trials was limited to cases when medicinal product was intended for the treatment of children's diseases or it was necessary to optimize the dosage/usage of the medicinal product for minors. Clinical trials of the medicinal product involving a minor were allowed only with a written consent of his/her parents, and availability of relevant information in an understandable form.

In 2014, the introduction of 7% VAT (instead of 20%!) for preparations and equipment used in clinical trials became an important incentive for further development of clinical trials. A year later two orders of MoH (Orders of the Ministry of Health No. 966 dated 18 December 2014 and No. 967 dated 18 December 201427), were adopted which, finally, allowed practical implementation of the new VAT rates.

In February 2015, the application procedure for clinical trials has been changed. Following the new procedure, the applicant submits an application for clinical trial to the CAC “Yedyne Vikno” (“One-stop-shop”) of the MoH of Ukraine, and dossier of the medicinal product - to the State Expert Center (SEC)29.

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29 A dossier includes a protocol of clinical trial of a medicinal product with all existing amendments to it, a brief summary (synopsis) of the protocol, individual registration form, reviewer brochures etc.
Figure 2.5. The Current Framework of the Procedure of Expert Review of Materials of Clinical Trials of Medicinal Products.

Source: State Expert Center of the MoH of Ukraine (www.dec.gov.ua), Regulations on the interaction between the Ministry of Health of Ukraine and the SOE “State Expert Center of the Ministry of Health of Ukraine” concerning execution of the decision of the Ministry of Health of Ukraine on conducting a clinical trial of medicinal product(s) or on approval of a substantial amendment or refusal to conduct clinical trials or on approval of substantial amendments.

Previously, all the documents were submitted directly to the SEC, where the applicant received the assessment report based on the expert reviewing of clinical trial materials, agreed by the MoH.

Presently, clinical trials of medicinal products in Ukraine can start only after their approval by the MoH. This approval is based on a positive recommendation of SEC which conducted the expert review of clinical trial materials. The current procedure for expert reviewing of clinical trial materials is shown in Figure 2.4. For the sake of transparency, the orders of MoH of Ukraine should be placed on the Ministry’s official website in the public domain. The applicants can receive the extracts from the orders of the MoH of Ukraine concerning a particular clinical trial. The MoH authorizes both clinical trials and import of the investigated medicinal products to Ukraine. For customs clearance of unregistered medicinal products and materials at the reduced 7% VAT rate, customs authorities demand a permit of MoH (order) on conducting clinical trials.

Amendments to the Procedure for Conducting Clinical Study of Medicinal Products and Expert Review of Clinical Study Materials cancelled controlling by SEC the provision of life/health insurance contract to the patient (volunteer). It was made in order to harmonize the procedure with the provisions of Law of Ukraine “On Medicinal Products” and “On Insurance” (the latter does not consider life/health insurance of the patient as a compulsory type of insurance). The responsibility for insurance contract was assigned to the customer of clinical trials (typically, this is a contracted research organization). This issue raised the concerns of patient organizations about the weakening of protection of the participants of clinical trials. The draft of new amendments to the Procedure for Conducting Clinical Study of Medicinal Products and Expert Review of Clinical Study...
Materials and the Standard Ethics Committee Statute (which appeared for public discussion on June 19, 2015) proposes to include a copy of the insurance contract in the package of documents to be assessed by the healthcare institution’s Ethics Committee.

**Problems**

The main regulatory problems in the area of clinical trials include the lack of transparency, inconvenience for the applicant, delays in conducting the expert review, and the lack of coordination between various governmental bodies. In the October 2015 survey of the representatives of pharmaceutical business, 40% of the respondents mentioned the non-transparency of the expert work, delays in conducting the expert review and the problem of informal payments among the most significant obstacles in conducting the preclinical/clinical trials of medicinal products.

1. **The inconvenience for the applicant** comes from the necessity of a direct interaction both with the regulatory authority (MoH of Ukraine) and the expert institution (SEC). In order to start clinical trials, the applicant should receive an approval of MoH. A formal introduction of the one-stop-shop principle in 2014 did not bring significant changes: The applicants still have to apply to the CAS “One-stop-shop” of the MoH, and at the same time, submit the materials of clinical trial to the SEC. Besides, during the expert reviewing process the applicant often needs multiple personal interactions with the experts for prompt resolution of issues raised by them. A badly regulated practice of interaction between the applicants and the experts creates risks of corruption. For comparison: In European practice, such meetings take place once in a collective format to consider all the existing comments. The results of these working meetings are recorded in minutes.

In order to import medicinal products for clinical trials, the applicant again comes to MoH for a letter of notification on import of unregistered medicinal products, standard samples and reagents. Thus, the applicants are continuously involved in obtaining different confirmations in different places instead of receiving all the necessary permits simultaneously in one place. This means that a full-fledged one-stop-shop is not yet fully implemented. Besides the inconvenience, this leads to the extended timelines of the expert review and delays in obtaining an appropriate permit. The situation is aggravated by the lack of electronic document flow between the MoH and SEC.

2. **Lack of transparency in expert assessment**

a) **Recommendations for conducting clinical trials** are given by the Scientific Expert Council of the SEC and constitute a mandatory basis for issuing a permit for clinical trials in MoH. No law stipulates the need to confirm the assessments of individual experts by the collective decision of SEC’s Scientific Expert Council (which functions are defined only by its own Charter). It turns to be an artificial and unnecessary requirement that prolongs the decision-making process (since the members of Expert Council meet normally once a month). In fact, the individual assessments of experts (for which the experts bear full responsibility) constitute a sufficient basis for making a decision on allowing clinical trials. The low efficiency of the collective decision-making on clinical trials of medicinal products and the non-compliance of this procedure with the international practices have been indicated in the Report on Evaluation of the Regulatory System for Medicinal Products Circulation in Ukraine conducted in 2008 by the WHO European Office, the Delegation of the European Commission in Ukraine and the US Agency for
International Development. However, so far the functions of the Scientific Expert Council remain unchanged.

b) Public information on the status of applications for clinical trials of medicinal products and on the on-going clinical trials in Ukraine is rather limited\(^{30}\). International practices demonstrate the need for a complete register of clinical trials in the form of a modern electronic database with the online access and a search function for all interested parties with an indication and information about clinical trial sites. For example, the European Register of Clinical Trials (Eudract Register) contains information on all officially registered clinical trials conducted in Europe including some information about the programs on the application of new drugs for reasons of humanity. The website of the European Register of Clinical Trials (www.clinicaltrialsregister.eu) can also be used to search for wide range of information on clinical trials. Recently, the European Medicines Agency (EMA) has instructed clients of clinical trials (sponsors) to disclose the information on implementation and findings of clinical trials in the European base (EudraCT). \(^{31}\).

In Ukraine, the issue of making a wider range of information available for public access was addressed in the amendments to MoH’s order that regulates the procedures of conducting clinical studies. In particular, the draft suggested supplementing the Procedure with a new requirement of each clinical trial to be registered in a publicly available database before the inclusion of the first investigated. This might increase the level of public awareness about the details of clinical trials (investigated patients, researchers and applicants). Since June 2015, the draft amendments are published on MoH’s website. However, they have not been adopted have not yet.

3. The violation of timelines in conducting expert review and the low level of protection of intellectual property rights.

Currently, the process of expert review often turns into the long queues of applicants and missed deadlines. The official deadlines include 47 days for the assessment of dossier of clinical trial in SEC, 27 days for making changes, and 5 days for making a decision by MoH. However, according to the anecdotal evidence from business representatives, in 75% of cases the delays in expert assessment, and consequently, in receiving the official confirmation of clinical trials reaches 1-1,5 months. Delays are mainly related to the absence of electronic document flow between the government agencies, and insufficient expert capacity. In addition, business complains about the risks of an unauthorized access to the information on innovative medicinal products and their trials. These risks are related to the absence of regulations on the protection of confidentiality of clinical trials dossier.

4. Poor implementation of regulatory decisions.

European Business Association raised concerns about the barriers for importing materials for clinical trials\(^{32}\), in particular, delays in customs clearance, and the application of 20% VAT rate instead of 7% (effective for this sector since 2014) by

\(^{30}\) \(\text{http://moz.gov.ua/ua/portal/register_clinical_tests}\)

\(^{31}\) The EU Clinical Trials Register is an open database containing excerpts from the materials of the European clinical trials database (Eudract). Since its launch in 2011, the EU Clinical Trials Register website has been constantly expanding the range and improving the quality of services that ensure the availability of information on the findings of clinical trials to the EU public. Recent innovations include enabled search for information on completed and ongoing clinical trials and access to findings published by the clients (sponsored) of the studies.

\(^{32}\) Taxing Drugs for Clinical Trials with 7% VAT: One Step before Final Result. Apteka Weekly, # 1002 (31), 17 August 2015, \(\text{http://www.apteka.ua/article/340838 http://www.apteka.ua/article/340838}\)
customs authorities. The 7% VAT rate for importing of medicinal products, medical supplies and medical equipment for clinical trials was introduced in April 2014. However, its practical implementation started almost a year later, in May 2015 after the changes to two orders of the MoH were made (MoH orders No. 966 and No. 967 of 18 December 2014). In November 2015, business still complained that part of supplies for on-going clinical trials were subject to 20% VAT. This was caused by the lack of effective collaboration between MoH and customs authorities (in the absence of the electronic document flow) and unclear requirements concerning the documents that confirm import for clinical trials. EBA pointed out that slow implementation of the regulatory decisions might cause Ukraine to lose new investment in clinical trials, since international sponsors might switch to the neighboring countries (such as Poland, Hungary, Romania) with favorable climate for the development of clinical trials.

5. **Problems in the contractual relationship between the client and the units that conduct clinical trials.**

a) **Differences in contract practices.** According to the international practice, one contract covers the relations between the sponsor (or its representative), researcher/researchers and the institution that carry out clinical trial. In Ukraine, the law requires separate agreements: one between the sponsor and the researcher, second between the sponsor and the institution where the clinical trial would be conducted, and the third one between the sponsor and the researcher. The Guidelines on Principles of Making Contracts in Clinical Study of Medicinal Products in Ukraine have been adopted in 2013, though the problem of legal differences was not overcome. It still requires additional administrative costs and reduces incentives to start new clinical trials for the domestic healthcare units.

b) **Insurance for physicians.** A standard request of foreign companies (sponsors of clinical trials) to ensure professional liability of the physicians and other researchers that participate in clinical trials is difficult to meet. Ukrainian legislation does not require compulsory insurance for the researchers in clinical trials. Consequently, the demand for such insurance is almost absent, and local insurance companies do not offer adequate insurance products. Besides, in case of voluntary insurance contracts there is a possibility for the insurance companies not to recognize the wrong doings of the researchers (that harmed the patient) as an insurance case.

c) **Lack of a legally defined methodology to determine the costs of clinical trials for healthcare institutions** reduces their incentives to participate in such projects. Most of the healthcare institutions are state- or municipally owned organizations that are financed from the state or regional budgets. In 2010, they were allowed to provide paid services of clinical trials. All their financial operations (in particular, the provision of paid services) are subject of a strict state control. The absence of the legally adopted methodology for calculating costs of services creates the risk to violate fiscal rules and makes the healthcare institutions an object for a potential pressure by fiscal authorities.

These problems hinder the opportunities of Ukrainian institutions to engage in clinical trials for international companies.

6. **A vast majority of the institutions that conduct preclinical and clinical trials in Ukraine do not meet GLP requirements.** Development of GLP-certified laboratories and institutions is constrained both by the general underfinancing of the healthcare sector, and the absence of national certification bodies for preclinical/clinical trials. This reduces the competitiveness of the domestic healthcare units as research sites
for clinical trials, despite the availability of professional personnel and relatively low cost of services.

**Recommendations**

<table>
<thead>
<tr>
<th>Action</th>
<th>Responsible agency</th>
<th>Timeframe</th>
<th>Priority</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Implement the one-stop-shop principle, creating the conditions for the applicant to submit the application materials and receive all the necessary permits for conducting clinical trials in one place. Establish transparent regulations for communication between the applicants and the experts during the assessment of clinical trial dossier. This will ease the administrative burden for applicants and make regulatory procedures in the area of clinical trials more transparent.</td>
<td>MoH, SEC</td>
<td>2016</td>
<td>high</td>
</tr>
<tr>
<td>2. Cancel the function of SEC’s advisory bodies (Scientific Expert and Science and Technology Councils to confirm individual expert assessments of the clinical trial dossier. Implement best practices of EU countries when decisions on allowing the conduct of clinical trials are based on the individual expert assessments (with a high personal responsibility of an expert for the assessment results). This will make the decision-making process shorter and more transparent.</td>
<td>MoH</td>
<td>Short-term 1&lt;sup&gt;st&lt;/sup&gt; half of 2016</td>
<td>high</td>
</tr>
<tr>
<td>3. Ensure the effective implementation of the current legislation concerning customs valuation and taxation of imports of medicinal products, medical supplies and/or medical equipment for clinical trials. Establish an electronic document flow between the governmental agencies (MoH, SEC and fiscal authorities), which will significantly accelerate all procedures</td>
<td>CMU, MoH</td>
<td>2016</td>
<td>high</td>
</tr>
<tr>
<td>4. Enable an electronic submission of application materials of clinical</td>
<td>MoH</td>
<td>2016</td>
<td>high</td>
</tr>
<tr>
<td></td>
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<td></td>
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<tr>
<td>---</td>
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<td></td>
</tr>
<tr>
<td><strong>trials</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>5.</strong> Create a full-fletched national register of clinical trials of medicinal products with the information on the completed projects and summary of their results, on-going projects, and all submitted applications (including the date of filing) and the public officials in charge. Open access to the register should be secured</td>
<td>MoH</td>
<td>2016</td>
<td>high</td>
</tr>
<tr>
<td><strong>6.</strong> Develop and adopt the methodology for calculating costs of services on conducting clinical trials of medicinal products.</td>
<td>MoH</td>
<td>2016</td>
<td>high</td>
</tr>
<tr>
<td><strong>7.</strong> Develop a regulatory framework for the national GLP-certification agencies and institutions that monitor the quality of conducting preclinical trials and clinical trials. GLP-certification should remain voluntary.</td>
<td>MoH, Verhovna Rada</td>
<td>2018</td>
<td>medium</td>
</tr>
<tr>
<td><strong>8.</strong> Introduce the liability insurance of the sponsor of clinical trials for damage for life and health of the participants of clinical trials by making amendments to the Law “On Medicinal Products” and to the Law “On Insurance”. Introduce professional liability insurance for the researchers (at the sponsor’s request) by amending the Regulation on conducting the clinical trial.</td>
<td>MoH, Verhovna Rada</td>
<td>2018</td>
<td>medium</td>
</tr>
</tbody>
</table>
CHAPTER 3. REGISTRATION PROCEDURES

State registration of drugs is a necessary condition for introduction a medicinal product to the market. It is aimed at ensuring its efficacy, quality and safety, and making it physically available for using in treatment. Registration procedures should be transparent, comfortable, flexible and business-friendly to minimize administrative costs for business.

Though Ukrainian pharmaceutical market is the second biggest market in CIS, it lags behind the European one both in terms of sales volume and the variety and structure of drugs present. For comparison: in Ukraine, the average annual expenditures on medicinal products per person amount to $100, while in the EU – $1,115. Presently, Ukraine is in the middle of the list of European countries by the number and the range of registered medicinal products (see Tables 3.1 and 3.2).

Table 3.1. Figures from the Ukrainian State Register of Medicinal Products (as of 06 October 2015)

<table>
<thead>
<tr>
<th>No.</th>
<th>Group of medicinal products</th>
<th>Domestic</th>
<th>Imported</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Finished medicinal products</td>
<td>3,215</td>
<td>6,738</td>
<td>9,953</td>
</tr>
<tr>
<td>2</td>
<td>In bulk</td>
<td>227</td>
<td>543</td>
<td>770</td>
</tr>
<tr>
<td>3</td>
<td>Prepackaging from in bulk</td>
<td>10</td>
<td>182</td>
<td>192</td>
</tr>
<tr>
<td>4</td>
<td>API (substances)</td>
<td>267</td>
<td>1,296</td>
<td>1,563</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>3,719</td>
<td>8,759</td>
<td>12,478</td>
</tr>
</tbody>
</table>

Source: State Register of Medicinal Products of Ukraine (www.drz.kiev.ua).

Currently, about 12,000 drugs are registered in Ukraine (given the number of marketing authorizations) including 10 thousand of finished medicinal products, while in Poland nearly 15,000 drugs are registered (given the number of trade licenses) and in Germany – more than 100 thousand.

Table 3.2. The Number of Registered Medicinal Products in Some Countries

<table>
<thead>
<tr>
<th>Country</th>
<th>Ukraine</th>
<th>Spain</th>
<th>Germany</th>
<th>Hungary</th>
<th>Latvia</th>
<th>Poland</th>
<th>Russia</th>
</tr>
</thead>
<tbody>
<tr>
<td>The number of registered medicinal products according to the number of marketing authorizations (trade licenses)</td>
<td>10,054</td>
<td>16,038</td>
<td>101,229</td>
<td>-</td>
<td>4,315</td>
<td>15,087</td>
<td>18,876</td>
</tr>
<tr>
<td>The number of registered medicinal products in view of dosages and packages</td>
<td>28,697</td>
<td></td>
<td>38,483</td>
<td>23,017</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>The number of registered API (substances, active substances)</td>
<td>1,525</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1,967</td>
</tr>
</tbody>
</table>

Sources: European Medicines Agency (www.ema.europa.eu); Federal Institute for Drugs and Medical Devices (http://www.bfarm.de/EN/Service/Statistik/AM_statistics/statistic-verkf-am-zustBfArM-en.html); Spanish Agency for Medicines and Health Products; National Institute of Pharmacy (Hungary); State Agency of Medicines (Latvia); Office for
In Ukraine, two thirds of the registered medicinal products are generics (60%), while innovative medicinal products cover 12% (It looks comparable with Spain where 65% of the registered medicinal products are generics, and the market share of original drugs is close to 20%). In terms of origin, biological medicinal products have 6%, homeopathic – 2%, vegetable medicinal products – 11% of the market, while 1% goes for own-name case-specific preparations.

A lot of modern medical products are not registered in Ukraine. A large gap is observed in the following groups of diseases: rare (orphan) (-73%), cardiovascular (-76%) and hematological (-72%) diseases (see Table 3.3).

Table 3.3. Drugs Registered in Ukraine by Pharmacological Groups and INNs

<table>
<thead>
<tr>
<th>ATC Code</th>
<th>Pharmacotherapeutic group</th>
<th>Total registered (number of registered preparations (RPs))</th>
<th>Domestic drugs (number of RPs)</th>
<th>Imported drugs (number of RPs)</th>
<th>Number of INNs* in the group that are not registered in Ukraine</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Digestive tract and metabolism</td>
<td>1399</td>
<td>560</td>
<td>839</td>
<td>216</td>
</tr>
<tr>
<td>B</td>
<td>Blood and blood circulation organs</td>
<td>519</td>
<td>228</td>
<td>291</td>
<td>86</td>
</tr>
<tr>
<td>C</td>
<td>Cardiovascular system</td>
<td>1650</td>
<td>445</td>
<td>1205</td>
<td>182</td>
</tr>
<tr>
<td>D</td>
<td>Preparations for application in dermatology</td>
<td>596</td>
<td>314</td>
<td>282</td>
<td>123</td>
</tr>
<tr>
<td>G</td>
<td>Urogenital system and sex hormones</td>
<td>500</td>
<td>108</td>
<td>392</td>
<td>118</td>
</tr>
<tr>
<td>H</td>
<td>Hormonal preparations for systemic use except sex hormones and insulins</td>
<td>146</td>
<td>38</td>
<td>108</td>
<td>29</td>
</tr>
<tr>
<td>J</td>
<td>Preparations for treatment of infectious diseases for systemic use</td>
<td>1378</td>
<td>348</td>
<td>1030</td>
<td>190</td>
</tr>
<tr>
<td>L</td>
<td>Antitumor and immunomodulatory drugs</td>
<td>708</td>
<td>97</td>
<td>611</td>
<td>133</td>
</tr>
<tr>
<td>M</td>
<td>Musculoskeletal system</td>
<td>593</td>
<td>175</td>
<td>418</td>
<td>69</td>
</tr>
<tr>
<td>N</td>
<td>Nervous system</td>
<td>1497</td>
<td>519</td>
<td>972</td>
<td>178</td>
</tr>
<tr>
<td>P</td>
<td>Antiparasitic drugs, insecticides and repellents</td>
<td>59</td>
<td>16</td>
<td>43</td>
<td>19</td>
</tr>
<tr>
<td>R</td>
<td>Respiratory system</td>
<td>889</td>
<td>316</td>
<td>573</td>
<td>110</td>
</tr>
<tr>
<td>S</td>
<td>Hearing organs</td>
<td>218</td>
<td>68</td>
<td>150</td>
<td>69</td>
</tr>
<tr>
<td>V</td>
<td>Other preparations</td>
<td>121</td>
<td>60</td>
<td>61</td>
<td>41</td>
</tr>
</tbody>
</table>

*INN – International Nonproprietary Name.

Source: State Register of Medicinal Products of Ukraine (www.drlz.kiev.ua).
With regard to the pharmacotherapeutic group the situation also looks unfavorable: Ukraine lacks 32% of the medicinal products included in the WHO Model List of Essential Medicinal Products required for developing countries (hereinafter – the WHO List). The 18th edition of the WHO List contains 134 International Nonproprietary Names (hereinafter – INNs). As of August 2015, Ukraine does not have medicinal products that would correspond to 81 INNs included in the WHO List and another 11 INNs from the list are available only in the form combined drugs registered in Ukraine. The greatest threat is the absence of some antiviral, antiprotozoal, and anti-neoplastic agents. Other challenging pharmacotherapeutic groups include narcotic drugs used in delivery of palliative care are (in Ukraine, 142 of such medicinal products are registered), antitumor drugs and medicinal products of limited use for treating orphan diseases (22 medicinal products are registered in Ukraine).

**This reflects a relatively low level of physical availability of some important drugs in Ukraine compared to other countries.**

The number of new registrations of medicinal products in recent years slowed down (see Figure 3.1). Foreign and domestic applicants/manufacturers of drugs are becoming less active in initiating registration of new drugs. In 2009-2014, the annual number of registered drugs decreased by 37.3% (from 1,200 in 2009 to 970 drugs in 2014). The growth is observed only in the number of applications for re-registration and making amendments to registration materials during the validity term of the marketing authorization.

![Figure 3.1 Registration of medicinal products in Ukraine](source: State Register of Medicinal Products of Ukraine (www.drlz.kiev.ua)).

The slowdown in drug registration can be caused by many factors (including poor macroeconomic situation in the country, unfavorable business climate, and specific business strategies of pharmaceutical companies). At the same time, the complexity and non-transparency of the registration procedures for drugs also play a significant role.
In Ukraine, the scope and the depth of drug registration are rather vast: state registration covers active pharmaceutical ingredients, in bulk products, finished medicinal products, including immunological medicinal products, substance or combination of substances contained in the drugs for medical use that can end up in the blood circulatory system, and also supplies that are defined by an order of the MoH of Ukraine to require registration as medicinal products. In addition to finished products, active ingredients (APIs) and drugs in bulk which are to be packaged by domestic pharmaceutical companies and registered as finished dosage forms shall also be registered. Medicinal products made of authorized active substances and excipients in pharmacies according to the doctors’ specification (magisterial formulas) or for healthcare facilities (officinal formulas) are not subject to state registration. In EU countries the registration does not cover APIs and drugs in bulk.

The state registration (re-registration) of a medicinal product is performed by the MoH of Ukraine on the basis of the SEC expert review of registration materials (registration dossier). The framework of the expert review of registration materials is shown in the Figure 3.2.

Figure 3.2 The Framework of the Expert Review of Registration Materials by the State Expert Center


Changes in registration of medicinal products

In 2011-2013, the significant changes were introduced to the registration procedure of drugs in order to harmonize the national legislation with EU standards, namely 1) the requirement for the registered drug to be compliant with GMP standards, and 2) the common registration procedure for drugs and medical immunobiological preparations (hereinafter – MIBP).

In 2012, GMP standards were introduced in Ukraine as a tool to ensure safety of medicinal products\(^{33}\). This concerned both domestically produced and imported

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33 Resolution of the Cabinet of Ministers of Ukraine dated 14 November 2011 No. 1165 “On Making Amendments to the Procedure for State Registration (Re-registration) of Medicinal Products”.

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medicinal products (in Ukrainian pharmaceutical market 8,000 drugs out of more than 12,000 registered drugs were imported). Besides the safety reasons, the implementation of good manufacturing practices was considered as a way to increase the competitiveness of domestically produced drugs and expand export opportunities of Ukrainian pharmaceutical producers.

All manufacturers of medicinal products registered in Ukraine had to bring their registration materials to conformity with the GMP standards and receive a confirmation of compliance of their manufacturing process with the GMP standards. The confirmation was issued by the State Service of Ukraine on Medicinal Products (SSUMP) under a procedure established by the MoH of Ukraine. While GDP compliance of Ukrainian pharmaceutical manufacturers was automatically recognized on the basis of a valid manufacturing license, foreign pharmaceutical manufacturers had to prove their GMP compliance even in case they already had a GMP certificate issued by the regulator in the developed country (US, EU, Australia, Japan, Switzerland and Canada). The assessment procedure included checking the relevant documentary dossier of the manufacturer and sometimes on-site inspection of production process (the cases for on-site inspections are regulated in the order N1130 by MoH).

In 2012, the by-laws regulating the access of MIBP to the Ukrainian market were streamlined, and MIBP were legally classified as medicinal products (previously, there MIBS were not included in medicinal products). As a result, the registration procedures for medicinal products and MIBP became similar. This unification was welcomed by foreign pharmaceutical companies. They started to submit their materials for registration of MIBP to SEC in the European CTD-format. Besides, new by-laws introduced free-of-charge and out-of-turn review of the registration materials for the following categories: a) original (innovative) drugs for the treatment of socially dangerous diseases (tuberculosis, HIV/AIDS, viral hepatitis and medicinal products with an original molecule for the treatment of rare diseases), MIBP for specific preventive treatment of infectious diseases, included in the official schedule of preventive vaccinations in Ukraine and registered in the country whose regulators apply high-quality standards in line with WHO-recommended standards; b) drugs for the treatment of tuberculosis or HIV/AIDS, MIBP for the specific preventive treatment of infectious diseases that are included in the immunization schedule by age, passed the pre-qualification procedure and included in the WHO list of pre-qualified drugs. Later, simplified/curtailed registration procedures for some medicinal products which availability in Ukraine is rather limited were introduced to the Law of Ukraine "On Medicinal Products".

An important event in the development of registration procedures was an introduction of one-stop shop in the Ministry of Health in 2011. It was expected to simplify the registration process, reduce the time and make the procedure of registration

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34 Starting from 01 July 2012, subsequently postponed to 01 July 2013.
35 Order of the Ministry of Health of Ukraine No. 1130 dated 27 December 2012 “On Approval of the Procedure for Confirmation of Medicinal Products Manufacturing Conditions Compliance with Good Manufacturing Practice Requirements”.
more friendly for business. It started its operations in 2013. The framework of drugs registration in Ukraine is shown in Figure 3.3.

![Diagram of Registration Process]

**Figure 3.3. Current Framework of Registration of Medicinal Products in Ukraine**

Source: State Expert Center of the Ministry of Health of Ukraine (www.dec.gov.ua).39

In 2014-2015, the legislative changes were aimed at achieving two objectives: to introduce perpetual re-registration and simplify registration procedures for certain groups of drugs. The three adopted laws made a number of changes to the Law of Ukraine "On Medicinal Products". They:

- introduced perpetual re-registration, and simplified registration procedures for original medicinal products registered by the European Medicines Agency (EMA);
- simplified the registration procedure of medicinal products for the treatment of tuberculosis, HIV/AIDS, viral hepatitis, cancer and rare (orphan) diseases that are registered by the competent authority of the United States, Switzerland, Japan, Australia, Canada or the European Union;
- introduced a special registration procedure of medicinal products to be procured by the international organizations.40

a) Implementation of perpetual re-registration was an important step towards the simplification of registration procedures and bringing them to conformity with the

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39 The Procedure for Expert Review of Registration Materials for Medicinal Products that Are Submitted for State Registration (Re-registration) and Expert Review of Materials on Making Amendments to Registered Materials throughout the Validity of the Marketing Authorization; Regulation on Interaction between the Ministry of Health of Ukraine and the SOE "State Expert Center of the Ministry of Health of Ukraine" with regard to preparation of the orders of the MoH of Ukraine on state registration (re-registration) of medicinal products (medical immunobiological preparations) and amendments to registration documents, processing and issuance of marketing authorizations.

40 Law of Ukraine No. 269-VIII dated 19 March 2015 “On Making Amendments to Some Laws of Ukraine with regard to Ensuring Timely Access of Patients to Required Medicinal Products and Medical Supplies through the Carrying-out of Public Procurements with Involvement of Specialized Procuring Institutions”. 

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European practices. Under the old rules, once registered the drug had to be re-registered every five years, which was very much alike a new registration. Though registration costs in Ukraine are rather moderate (25-100 EUR of stamp duty plus costs of expert review that on the average constitute 60 000 Hrv), administrative costs for business were rather high (including time costs, salaries of adequately qualified managers or fees for specialized consulting companies’ services). Besides, every five years the companies had to face all procedural problems (risks of expert review delay, non-transparency of the regulatory procedures etc.) and associated corruption risks. In case of delays in the re-registration of their products, they fall under a threat of all transactions with the drug being stopped. The state also bore high administrative costs to ensure the organizational process. Most importantly, this costly and continuously repeated regulatory process could ensure the safety and effectiveness of marketed drugs.

Incidentally, the number of negative decisions on drugs’ registration is rather low – 1 case in 5 years and for re-registration – 10 cases in 5 years. In August 2014, the regular re-registration was abolished by law 41, and the first re-registration (after 5 years of the drug to be present on the market) become perpetual. These changes fully complied with the Directive 2001/83/EC, and created favorable conditions for businesses to supply Ukrainian market with necessary drugs.

b) The registration procedures were simplified for original medicinal products registered by the European Medicines Agency. Previously, these drugs along with others had to pass an expert review under the full procedure of 210 days. This was a duplication of the review made in accordance with the EU standards. This duplication provided no additional guarantee of safety and/or effectiveness of the medicinal products. However, it increased the regulatory burden on business and slowed down an introduction of original (innovative) drugs in the Ukrainian market. In March 2015, CMU Resolution No. 125 “On Making Amendments to the Procedure for State Registration (Re-registration) of Medicinal Products” 42 simplified the registration procedure for the original drugs. The requirement of an additional expert review was canceled. The registration was made on the basis of the application, registration documents, including the assessment report that is a part of EMA registration dossier, and the SEC conclusion on whether the instruction on drug’s application and quality control matches with the registration materials. The procedure of conformity verification was specified by MoH. These regulatory initiatives are expected to improve the access of innovative medicinal products to the Ukrainian pharmaceutical market, and provide Ukrainian patients with modern treatments.

c) The registration procedures were simplified 43 for certain groups of drugs (including drugs for treating TB, HIV/AIDS, viral hepatitis, cancer and rare (orphan) diseases and registered by the competent authority of the United States, Switzerland, Japan, Australia, Canada or the European Union as a medicinal product). Like in case of original drugs, the duplication of registration was eliminated in case when regulatory procedures had been done by the regulatory authorities that are guided by high standards for quality and safety. As a result, this group of drugs is registered on the basis of application and

41 Law of Ukraine No. 1707-VII dated 20 October 2014 “On Making Amendments to the Law of Ukraine “On Medicinal Products” with regard to the Circulation of Medicinal Products and State Control of the Quality of Medicinal Products Brought into the Customs Territory of Ukraine”.
42 Resolution of the Cabinet of Ministers of Ukraine dated 18 March 2015 No. 125 “On Making Amendments to the Procedure for State Registration (Re-registration) of Medicinal Products”.
43 Law of Ukraine No. 1637-VII dated 12 August 2014 “On Making Amendments to the Law of Ukraine “On Medicinal Products” with regard to Improvement of the Procedure for Providing the Population with Medicinal Products Meant for Treatment of Socially Dangerous and Heavy Diseases”.

44
recommendation by SEC which verifies the materials attached to the application according to the procedure established by MoH. Registration procedures were simplified in order to improve the access of Ukrainian patients to the modern drugs for treatment of socially dangerous and serious diseases. The safety barriers were not lowered, since this simplification concerned only medicinal products registered with the leading regulatory authorities around the world.

d) Finally, in 2015, the registration procedures for drugs procured through international organizations using public funds were simplified. It was pushed forward by several failures in public procurement of drugs in 2014–15 associated with the lack of transparency. The threat of shortages of some drugs in the healthcare facilities and risks of interruption in treatment of socially dangerous and serious diseases (tuberculosis, HIV/AIDS, viral hepatitis, cancer and hematological diseases) spurred searching for more transparent mechanisms of public procurement in a very compressed timeframe. As a result, in March 2015 the Law of Ukraine was approved on public procurement involving international organizations. The Law introduced a special purchasing procedure for the medicinal products procured using public funds through the international organizations (such as World Health Organization (WHO), United Children’s Fund Nations (UNICEF)), and established a simplified registration procedure for these medicinal products. It is based on the application and recommendation of SEC that confirms authenticity of the registration materials, and carried out by MoH. No stamp duty is paid, and no copy of the document to confirm the compliance of the manufacturing conditions of the product submitted for registration with the requirements for production of medicinal products in Ukraine is requested. This procedure will be effective in Ukraine until December 31, 2019. However, the circulation of these drugs after December 31, 2019 may be exposed to certain risks. In the absence of registration materials, such drugs cannot be re-registered under the established procedure. In addition, if the decision on registration of such drug is taken after 31 December 2019, the validity of its marketing authorization will be less than 5 years, which also contradicts the current law.

Despite the attempts to simplify and harmonize the registration procedures in Ukraine with the EU standards, they remain problematic, complex, often nontransparent and, therefore, are fairly criticized by business. This criticism includes high regulatory costs that business has to bear in the process of drug registration. It is not the officially established length and cost of registration to be problematic. The legal deadlines of expert review are generally consistent with the Directive 2001/83/EC, and

44 Resolution of the Cabinet of Ministers of Ukraine No. 597 dated 12 August 2015 “On Making Amendments to Resolution of the Cabinet of Ministers of Ukraine No. 376 dated 26 May 2005”.
45 within 210 business days – for a full and independent application (original / innovative medicinal product submitted for registration with a full dossier);
- within 90 business days:
  - for original (innovative) drugs designed for the treatment of socially dangerous diseases (tuberculosis, HIV/AIDS, viral hepatitis as well as medicinal products with an original molecule for the treatment of rare diseases) that have been registered in the country whose regulatory authorities apply high standards for the quality that meets the standards recommended by WHO,
  - for drugs used in treatment of tuberculosis and HIV/AIDS that have passed the pre-qualification procedure and included in the WHO list of pre-qualified drugs,
  - for medicinal products that are submitted for state registration under other types of applications listed in Annex 1 of the Procedure;
  - for active pharmaceutical ingredients or active substances;
  - for medicinal products submitted for state re-registration;
  - for traditional medicinal products and own-name medicinal products (produced in accordance with approved specifications);
  - for the changes requiring new registration.
- within 60 business days — for materials on amending the registration documents of type I or II.
the cost of expert review in Ukraine is significantly lower than in many countries. In Ukraine, registration costs for medicinal products consist of the stamp duty (that ranges from EUR 25 to EUR 100) and the cost of expert review (on the average 60,000 Hrv depending on the application type). For comparison, in the EU countries, the cost of a trade license (under the centralized procedure) for one dosage associated with one pharmaceutical form and one pack size is EUR 278,500. In 2012, in the United States (where the prices are set annually), the costs of expert review of the application that requires submission of clinical data (innovative, original drug) amounted to $1,841,500, and that for the applications that do not require submission of clinical data (generic drugs) equaled $920,750.

Problems

Poor implementation of the adopted regulatory changes is the main problem underlined by pharmaceutical business.

1. The lack of by-laws for the implementation of legal changes slows down enacting of the progressive decisions.

   a) The rule of permanent re-registration was enacted on October 30, 2015 after a year since the legal changes were adopted. However, no permanent marketing authorization has been issued yet as was recently pointed out by EBA. Besides, obtaining a permanent re-registration still remains an additional regulatory burden for business. If the medicinal product has already passed several re-registrations, it still needs to go through this procedure once more for obtaining a permanent marketing authorization. Pharmaceutical business complains that such a procedure is unnecessary for the medicinal products that have already been registered and re-registered in Ukraine.

   a) Despite the recent adoption of by-laws, simplified registration procedures have not yet started both for the medicinal products procured using public funds through international procurement organization, and for the drugs registered by the European Medicines Agency; medicinal products intended exclusively for the treatment of tuberculosis, HIV/AIDS, viral hepatitis, cancer and rare (orphan) diseases that are registered by the competent authority of the United States, Switzerland, Japan, Australia, Canada or European Union.

2. Poor organization prevents effective implementation

   a) Implementation of GMP resulted in the need for all foreign manufacturers of drugs to confirm their compliance of production of medicinal products with the current Ukrainian good manufacturing practice requirements. While domestic pharmaceutical manufacturers have to pass tests for production conformity in accordance with the national legislation, all foreign pharmaceutical manufacturers have to undergo re-assessment of

46 Order of the Ministry of Health of Ukraine No.460 dated 23 July 2015 was published.
47 The Law of Ukraine «On Amending the Law of Ukraine “On Medicines” regarding the circulation and the state quality control of medicines imported to the customs territory of Ukraine» (No.1707-II) was adopted on the 20th of October 2014.
48 http://www.apteka.ua/article/343604
compliance with the GMP requirements. Even Ukraine’s membership in PIC/S did not change the situation. This function is assigned to SAUMP which issues a confirmation certificate that is required for registration / re-registration of a medicinal product. The conflict between the national laws contributes to the problem: under the current Ukrainian law and regulations of PIC/S, there is no need to get GMP confirmation by SAUMP if the series of the finished product are certified by the manufacturer from the EU country or from the country which signed with the EU an agreement on mutual recognition of inspection findings, and the regulatory authority in this state is a member of PIC/S. However, this requirement was artificially introduced by the Resolution No. 902 of CMU from September 14, 2005 and the Order of MoH from December 2012. Therefore, all drug manufacturers that are not Ukrainian residents are obliged to pass GMP confirmation procedures with SAUMP. If failed, they cannot register (re-register) their drugs and subsequently are not allowed to bring them to Ukraine.

This double GMP confirmation looks unreasonable when production facilities are located within the territory of a PIC/S member state or in the EU territory and certified by the European certifying body. It produces an additional regulatory barriers, since the issuance of the confirmation by SAUMP is often delayed due to the subjective factors (the lack of available inspectors, low competence of experts). It also rises the risks of corruption.

The survey of pharmaceutical market representatives in October 2015 shows that 67% of the respondents identified procedure as a significant obstacle for doing business.

b) Registration procedures are inconvenient since one-stop-shop approach is not fully implemented

Like in case of receiving a permit for clinical trials, registration of the medicinal product requires from the applicant a direct interaction with several regulatory authorities. The applicants have to submit their application to the CAS “One-stop-shop” of the Ministry of Health, bring their registration materials for an expertise to the State Expert Center, and apply for the GMP confirmation certificate to the SAUMP. In addition, the timeframes for expert reviews and decision making are often not met. The situation is aggravated by the lack of electronic document flow between the regulatory authorities. This means that one-stop-shop principle – when the applicant can submit all the requested materials and receive a positive or negative decision concerning the permit in the same place- does not work.

Besides, during the expert reviewing process the applicant often needs multiple personal interactions with the experts for prompt resolution of issues raised by them. A badly regulated practice of interaction between the applicants and the experts creates risks of corruption. For comparison: In European practice, such meetings take place once in a collective format to consider all the existing comments. The results of these working meetings are recorded in minutes.

49 “On Approval of the Procedure for Carrying out State Control of the Quality of Medicinal Products Brought into the Customs Territory of Ukraine” and Order of the Ministry of Health of Ukraine No. 1130 dated 27 December 2012 “On Approval of the Procedure for Confirmation of Medicinal Products Manufacturing Conditions Compliance with Good Manufacturing Practice Requirements”. 
The main complaint of business in the area of registration is the delay in certain regulatory procedures. More than two-thirds of the representatives of the pharmaceutical market surveyed in October 2015 mentioned the violation of timeframes for expert review and decision-making on registration of a drug as well as for re-registration of drug as the main regulatory barriers in area of registration. The timeframe for the expert review is up to 90 days for original products, and 210 for generics. The decision on registration of drugs should be taken by MoH within one month. The anecdotal evidence shows that registration procedure for original drugs might last a year. While delays, according to the opinion of business representatives, are common for the registration procedures in Ukraine, the regulatory authorities have no liability for the delays. In addition, there is no efficient mechanism for business to appeal the decisions of MOH and SEC in the area of registration.

c) Making amendments to the registration materials is time-consuming. It does not differ from a standard registration procedure, though many amendments (like change in the address of the company, change in the name of trade mark of the drug) do not impact safety or quality of the drug, and therefore, do not require a full-fledged expertise. The absence of a simplified procedure for making amendments to the registration materials causes problems both for business and governmental authorities. Over the last three years the total number of registrations, re-registrations and amendments of registration materials in Ukraine grew up. However, the capacity of the regulatory bodies did not change significantly. This (among other reasons) causes delays in different registration procedures, an consequently, raises regulatory costs for business and limits the access of medicinal products to the market.

In EU, there is a simplified procedure for making insignificant amendments to the registration materials which uses the declarative principle. In case of insignificant changes-type 1A (e.g. the name of the company), the company sends full information on the changes to the regulatory authority and continues operations without any confirmation. In case of insignificant changes-type 1B, the applicant provides all the necessary materials to the regulatory authorities, and continues operations. All changes are considered to be officially confirmed if no negative decision is issued by the regulatory authority within 30 days.

A simplified procedure for making insignificant amendments to the restoration materials reduces administrative costs for business and regulatory authorities. It should be considered for the implementation in Ukraine.

3. Like in case of clinical trials, recommendations regarding registration, re-registration and amendments of registration materials are provided by the SEC’s Scientific Expert Council or Science and Technology Council. No law stipulates the need to confirm the assessments of individual experts by the collective decision of SEC’s Scientific Expert Council. It prolongs the decision-making process (since the members of Expert Council meet normally once a month) and dilutes the individual responsibility of experts for their assessments.
4. The registration of API substances and products in bulk increases regulatory costs for business with no effect on safety/quality of products. In EU practices, there is no registration of API and in bulk products. This registration makes no sense, since ensuring drug’s safety should concern rather final then intermediary product. In Ukraine, APIs that are used as ingredients by the domestic pharmaceutical producers, become subject of registration. During the registration process, business entities pay for the expert review (about UAH 10,000) which is conducted formally without a laboratory control of API’s quality. The requirement of API’s registration reduces flexibility of the domestic producers in choosing appropriate suppliers, and make a switch to the new APIs rather costly. Presently, the only justification for APIs registration is related to the possibility to import them on the basis of 7% VAT rate instead of 20% in case they are registered. However, this problem concerns the administration of taxes and customs duties, and should be addressed differently from registration requirements. It needs a careful discussion with experts and business representatives.

5. The level of protection of intellectual property rights and exclusivity of the registration dossier data relating to innovative medicinal products raises concerns of pharmaceutical companies. On the one hand, there is a legal basis for protection of intellectual property rights for medicinal products. According to the Law of Ukraine "On Medicinal Products", the information contained in the registration dossier of medicinal products is subject to state protection against disclosure and unfair commercial use. CMU Order N376 puts the responsibility for the protection of such information on MoH and SEC. On the other hand, there are neither clearly defined instruments of ensuring this protection nor division of responsibilities between MoH and SEC in this important area. In addition, there is no liability of the regulatory authorities for breaching the privacy of the registration dossier. Therefore, the possibility of violation the confidentiality of the registration dossier raises concerns among the companies that deal with original products. The weakness of the regulatory framework is aggravated by the weakness of judicial system in Ukraine which, in opinion of businesses, does not provide a possibility for fast and transparent settlement of conflicts related to the protection of intellectual property rights.

Strengthening of the protection of intellectual property rights would need clarification and strengthening the responsibility of the regulatory bodies for protecting the exclusivity of the registration dossier. Besides, it is worthwhile to consider a patent protection system based on the US model. It implies that manufacturing company of an original medicinal product notifies the regulator and the industry about its patent. The regulator maintains a registry of patents in force. The manufacturing company of a generic medicinal product notifies the innovative companies about its application for a marketing permit concerning the medicinal product. If there is any misunderstanding between the innovative companies and the manufactures of generic medicinal products, the regular suspends consideration of the application for marketing of the generic drug until the dispute is over.

While ensuring the protection of intellectual property rights, the regulatory system should allow expediting market penetration by generic drugs (generics are cheaper compared to original drugs and therefore more affordable for the hospitals and population). The term of patents in Ukraine is similar to that in EU-20 years. The exclusivity of registration dossier data
(which is related to the registration of the drug) in Ukraine is protected for 5 years (8-10 years in EU according to Directive 2004/27/EC). However, often foreign companies register their medicinal product in the Ukrainian market after the patents are expired or close to expiring. Therefore, an introduction of the generic drug to the Ukrainian market can take long- 25 years and more. So called Bolar provision offers a possibility to speed up market introduction of generics. The Bolar provision defines a principle which is called to settle relations between the manufacturers of generic and original medicinal products. The core of this provision is that the manufacturer of the generic medicinal product may initiate a certain spectrum of research and registration actions before the exclusivity term (or patent) for the original medicinal product is expired. Companies that intend to manufacture generic medicinal products are allowed to submit an application for registration of the generic drug before the expiration of the exclusivity term (or patent) for the original medicinal product. Once the time restrictions are over, the company may immediately start manufacturing the generic drug since its registration is completed, which reduces the time required for putting generic drugs on the market. The Bolar provision can be introduced only when there is no conflict between the manufacturer of original drugs and that of generic ones.

**Recommendations in the area of registration of medicinal products**

<table>
<thead>
<tr>
<th>Actions</th>
<th>Responsible body</th>
<th>Timeframe</th>
<th>Priority</th>
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<tbody>
<tr>
<td>1. Ensure the issuing of permanent marketing authorizations for medicinal products that were re-registered after the Law No. 1707-VII (of November 5, 2014) was enacted. Replace already issued marketing certificates with the permanent ones after completion of this procedure.</td>
<td>MoH</td>
<td>2016</td>
<td>high</td>
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<td>2. Abolish the requirement to have a GMP conformity confirmation from the national regulatory body for the foreign manufacturers that have GMP certificates issued by the competent authority of the PIC/S member. To cancel this requirement amend the following regulatory acts:</td>
<td>CMU, MoH</td>
<td>2016</td>
<td>high</td>
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<td>- Resolution of the Cabinet of Ministers of Ukraine No. 902 of September 14, 2005 “On Approval of the Procedure for Carrying out State Control of the Quality of Medicinal Products Brought into the Customs Territory of Ukraine”,</td>
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<td>- Order of the Ministry of Health of Ukraine No. 1130 of December 12, 2012 “On Approval of the Procedure for Confirmation of Medicinal Products Manufacturing Conditions Compliance with Good Manufacturing Practice Requirements”. Conclude intergovernmental agreements on</td>
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<td>3.</td>
<td>Ensure full implementation of the one-stop-shop principle in registration of drugs. The applicant should be able to submit all the requested materials and receive a positive or negative decision in one shop. Provide a regulatory framework for the interaction between the applicants and the experts during the expert reviewing of the registration dossier.</td>
<td>MoH</td>
<td>2016</td>
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<td>4.</td>
<td>Conclude intergovernmental agreements on the mutual recognition of GMP certificates</td>
<td>CMU, MoH</td>
<td>2016-2018</td>
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<td>5.</td>
<td>Provide for an electronic document flow between the MoH, SEC and SSUMP to improve their coordination in the registration procedures. Provide for electronic submission of registration materials by the applicants.</td>
<td>CMU, MoH, SEC, SSUMP</td>
<td>2016</td>
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<td>6.</td>
<td>Introduce a simplified procedure for insignificant amendments of the registration dossier based on the declarative principle: do-tell principle - for minor changes of type IA, and tell-wait-make principle – for minor changes of type IB.</td>
<td>CMU, MoH</td>
<td>2016</td>
</tr>
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<td>7.</td>
<td>Cancel the function of SEC’s advisory bodies (Scientific Expert and Science and Technology Councils) to confirm individual expert assessments of the registration dossiers. Implement best practices of EU countries when decisions on drug registration are based on the individual expert assessments (with a high personal responsibility of an expert for the assessment results). This will make the decision-making process shorter and more transparent.</td>
<td>MoH</td>
<td>2016</td>
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<td>8.</td>
<td>Develop and introduce a transparent mechanism for appealing the resolutions of MoH and SEC concerning the drug registration. Introduce the liability of MoH and SEC for the delays (over the official deadlines) in expert reviews of the registration dossier and making decisions on drug registration.</td>
<td>CMU, MoH</td>
<td>2016</td>
</tr>
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<td>9.</td>
<td>Clarify the responsibilities of MoH and SEC of in protecting the exclusivity of the registration dossier. Introduce the liability of the regulatory authorities for breaching the privacy of the registration dossier</td>
<td>CMU, MoH</td>
<td>2016</td>
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<td>10.</td>
<td>For strengthening the protection of intellectual property rights consider the introduction of a</td>
<td>MoH, CMU, Verhovna</td>
<td>2018</td>
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<td>Number</td>
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<td>11.</td>
<td>Consider the introduction of Bolar provision for enhancing the access of new international or domestically-produced generics to the Ukrainian market.</td>
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<td></td>
<td>MoH, CCMU, Verhovna Rada</td>
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<td>medium</td>
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<td>12.</td>
<td>Abolish mandatory registration of API and products in bulk (respective changes need to be made to the Law of Ukraine “On Medicinal Products” and corresponding by-laws). It will reduce the level of regulatory burden on business entities and increase their flexibility in choosing appropriate suppliers. Ensure that 7% VAT rate is used for importing of API's.</td>
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<td></td>
<td>MoH, Verhovna Rada</td>
<td>2016</td>
<td>high</td>
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CHAPTER 4. LICENSING OF ECONOMIC ACTIVITIES

The main purpose of licensing is to ensure that the activities in the pharmaceutical market (manufacturing and trade) are safe for the consumers. Thus, licensing is an instrument of state control of market players concerning their compliance with qualification, organizational, technological and other requirements set by law. Manufacturing and importing of medicinal products, wholesale and retail trade in medicinal products require licensing in Ukraine. State Service of Ukraine on Medicinal Products and Drugs Control (SSUMPDC) is responsible for licensing these activities. (Figure 4.1).

**Figure 4.1. Pharmaceutical Market: Licensing Components**

In Ukraine, industrial manufacturing of medicinal products is defined as an activity related to serial production of medicinal products, which encompasses all or at least one stage of manufacturing process including procurement of products and materials, pre-packaging, packaging and/or labelling, storage, appropriate control, issue of permits for production (sale) and wholesale trade (distribution) of own products. Medicinal products may also be prepared in pharmacies. This includes preparation of medicinal products in accordance with medical prescriptions for individual patients or upon request of healthcare facilities, and production of intermediate products for internal purposes.

**Figure 4.13 The Number of Wholesale Licenses for Medicinal Products Issued by the State Service of Ukraine on Medicinal Products in 2010-2015**


Import license might be held by a legal entity, resident of Ukraine, that acts under the agreement (contract) with a foreign manufacturer or supplier of medicinal product and holds marketing authorization for such medicinal product.
Wholesale trade in medicinal products is permitted only through pharmaceutical warehouses (Figure 4.2). Retail trade in medicinal products is permitted only through pharmacies and their units (pharmacy outlets).

Whereas in most of the foreign countries licensing/marketing authorization along with licensing for manufacturing activities allows medicinal products to be marketed, in Ukraine licensing is required together with registration of the medicinal product. Licensing of the activities related to medicinal products are regulated by the Law of Ukraine “On Medicinal Products” and the Law of Ukraine “On Licensing of Economic Activities”. The licensing procedure is shown in Figure 4.3.

![Image of the Licensing Procedure for Manufacturing, Importing and Trading of Medicinal Products]

**Figure 4.3. The Licensing Procedure for Manufacturing, Importing and Trading of Medicinal Products**

In Ukraine, the terms for decision-making on issuing a license are rather short—ten working days after the application is accepted by the licensing agency. The license fee is low—one minimum monthly wage (as of early November, the minimum monthly wage equals to UAH 1,378 or almost 60 US dollars). In the EU, obtaining license takes up to 90 days. In the EU member states, the price for licensing is much higher than in Ukraine (for example, in Poland it constitutes PLN 8,000, or approximately UAH 45,000).

**Changes in Licensing Terms for Medicinal Products**

*Over the last 5 years, there were attempts to increase the rigidity of national licensing requirements and start their approximation to European standards.* Ukraine followed best practices of the countries which enhanced the state control over the operators in pharmaceutical markets. Since 2011, the State Service of Ukraine on Medicinal Products (SSUMP) has been a member of the European Pharmacopoeia and a full member of the Pharmaceutical Inspection Cooperation System (PIC/S), which brings together 42 countries with the strict regulatory systems. This opened the way for active international cooperation of Ukraine in the field of good manufacturing practice (GMP), inspection and
licensing, and facilitate the implementation of an international system of standards for mutual recognition of inspection results. GMP and GDP Inspectorates were established within the SSUMP. All GMP and GDP inspectors have received a special training on GMP and GDP requirements.

The major achievement over the last 5 years has been an implementation of GMP standards as a compulsory requirement for manufacturing and importing of medicinal products. National GMP Regulations are amended regularly in order to reflect recent changes in the EU standards. In August 2014, the Ministry of Health of Ukraine adopted the Regulation “Medicinal Products. Good Distribution Practice. ST-N MHCU 42-5.0:2014” (Order of MoH No. 593 from 22 August 2014) in order to harmonize national requirements with the revised version of the EU GDP Guidelines. Presently, GDP standards become compulsory for the wholesale traders of medicinal products in Ukraine.

However, some developments were controversial.

a) The introduction of import licensing for medicinal products was very controversial. It was introduced on the 1st of March 2013. The expected goals were a) to harmonize the domestic regulations with the EU standards; and b) to strengthen the responsibility of foreign manufacturers in Ukraine for quality of the imported medicinal products. However, neither of the declared goals has been reached.

- Import licensing became an example of "pseudo harmonization" with the EU standards. Directive 2001/83/EC does not require a special import license for medicinal products, since the latter is a part of the manufacturing authorization (clause 3 of Article 40 of Directive 2001/83). Instead, importers need the manufacturing authorization for medicinal products to be imported. In the EU countries, an importer is often also a holder of marketing authorization.
- The introduction of import licensing failed to enhance the responsibility for quality of the imported medicinal products, and brought about only some legal conflicts.
- The introduction of import licensing was poorly prepared. The law on introduction of import licensing was adopted in July 2012, however, the licensing procedure was approved by the Ministry of Health of Ukraine only 6 days before deadline for receiving such licenses was to expire (1 March 2013). Despite the attempts to use a simplified licensing procedure for the transitional period, the volume of the imported medicinal products in 2013 fell by 6.3 percent compared to 2012 (from 3,308.5 to 3,100.8 mln US dollars). This happened for the first time since the crisis in 2009. This tendency continued in 2014 when respective indicator fell by 19.4% (till 2,100 mln US dollars). In the first 9 months 2015, import of pharmaceutical goods fell by 49% compared to the respective period in 2014.

b) The introduction of import licensing for active pharmaceutical ingredients (API) was another controversial measure. This measure was in contradiction to best international practices, and put at risk 116 domestic pharmaceutical companies which were close to stop their manufacturing operations. It was canceled in a month after its enforcement on the 1st of January 2015.

c) Delays in the implementation of Law of Ukraine No. 222-VIII “dated 2 March 2015 On Licensing of Economic Activities” caused problems for the pharmaceutical market.

- According to the Law, functions of the licensing agency were transferred to the State Service of Ukraine on Medicinal Products and Drugs Control (Resolution of

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50 In late July 2015, the Ministry of Health of Ukraine approved new Regulations ST-N 424.0:2015 “Medicinal Products. Good Manufacturing Practice” amending the Sections “Premises and Equipment”, “Manufacturing Process”, “Quality Control” etc. (effective in the EU since September and October 2014 and March 2015).
the Cabinet of Ministers of Ukraine No. 609 which became effective on 26 August 2015. This new agency was expected to be a result of a merge of two agencies-the State Service of Ukraine on Medicinal Products and the State Service on Drug Control. Presently, the re-organization of state agencies still is not completed, therefore the licensing of business activities in the pharmaceutical market is not performed. Presently, business entities are not able to obtain new licenses or make changes to their effective ones because of the absence of the licensing agency. Problems in obtaining import licenses increase the risks of temporary shortages of the imported medicinal products in the Ukrainian market. It might hurt the patients whose treatment depends on the availability of the imported medicinal goods. In its open letter to the Ukrainian Government, the European Business Association warns that delays in the renewal of import licenses for medicinal products might cause an interruption in importing of over 100 medicinal products in the nearest future.51

Problems

1. Most licensing problems arise from the burdensome procedures for the verification of GMP compliance for foreign manufacturers.

   - According to the Ukrainian law, the experts need to visit manufacturing sites, including those situated abroad, in order to conduct their inspections. (Only the foreign holder of the GMP certificate issued by the competent authority of a PIC/S member is relieved from visiting its manufacturing site by the Ukrainian inspectors). SSUMP is often unable to cover expenses of the inspectors’ visit, and the latter are shifted to the business applicants.

   - The requirements to the application for the confirmation of GMP certificate in Ukraine are sometimes burdensome. The foreign holder of the GMP certificate issued by the competent authority of a PIC/S member has to submit to the SSUMP the copy of the Site Master File. If production facilities are located abroad, the applicant also needs to submit a copy of the report of the last inspection conducted by the competent authority of a PIC/S member state. The SSUMP verifies and processes the application (including initial and specialized expert reviews). This is an example of duplication of the control requirements, since GMP certificate as such (even without a copy of Site Master File and a copy of the last inspection’s report) is a sufficient confirmation of good manufacturing practices.

2. New licensing terms are not yet adopted. According to the Law, the Licensing Terms should be adopted by the KMU. The licenses that were effective on the day the Law came into force remain valid. However, in the absence of the new licensing terms the market players cannot open new outlets, amend effective licenses, or as far as import licensing for medicinal products is concerned, they cannot make any changes to the annex to the license when replacement of marketing authorization for the medicinal product is needed for the re-registration etc. The absence of new licensing terms creates additional obstacles for conducting business activities by participants of the pharmaceutical market. The survey conducted among the representatives of the pharmaceutical market in October 2015 revealed that the list of the most frequently mentioned obstacles for licensing include the following:

- permissive instead of declarative principle of granting licenses (71% of those who responded);
- import licensing procedure does not make any sense (67% of the respondents);
- reasons for refusing a license are not transparent (62% of those who responded);
- the licensing procedure and licensing terms permit arbitrary decisions of public officials (57% those who responded).

3. *Retail trade in medicinal products is permitted in pharmacies only.* Current licensing terms prohibit allowing selling medicinal products only in pharmacies (except of some cases, specified in Article 3.5.2 of Section II of the Licensing Terms). It might limit the physical availability of medicinal products in the rural areas where pharmacy chains are poorly developed. Some countries (for example, Poland and Georgia) propose liberal trading rules for popular non-prescription medicinal products and selling them in the supermarkets.

**Recommendations to improve licensing**

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<th>Action</th>
<th>Responsible agency</th>
<th>Timeframe</th>
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<td>1. Complete the restructuring and ensure full operations of the newly established State Service on Medicinal Products and Drugs Control with clear and transparent functions.</td>
<td>Cabinet of Ministers, MoH</td>
<td>2016</td>
<td>High</td>
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<td>2. Adopt new licensing terms with a clear and exhaustive list of requirements for businesses.</td>
<td>Cabinet of Ministers, MoH</td>
<td>2016</td>
<td>High</td>
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<td>3. Cancel import licensing for medicinal products for business entities from countries with a strict regulatory system (EU member states and PIC/S members).</td>
<td>Cabinet of Ministers, MoH</td>
<td>2016</td>
<td>High</td>
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<td>4. Cancel the confirmation of GMP certificate by the SSUMP for foreign companies that hold GMP certificate issued by the competent authority of a PIC/S member state.</td>
<td>Cabinet of Ministers, MoH</td>
<td>2016</td>
<td>High</td>
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<td>5. Consider allowing the institutions other than pharmacies to distribute certain types of popular non-prescription medicinal products that do not require special storage and dispense conditions.</td>
<td>Cabinet of Ministers, MoH, Verhovna Rada</td>
<td>2017</td>
<td>Medium</td>
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CHAPTER 5. POST-REGISTRATION CONTROL OF QUALITY AND CIRCULATION OF MEDICINAL PRODUCTS

The quality of medicinal products is ensured by the post-registration control and surveillance conducted by the SSUMP. It includes the quality control of medicinal products during the import operations, the quality control in wholesale and retail trade, and pharmacovigilance coordinated by SEC. Such control ensures that poor quality, non-registered or counterfeit batches of medicinal products are prohibited for sale and get withdrawn from the market. In some cases, medicinal products are prohibited for use due to a termination of their marketing authorization (detailed scheme is shown in Figure 5.1).

Figure 5.1 The Mechanism of Post-Registration Surveillance and Control of Medicinal Products in Ukraine

The import quality control procedure includes the following steps\(^5\):

1. The business entity submits an application for obtaining a conclusion/opinion on the quality of the imported medicinal product (\textit{up to 5 business days}).
2. The supervisory agencies conduct control measures (\textit{up to 8 business days}): a. examine the submitted documents, verify of freight for compliance with the customs declaration;

\(^5\) Resolution of the Cabinet of Ministers of Ukraine No. 902 dated 14 September 2005 “On Approval of the Procedure for Carrying out State Control of the Quality of Medicinal Products Brought into the Customs Territory of Ukraine”.

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b. conduct visual inspection \((up \ to \ 3 \ business \ days)\).

3. A decision on laboratory testing is taken, if necessary, and samples are selected for tests \((up \ to \ 3 \ business \ days)\).

4. Laboratory testing is conducted \((up \ to \ 14 \ business \ days/ or \ as \ required)\).

5. An opinion from the government supervisory agency is issued \((1 \ business \ day)\).

The maximum overall duration of the procedure is between 14 and 29 business days. It can be extended at the stage of the laboratory testing. The quality control of medicinal products in circulation consists of two components: incoming quality control by pharmacies and scheduled and unscheduled inspections of medicinal products in circulation during the manufacturing, storage, sales (trade) and usage for medical purposes.\(^{53}\)

Medicinal products in circulation are subject to scheduled and unscheduled inspections. The procedure for scheduled and unscheduled inspections includes sampling of medicinal products for laboratory testing in the SSUMP laboratories.\(^{54}\) Scheduled checks are taken according to the quarterly plans approved by the decree of the government surveillance agency. These plans are published on the official website of SSUMP. If the inspection reveals counterfeit medicinal products, the SAUMP may issue an order to impose a temporary prohibition on the manufacturing, sales, storage, transportation and usage of such medicinal products.

If certain medicinal products are suspected of being counterfeit, in addition to laboratory studies the SAUMP and its local units might conduct investigations into the origin and distribution of such medicinal products. Checks of compliance with licensing terms are also done via scheduled and unscheduled inspections. They are focused on the verification of compliance with licensing terms including GMP requirements.\(^{55}\)

Pharmacovigilance plays a vital role in ensuring the appropriate quality of medicinal products. Adverse reactions to medicinal products may be caused by the inappropriate quality or the specific properties of such products or a peculiar response of the organism to taking them. Therefore, a constant surveillance over safety of medicinal products is needed. Pharmacovigilance represents a system of collection and scientific assessment of the information on adverse effects resulting from the use of medicinal products. It is a basis for adequate regulatory decisions.

\(^{53}\) Internal control procedures for incoming medicinal products delivered and stored at the enterprise are regulated by Order of the Ministry of Health of Ukraine No. 677 of September, 26 2014. State quality control of medicinal products is regulated by the Order of MoH No. 260 of February3, 2010. The procedure for probation and renewal of circulation of medicinal products is regulated by Order of the Ministry of Health of Ukraine No. 809 dated 22 November 2011.

\(^{54}\) Order of the Ministry of Health of Ukraine No. 677 of September 2014 “On Approval of the Procedure for Quality Control of Medicinal Products in Wholesale and Retail Trade” and Order of the Ministry of Health of Ukraine No. 584 dated 16 December 2003 “On Approval of Terms and Conditions of Storage and Quality Control of Medicinal Products in Healthcare Facilities”.

\(^{55}\) Law of Ukraine No. 877-V of April 2007 “On Fundamental Principles of State Surveillance (Control) of Economic Activities”.

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All countries apply the same pharmacovigilance approaches defined by the World Health Organization (WHO).

In Ukraine, pharmacovigilance is regulated by the relevant Procedure\(^{56}\) and has the following levels:
- central (unit of the SEC);
- regional (SEC's regional divisions operating in all oblasts of Ukraine and in Kyiv);
- local (employees responsible for pharmacovigilance in the healthcare institutions).

Apart from the state pharmacovigilance system, every company that registers medicinal products in Ukraine should maintain its own internal pharmacovigilance system along with the quality control system.

The WHO recommends countries to receive at least 100 adverse drug reaction reports per 1 million people. In 2013, in Ukraine this indicator reached 365 reports per 1 million people. Notably, during the last 3 years, healthcare institutions and physicians have become more active in their pharmacovigilance activities. However, the main concern is that adverse drug reaction reports are submitted only by 57\% of the Ukrainian healthcare facilities\(^{57}\). Not all the regions are actively providing information about adverse drug reactions. Such situation is largely determined by the absence of clinical pharmacists responsible for pharmacovigilance in healthcare institutions and low personal responsibility of the physicians for providing this information.

**Changes in the Post-Registration Control System**

The changes in the post-registration control system were aimed at implementing international quality control standards, strengthening the fight against the counterfeit medicinal products, and certain deregulation.

**Quality Control of the Imported Medicinal Products**

- In 2011, Ukraine joined the Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme (PIC/S). It was the main step in the implementation of international standards. PIC/S membership is usually accompanied by concluding of intergovernmental agreements on mutual recognition of GMP certificates\(^{58}\). This significantly improves the quality of regulatory procedures for businesses and reduces administrative costs for governmental bodies. Ukraine declared her commitment conclude these intergovernmental agreements. However, nothing has been achieved so far. The only advantage of Ukraine’s membership in

\(^{56}\) Order of the Ministry of Health of Ukraine No. 898 of December, 26 2006 “On Approval of Procedure for Surveillance over Adverse Reactions to Medicinal Products Permitted for Medical Use”.

\(^{57}\) November 2014, http://www.apteka.ua/article/314135

\(^{58}\) “Ukraine Welcomes PIC/S Members”, Apteka Newspaper, 8 October 2012. Available at: http://www.apteka.ua/article/164188
PIC/S is the cancelation of the laboratory control for the imported medicinal products that are manufactured by the companies in the territory of PIC/S member states.

- Since November 2014, products in bulk that are imported for domestic production of drugs are no longer subject of import quality control. It reduced the regulatory burden on the domestic manufacturers.

- Introduction of the legal provision imposing liability for quality on business entities that import active pharmaceutical ingredients (substances) creates obstacles for pharmacies that are manufacturing medicinal products on their own. Pharmacies holding manufacturing authorizations have to pass this verification procedure because they are unable to buy substances with an opinion on the quality of imported medicinal product. This may reduce the manufacture of medicinal products by pharmacies. In this case, the latter will have to stop the manufacturing process or send samples of substances to the competent laboratory before using them. For the latter purpose, pharmacies have to buy substances taking into account necessary amount of samples for tests and pay for them. This will increase the cost of medicinal products.

**Quality Control of Medicinal Products in Circulation**

- Over the recent years, Ukraine has been implementing the European regulations to ensure quality, safety and efficacy of medicinal products. In 2011, Ukraine has introduced the criminal liability for counterfeit medicinal products. In the same year, Ukraine joined the MEDICRIME Convention (Council of Europe Convention on the Counterfeiting of Medicinal Products and Similar Crimes Involving Threats to Public Health), ratified it one of the first in 2012. 10 quality control laboratories were completely re-equipped.

- Ukraine has also ratified the European Pharmacopoeia which implies the implementation of strict quality standards for the medicinal products.

**Pharmacovigilance**

Over the recent years, Ukraine started to harmonize its national pharmacovigilance system with the European standards. In 2011-2012, a number of amendments were made to the Procedure for Surveillance over Adverse Reactions to Medicinal Products Permitted for Medical Use. It widened the range of sources of information on the suspected adverse reactions or lack of efficacy of medicinal products. Presently, they include applicants, physicians, nurses, surgeon’s assistants, obstetricians, pharmacists, pharmaceutical chemists, patients and their professional organizations.

**Some changes in the control system were controversial.**

- 2012-2013 were marked by an extensive debate over the introduction of labelling of medicinal products to trace the medicinal products from entering the market till their
sale in pharmacies. It was considered as a tool to combat counterfeiting in the pharmaceutical market and reduce corruption in the hospitals associated with the trade of medicinal products procured with public funds. The necessary software was procured, and labelling costs were estimated (UAH 0.01–0.08 per package). This was a response to the EU intentions to make labelling compulsory for the prescribed medicinal products in the next few years. The market players were concerned about the potential growth of the counterfeit medicinal products in Ukraine if the same system was not introduced. However, this project proved to be very costly and was not implemented.

- In December 2014, a two-year moratorium was imposed on checks of small businesses with a turnover below UAH 20 million. This moratorium removed the legal grounds for the scheduled and unscheduled quality checks of the medicinal products in the retail network since many pharmacies met this small-size criteria. Ban on inspections was partially compensated by the checks for criminal proceedings. Nevertheless, an increase in prices for medicinal products together with a weakened quality control increased the risks of spreading the counterfeit medicinal products. Presently, the Government intends to extend moratorium till the end of 2016. In pharmaceutical market, it might have a negative impact combating low quality and counterfeit products.

**Problems**

There are problems in all the areas of quality control and circulation of medicinal products. Like in other areas, some positive regulatory steps were undermined by poor implementation, while non-transparent criteria provoked arbitrary decisions and increased time and financial costs for businesses. In addition, there is no reliable system of monitoring the efficiency of quality control system itself, i.e. to evaluate the efficiency of the control system to ensure safety and quality of the medicinal products.

1. **The pace of implementation of the international standards in the field of control is rather slow.** In spite of Ukraine’s PIC/S membership, no agreement on mutual recognition of GMP certificates between the Ukraine and PIC/S members has been signed so far. The mutual recognition of the results of GMP inspections of medicinal products in the third countries by the EU is regulated by special sectoral annexes under the Association Agreement. Such annexes ensure the mutual recognition of the results of GMP inspections of medicinal products in the countries that signed the agreement. As of today, such agreements have been made between the EU and Australia (fully operational), Canada (operational with exceptions), Japan (operational with exceptions), New Zealand (fully operational), Switzerland (fully operational), Israel (partially operational) and the US (not operational). Thus, conclusion of the Mutual Recognition Agreement on Conformity Assessment in Relation to Medicinal Products Good

Manufacturing Practice Inspection between the Ukraine and EU might reduce the regulatory burden for Ukrainian exports to these countries. The government should be more active in concluding such agreements. Otherwise, the advantages of PIC/S membership for Ukraine will not be fully exploited.

2. For almost ten years, there is no by-laws to regulate the termination of marketing authorizations for medicinal products. Consequently, the decision of MoH to terminate the marketing authorization for a certain medicinal product in circulation (e.g. on which there are complaints concerning the adverse reactions or lack of efficacy, or in case of invalid information found in the registration materials) might be easily stopped by court. At the same time, such situation creates favorable conditions for taking unreasonable decisions. limits country’s capability to control safety and quality of medicinal products available on the market in an unbiased and legitimate manner.

3. The lack of transparency in quality control procedures for the imported medicinal products increase the regulatory burden for business. The maximum duration of the procedure is between 14 and 29 business days. However, it can be extended for the laboratory testing. Market participants complain that in the absence of unambiguous criteria for laboratory tests, the medicinal products are often sent there as a result of the arbitrary decisions by the public officials. In this case, the importers face significant costs of paying the fees for laboratory services, and temporary storage of the medicinal products in quarantine (while their distribution is prohibited). This measure has a low effect on fighting low quality goods, since, evidently, in most cases the tested medicinal products complied with the quality standards. Besides, the state–owned laboratories often lack sufficient financing for buying pharmacopoeia standards and laboratory reagents. Consequently, these costs are often covered by the importers themselves.

4. Some control procedures are useless for verifying the quality of medicinal products, and impose an additional regulatory burden.

- The incoming quality control by pharmacies makes no sense. The Order of MoH No. 677 requires pharmacies to have an authorized employee in order to perform the incoming quality control of the medicinal products. The authorized employee is charged with preparing an incoming control opinion and maintaining the registry of the medicinal products delivered to the entity. This registry contains the information from the delivery notes, i.e. basically the accounting information that has nothing to do with quality control. Incoming quality control of medicinal products in pharmacies is a pure formality and does not facilitate the process of ensuring quality and safety of medicinal products. In EU, no pharmacy has
authorized employees for incoming quality control. According to the EU, the responsibility for the quality of medicinal product is on the side of a manufacturer/marketing authorization holder (if it is not the same entity). In fact, incoming control is the quality-based acceptance of products.

- Quality control of medicinal products in pharmacies has controversial effects. When pharmacies are inspected for compliance with quality standards for medicinal products, any detected problem (for example, inadequate average pill weight or presence of solid particles in ampoules), causes fines for the PHARMACIES. The latter are expected to demand reimbursement of fines from the manufacturers of medicinal products. However, given the weak judicial system, such practice proved to be ineffective and costly for pharmacies. In fact, they are held liable for the problems they should not be accountable for. In the EU, quality inspections of medicinal products in circulation mean laboratory tests of the medicinal products selected according to approved plans (including in the pharmacies). They are focused on the responsibility of the manufacturer (not the pharmacy) for any inconsistencies. In Poland, for instance, the annual general list of all medicinal products to be inspected and sampling plan is publicly available. The pharmacies are responsible for the compliance with the licensing terms but not for the quality of medicinal products.

5. **Organization of inspections to check the quality of medicinal products in circulation is not very efficient.** The control agency should warn business units about the scheduled inspection 10 days in advance. Even the representatives of pharmacy business agree that this “warning” clause makes it is almost impossible to reveal during the checks the counterfeit or low quality in products in circulation.

6. The state control bodies bear no financial responsibility for the financial damage caused to the market participants. For example, when an inspector during the import quality control sends the medicinal products for the laboratory rests, the whole batch is placed in the quarantine and temporary withdrawn from the circulation. Given the badly defined criteria for making laboratory tests, the state control bodies might make arbitrary decisions. The temporary withdrawal from the market for 90 days may be further extended to 180 days. It causes financial losses for business. If tests confirm a standard quality of medicinal products, this losses are not reimbursed and the government agency bears no responsibility for such losses. This creates incentives for corruption.

7. **The mechanism of appeal against the decisions of regulatory/control agencies does not work.** Many businesses in the retail market (pharmacies) claim that opportunity to appeal against the decisions of state control agencies is very limited. Although the legal basis for an
appeal is in place, a distrust to the judicial system and a considerable length of court proceedings restrain business from using this tool.

8. **Duplication of checks/inspections increases the regulatory tax for business.** Checking compliance with licensing terms is often carried out separately from the quality control, although both control functions are performed by the same experts and could be done within the same inspection. It doubles the time of inspections, leads to inefficient use of human resources by the controlling bodies, and increases the regulatory tax for business which suffers double interruptions in its operations.

9. **The system of public monitoring and efficiency assessment of the state control agencies is poorly developed.** Public information on the quality of medicinal products in circulation is limited or non-existent (like the data on the revealed counterfeit medicinal products). There is no public database on the counterfeit medicinal products and no methodology for calculating the share of counterfeit products in the pharmaceutical market. It makes difficult to monitor the results of fight against the low quality and counterfeit medicinal products, and to make performance evaluation of the state control bodies. The latter should be based on the assessment of the efficiency in using financial resources for ensuring quality and safety of the medicinal products, showing up in a decline of the share of poor-quality and counterfeit medicinal products in the national market. However, in reality, the quantity of inspections turns out to be the main performance and success indicator for the control agencies.

10. **Control agencies and laboratories are badly equipped.** Insufficient financing prevents control agencies to perform the functions efficiently. For example, for a long time, the SSUMP laboratories received only part of the pharmacopoeia standards and reagents needed for the tests. As a result, business entities had to buy necessary materials and cover the costs of laboratory tests conducted by the SSUMP laboratories. Therefore, business was involved in the financing of control activities of the governmental agencies. This distorts the relations between the supervisory agency and the business entity under control and promotes corruption. The problem of underfinancing of the control functions in the pharmaceutical market should be urgently addressed. It is worthwhile to reconsider both the scope/organization of quality control, and the size of financing. An increase in financing of the control bodies might be achieved either by the allocation of additional funds from the state budget, or by increase in the fees for services (e.g. registration fee).

The above mentioned problems of quality control system constitute serious regulatory barriers for business. According to the results of survey of October 2015, the main problems in the area of quality control in the pharmaceutical market are the following:
• unclear criteria used by control agencies to select the medicinal products for laboratory tests (76% of those who replied to the question);
• additional costs incurred during the inspections of quality of the medicinal products (76% of those who replied to the question);
• the lengthy quality control procedure for medicinal products (72% of those who replied to the question);
• a significant impact of subjective factors on quality control results (72% of those who replied to the question);
• insufficient number of the well-equipment laboratories for conducting quality tests of the medicinal products (72% of those who replied to the question).

Recommendations in the area of quality control

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<th>Action</th>
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<th>Timeframe</th>
<th>Priority</th>
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<tr>
<td>1. Enhance the transparency of quality control procedure for the imported medicinal products by improving criteria for sending medicinal products for the laboratory tests. The list of criteria should be clear, unambiguous and exhaustive in order to minimize the risks of an arbitrary decision by control agencies and reduce the “regulatory costs” for business</td>
<td>CMU, MoH</td>
<td>2016</td>
<td>high</td>
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<td>2. Define and implement the liability mechanism (including financial liability) for the state control agencies for unjustified sending of the medicinal products to the laboratory tests during the import quality control procedures.</td>
<td>CMU, MoH</td>
<td>2016</td>
<td>high</td>
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<td>3. Adopt by-laws to regulate the termination of marketing authorizations for medicinal products (based on requirements of the Directive 2001/83/EC) for a clearly defined list of cases.</td>
<td>CMU, MoH</td>
<td>2016</td>
<td>High</td>
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<td>4. Replace the incoming quality control in pharmacies by an introduction of the GPP quality management system</td>
<td>CMU, MoH</td>
<td>2016</td>
<td>Medium</td>
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<td>5. Replace the quality control of</td>
<td>CMU, MoH,</td>
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<td>pharmacies by the quality control of medicinal goods focusing on manufacturer's responsibility (including fines). Implement the European approach of taking samples of medicinal products in pharmacies for quality control according to the regular plans of inspections that are publicly available.</td>
<td>SSUMP</td>
<td>2016</td>
<td>High</td>
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<td>6. Refrain from the ban on quality control inspections of manufacturers and traders of medicinal products.</td>
<td>CMU, Verhovna Rada</td>
<td>2016</td>
<td>Medium</td>
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<td>7. Reconsider the &quot;warning&quot; requirement while conducting scheduled inspections of the medicinal products in circulation. The scope and frequency of the inspections should be risk-related, and the mandatory warning of business before the inspection might be cancelled.</td>
<td>CMU, MoH</td>
<td>2017</td>
<td>Medium</td>
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<td>8. Make an audit of SSUMP’s activities and functions.</td>
<td>CMU, MoH</td>
<td>2016</td>
<td>High</td>
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<td>9. Make sure that control functions of the SAUMP are covered by sufficient financial resources. In case of necessity, reconsider both functions and financing. Use the outsourcing of tests of medicinal products to the certified laboratories on the basis of transparent tariffs for services. Consider raise in registration and re-registration fees for medicinal products as a source of additional finance for the system of quality control.</td>
<td>CMU, MoH</td>
<td>2016</td>
<td>high</td>
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<td>10. Develop a methodology for calculating the share of the counterfeit and poor-quality</td>
<td>MoH, SSUMP</td>
<td>2016</td>
<td>high</td>
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| 11. Develop the assessment criteria for public monitoring the efficiency of quality control system for medicinal products. These criteria should be result-oriented and show among others the results in fighting against the low-quality and counterfeit drugs. Ensure public access to the information on performance indicators of the control agencies. It will enhance the transparency of quality control system for medicinal products. |
| CMU, MoH, Professional Pharmaceutical Associations |
| 2016 |
| High |

| 12. Conclude the bilateral agreements with the governments of PIC/S member states on the mutual recognition of GMP certificates. Introduce the indicator of signed bilateral agreements as one of the success indicators of the CMU’s performance. |
| CMU, MoH |
| 2016-2017 |
| high |

| 13. Consider the implementation of labelling of prescription medicinal products that enter the Ukrainian market in order to facilitate detection of counterfeit medicinal products and fight corruption in public procurements of medicinal products. |
| CMU, MoH, Verhovna Rada |
| 2019 |
| Medium |


CHAPTER 6. THE INSTITUTIONAL FRAMEWORK FOR REGULATING PRODUCTION AND DISTRIBUTION OF MEDICINAL PRODUCTS

The regulation of pharmaceutical market has its institutional framework. Regulatory institutions of the pharmaceutical market should fulfil several tasks. Firstly, they should ensure access to the market for efficacious, quality and safe medicinal products. Secondly, they should create conditions necessary to bring a broad range of eligible medicinal products to the market and encourage the development of innovative medicinal products. Thirdly, they should facilitate the affordability of medicinal products for the patients. Fourthly, they should perform their regulatory functions while minimizing administrative costs for business units.

The main functions of the regulatory authorities in the pharmaceutical market include the following:

1. creating and maintaining systems that ensure compliance with pharmaceutical requirements at all stages: development, import, production, transportation, sale (trade), consumption, disposal etc.;
2. authorizing (registering) medicinal products;
3. monitoring (pharmacovigilance) market agents’ activities in order to ensure safety and quality of medicinal products at all stages of their circulation;
4. issuing licenses for business activities;
5. developing pricing policies and reimbursement strategies.

In the European Union, there is a multilevel state regulatory system of the pharmaceutical market. It consists of:

1) supranational regulators (European Medicines Agency (EMA) and European Directorate for the Quality of Medicines & HealthCare (EDQM), see Box 6.1);
2) Heads of Medicines Agencies - a network (Assembly) of the heads of the National Competent Authorities whose organizations are responsible for the regulation of medicinal products for human and veterinary use in the European Economic Area;
3) national regulators.

The producer may use several ways to enter the market. Entering the European market might be done in accordance with the centralized procedure. A centralized procedure is mandatory for all innovative medicinal products (containing a new pharmaceutical ingredient, previously not marketed), the drugs that are produced by biotechnological processes and designed for treatment of orphan diseases, acquired immune deficiency syndrome, cancer, neurodegenerative disorder, diabetes autoimmune diseases and other immune dysfunctions, as well as viral diseases. Another way to enter national markets of some EU states is using the mutual recognition procedure. After being authorized in one of the EU countries in accordance with the decentralized procedure, the trade license holder may apply for authorization in accordance with the Mutual Recognition Procedure for marketing in other EU countries.
A third possibility is related to the national (decentralized) procedure that provides an access exclusively to a certain national market (following relevant procedures established by a particular regulator). Each EU Member State has its own national authorization procedure for the medicinal products that fall outside the scope of the centralized procedure (may not be marketed throughout the entire EU). These are national procedures that do not provide for the use of the Mutual Recognition Procedure. In other words, when making a decision to enter the other market(s) the trade license holder has to submit a new marketing authorization application. In EU, marketing authorization is regulated and controlled separately (by other agencies) from pricing, reimbursement and procurement. In Ukraine, most of these functions are regulated/controlled by the Ministry of Health.

**Box 6.1. The European regulatory framework consists of two main elements**

1) The European Medicines Agency (EMA). The EMA is the central body of the European network to control the circulation of medicinal products. EMA coordinates the activity of 40 national regulatory agencies from the European Commission and European Parliament, as well as decentralized European ones. The EMA’s main responsibility is the protection/promotion of public and animal health through the assessment and supervision of medicinal products for human and veterinary use. The Agency is responsible for the scientific assessment of the applications for EU marketing authorizations for human and veterinary medicinal products in the centralized procedure. It works with a network of over 4,500 experts. The EMA is responsible for coordinating the safety monitoring or ‘pharmacovigilance’ system for medicinal products. The Agency is also responsible for coordinating inspections to ensure compliance with GMP, GCP, GLP or pharmacovigilance quality-assurance systems. In addition, the EMA maintains a database of medicinal products registered in accordance with the centralized procedure.

2) The European Directorate for the Quality of Medicines & HealthCare (EDQM) is an organization (institution of the European Council) that protects public health by enabling the development, supporting the implementation and monitoring the application of quality standards for medicinal products and their safe use.

The EDQM is the publisher of the European Pharmacopoeia which contains medicinal product quality standards. The EDQM is responsible for coordination of the European Network of Official Medicines Control Laboratories (OMCLs). The OMCLs support regulatory authorities in controlling the quality of medicinal products available on the European market. Thus, OMCLs test these products independently from manufacturers.

*Source: EMA, EDQM.*

There is no single approach to organizing the activities of the national regulators. European directives also do not contain any recommendations on the application of one- or multilevel approach. This is a choice of the national governments. For example, in Poland, a multiple institution approach is applied (see Box 6.2).
Box 6.2. The National Regulatory Framework of Poland. The Polish pharmaceutical market is regulated by the following agencies

1) The Bureau for Registration of Medicines, Medical Devices and Biocides is responsible for registration of medicinal products;

2) The Medicines Institute controls the activity of the Official Medicines Control Laboratories Network and is responsible for assessment of quality, safety profile and therapeutic effectiveness of medicinal products;

3) The Main Pharmaceutical Inspectorate is responsible for testing medicinal products available on the market and inspecting the production environment;

4) The Polish National Unit for Monitoring Adverse Drug Reactions is responsible for monitoring safety profiles of registered medicinal products at the post-marketing stage.

Sources: URPLWMPB, IL, GIF, PNUMADR.

Several agencies regulated the pharmaceutical market in Hungary till 2011 when they merged into a single institution, i.e. the National Institute for Quality and Organizational Development in Healthcare and Medicines.

Regardless of the institutional framework (one or several authorities), these countries also have ministries responsible for the healthcare, though their responsibilities are limited to shaping an overall pharmaceutical policy. Both the multiple- the single agency model have their advantages and disadvantages. The advantages of a multiple agency model are clear assignment of functions, higher specialization (thus, a higher professional competence) of authorities, a better protection against mistakes (if the agencies are really independent from one another) and a possibility to correct such mistakes at the following stage of control exercised by another agency. At the same time, it is more difficult to manage and coordinate the activities of such agencies, while their responsibilities may overlap, and bureaucracy may slow down the regulatory, supervisory and decision-making processes. A single agency model often allows quicker response to the changes in the market, and better opportunities to simplify administration processes. However, it is more likely that regulatory mistakes need longer to be corrected.

_Licensing, advisory and quality control functions are to be performed both in a single- and the multiple agency model._

**Organizational Changes in the Institutional Framework of Ukraine**

_Ukraine has applied various institutional models for regulating the market_. Till 1998, the Ministry of Health had been the main regulatory authority on the pharmaceutical market with the State Pharmacological Committee and State Inspectorate for Medicinal Products Quality Control, though being separate entities, were directly subordinated to the MoH.
In 1999, the National Agency for Controlling the Quality and Safety of Food, Medicines and Medical Supplies was established to regulate the circulation of medicinal products and special food items (like the US FDA). However, in 2000 it was liquidated.

The State Service of Ukraine on Medicinal Products and Medical Supplies (SSUMPMS) started to operate in 2004. It was authorized to license the production and circulation of medicinal products, register medical supplies and immunobiological drugs, etc. In 2008, the State Inspectorate for Medicinal Products Quality Control (SIMPQC) was established as a central authority to combine its own functions (as a former part of MoH) with the functions of SSUMPMS. There was an attempt to put the registering of medicinal products outside MoH. Also significant efforts were done to concentrate regulatory and licensing functions in one agency, and establish an effective control over prices for medicinal products. Meanwhile Ukraine incorporated GMP requirements into the licenses adoption and became a member of PIC/S. After the administrative reform in 2011, SSUMPMS was reorganized into the State Service for Medicinal Products, and in 2014 it merged with the State Service for Drug Control into one agency - the State Service of Ukraine on Medicinal Products and Drugs Control (the reorganization process is still not completed).

Continuous reorganizations negatively affected the regulatory environment, since every merger/split disrupted the normal activity of the regulatory agencies for approximately 6-9 months.

In 2008, a team of experts from WHO, the European Commission and US Agency for International Development assessed the regulations in the Ukraine’s pharmaceutical market and prepared recommendations on their improvement in line with the EU-integration vector of Ukraine. The experts pointed out that Ukrainian regulatory system of pharmaceutical market is hampered by structural defects, the lack of coordination as well as conflicts of interest between the agencies increasing risks of corruption. They recommended to review the operation of the national pharmaceutical regulatory agency and reorganize it in the long run to ensure harmonized and coordinated approaches to all medicinal products and medical supplies with due regard to all regulatory functions. The expert team highlighted that all these functions might be performed by a single competent authority.

As of early November 2015, Ukraine employs the multiple agency model, consisting of 3 elements: the Ministry of Health (MoH), State Service of Ukraine on Medicinal Products (SSUMP) and the State Expert Center of the MoH of Ukraine (SEC) (see Figure 6.1).

1. **The Ministry of Health of Ukraine**. The MoH has the following responsibilities concerning the pharmaceutical market:

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60 Огляд системи регулювання лікарських засобів в Україні з особливим наголосом на лікарських засобах для лікування ВІЛ, СНІД та туберкульозу, та пов’язаних з цим виробах медичного призначення. Спільна місія з оцінки Європейського регіонального бюро ВООЗ, Представництва Європейської Комісії в Україні та Агенції США з міжнародного розвитку, 7 – 12 липня 2008 р. Київ, Україна

61 Functions and authorities of the MoH are defined in the relevant Regulation adopted by Resolution of the Cabinet of Ministers No. 267 of 25 March 2015: http://zakon2.rada.gov.ua/laws/show/267-2015-%
1) to ensure the design and implementation of the state policy (including regulatory framework) on the development, production, quality control and sale of medicinal products, immunobiological drugs and medical supplies;
2) to approve national and industry standards, guidelines, methods and methodologies, forms and blanks, lists of medicinal products and required drugs for pharmacies, changes in wholesale and retail prices,
3) to approve rules and procedures for verifying compliance with the licensing conditions, inspecting business entities, issuing marketing authorizations, prohibiting / withdrawing medicinal products from the market, monitoring the safety of medicinal products in healthcare facilities, conducting various examinations, etc.
4) to conduct the state registration (re-registration) of medicinal products including immunobiological drugs; issue marketing authorizations for medicinal product; and maintain the State Register of Medicinal Products;
5) to issue permits for importing medicinal products not registered in Ukraine;
6) to decide on the approval and implementation of clinical development programs.

In addition to a direct impact on regulations in the pharmaceutical market, the MoH has also indirect instruments of control. In particular, the MoH:
    a) approves the healthcare standards, in particular clinical protocols and standards, and ensures compliance with such standards (thus influencing the authorization of certain groups or forms of medicinal products);
    b) approves accreditation criteria and standards for the healthcare units (thus influencing the preclinical/clinical trial base);
    c) approves the unified qualification requirements for the specialists who conduct different medical and pharmaceutical activities (thus influencing the scope of persons admitted to all lifecycle stages of medicinal products);
    d) makes decisions on the approval and implementation of programs for clinical trials of medicinal products.

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Ministry of Health

The State Service of Ukraine on Medicinal Products and Drugs Control / State Service of Ukraine on Medicinal Products

SOE “State Expert Center of MoH of Ukraine”

Central executive body coordinated through the Minister of Health

State enterprise, subordinated to MoH

Figure 6.1. The Institutional Framework for Regulating the Ukrainian Pharmaceutical Market.
2. The State Service of Ukraine on Medicinal Products and Drugs Control (its establishment was scheduled for September 2015 and still is not completed). The agency is expected to ensure the implementation of the state policy on quality control and safety of medicinal products including immunobiological drugs, medical equipment and devices, and on circulation of drugs, psychotropic substances and precursors, as well as drug trafficking counteraction. The SSUMPDC’s functions include the following:

- drafting and implementing the targeted state programs on quality control of medicinal products and medical devices, control of drugs’ circulation, as well as fighting against drug counterfeit;
- certifying pharmacists, and the laboratories for medicinal products quality control;
- creating/maintaining the Register of Agents Responsible for Authorization of Medical Devices, Active Implantable Medical Devices and In Vitro Diagnostic Medical Devices;
- licensing the production, import, and retail/wholesale distribution of medicinal products, creating/maintaining the Register of Licensed Business Activities related to Production, Import, Retail and Wholesale of Medicinal Products;
- selecting samples of medicinal products and medical devices to test their quality;
- ensuring state control over:
  - compliance with the legislation on quality and safety of medicinal products and medical devices at all stages of circulation,
  - compliance with the requirements of licenses for production, import, and retail/whole-sale trade of medicinal products;
  - compliance with the requirements of technical regulations related to medicinal products;
  - importing of medicinal products into the customs territory of Ukraine;
- making decisions on the withdrawal from the market and prohibition (suspension) of production, sale and application of medicinal products and medical devices which fail to meet the legal requirements, and which are imported into Ukraine and exported from Ukraine in violation of the legally established procedures;
- granting permits for importing/exporting drugs, psychotropic substances and precursors and transporting them through the territory of Ukraine;
- inspecting storage, retail and other facilities used by legal entities to distribute drugs, psychotropic substances and precursors.

3. The SOE “State Expert Center of the Ministry of Health of Ukraine” (SEC) is a specialized expert institution for conducting preclinical trials, clinical trials and state registration of the medicinal products (including immunobiological drugs). It is a central authority in the field of pharmacovigilance, healthcare standardization, medical, and particularly pharmaceutical, service provision, including the preparation of medical and

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62 Functions and authorities of the SAUMP are defined in the relevant Regulation adopted by Resolution of the Cabinet of Ministers No. 647 of 12 August 2015 [http://zakon2.rada.gov.ua/laws/show/647-2015-%D0%BF](http://zakon2.rada.gov.ua/laws/show/647-2015-%D0%BF)
technical documentation and drafts of the regulatory documents. It is a state-owned enterprise subordinated to the MoH.

Table 6.1. Allocation of Functions to the Elements of the Institutional Framework

<table>
<thead>
<tr>
<th></th>
<th>MoH</th>
<th>State Expert Center</th>
<th>SAUMP</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Decision-making</strong></td>
<td>makes decisions on registration/re-registration of medicinal products, and on conducting clinical trials; grants permits to import unregistered medicinal products, standard samples, reagents necessary to conduct preclinical trials.</td>
<td>provides resolutions on the efficacy, safety and quality of medicinal products based on the assessment of registration materials; provides permits for clinical trials of medicinal products.</td>
<td>grants produce and sales permits for medicinal products; grants permits to import and market the medicinal products (suspends circulation of such medicinal products); certifies (accreditate) the laboratories for testing the quality of medicinal products, including laboratories of its own and producers, etc.; certifies the pharmacists</td>
</tr>
<tr>
<td><strong>Expert functions</strong></td>
<td>does not perform expert functions. The MoH formally approves resolutions of the SEC by the relevant order.</td>
<td>examines materials of preclinical trials of medicinal products; examines materials of clinical trials; examines medicinal product registration materials; provides laboratory control of the drug's quality during its registration;</td>
<td>conducts pre-license inspections (examinations); conducts inspections (examinations) prior to issuing (recognizing) GMP certificates; reviews medicinal products quality at all stages of circulation (production, import, registration etc.);</td>
</tr>
<tr>
<td>(including laboratory functions)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Control/oversight</strong></td>
<td>makes the decisions to completely or partially prohibit an application of the medicinal products by cancelling their marketing authorization.</td>
<td>conducts audits of preclinical trials and clinical trials of medicinal products; ensures quality control of immunobiological drugs when</td>
<td>ensures control of circulation of medicinal products at all stages; ensures control of compliance of business entities with licensing</td>
</tr>
<tr>
<td>functions**</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(including laboratory functions)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
According to the enterprise's current Charter, the State Expert Center has the following authorities:

1) examine registration materials on drugs to ensure their efficacy, safety and quality;

2) carry out the following activities:
   - prepare, develop and submit for approval to the MoH drafts of regulatory documents relating to medicinal products trials, as well as registration materials necessary for state registration (re-registration) and introduction of changes to registration materials during the validity of the marketing authorization, pharmacopoeia articles or materials on methods for medicinal products quality control, post-registration oversight, the system for providing the population with medicinal products and rational pharmacotherapy, particularly pharmacoeconomics, reimbursement and medicinal products pricing;
   - examine materials on creation (development), production (manufacture), preclinical trials and clinical trials of medicinal products, as well as control their quality or additional studies including inspection of their production prior to registration;
   - examine materials on active substances and additives used in production of medicinal products and provide the MoH with recommendations concerning the possibility of their usage, state registration (re-registration) and introduction of changes to registration materials during the validity of the marketing authorization;
   - conduct audits of preclinical study and clinical audits of clinical trials of medicinal products, as well as inspections of their production prior to registration;
   - conduct post-registration oversight over medicinal products registered in Ukraine and submit proposals to the MoH concerning complete or partial prohibition (suspension) of their application (circulation), as well as post-registration monitoring (of safety and efficacy);
   - carry out pharmacovigilance activities;

3) make recommendations on in the area of import of medicinal products not registered in Ukraine, their registration, storage, application and disposal; pharmacovigilance, standardization in the field of medicinal products and medical care delivery;

4) compile lists of medicinal products sold without prescription and lists of medicinal products which are forbidden to advertise and sold without prescription, as well as submit them for approval of the MoH;

5) participate in maintenance and administration of the State Register of Medicinal Products of Ukraine;

6) provide postgraduate training of employees specializing in clinical pharmacology, pharmacy and pharmacovigilance;
7) ensure operation of the National Register of Hemopoietic Stem Cells (Bone Marrow) Donors of the MoH;
8) provide material and technical resources to the Central Formulary Committee of the MoH.

The summary of functions of regulatory agencies across the three dimensions (decision-making, expertise, and control) is presented in Table 6.1.

Despite the functions being distributed among several regulatory agencies, the overall performance of the regulatory institutions in the Ukrainian pharmaceutical market still lacks efficiency.

<table>
<thead>
<tr>
<th>Box 6.3. Results of the survey on the pharmaceutical market representatives’ attitudes to the idea of the single regulatory authority</th>
</tr>
</thead>
<tbody>
<tr>
<td>49% of the expert community considers having a single regulatory authority to be better for simplifying the regulatory procedures. 41% of the experts considers creating a single regulatory authority as a bad idea that can give a larger “space for corruption”.</td>
</tr>
</tbody>
</table>

**Problems**

1. **There is no clear and univocal assignment of responsibilities among the regulatory agencies.** All the three elements of the regulatory framework are engaged in development of the state policy in the pharmaceutical field (MoH, SSUMP and the State Expert Center). Control and oversight functions are simultaneously performed by two institutions (SSUMP and the State Expert Center); registration of medicinal products and medical devices is carried out by two agencies (MoH and SSUMP). Moreover, a continuous change in functions has been observed for many years, with the MoH delegating certain authorities to the SSUMP and then pulling them back.

2. **One-stop-shop principle is not fully applied.** Though one-stop shop principle was officially introduced in the pharmaceutical market in 2011, it is not yet fully implemented. As we demonstrated in Chapter 3, in order to register the medicinal product the company has to submit an application to MoH, the registration dossier- to the State Expert Center, and apply to SSUMP for a confirmation of GMP compliance with GMP. A lack of electronic data flow between the agencies and the absence of a real one-stop shop increases administrative costs for business.

3. **The pace of improvement of the regulatory framework in the pharmaceutical market is rather slow.** As we stressed in the Chapter 4, an organizational restructuring caused by a merge of SSUMP with the State Service for Drug Control is not completed. It lasts too long and causes disruptions in the licensing process.
4. The level of potential interference of MoH in operational activities of SSUMP is excessive. The Minister of Health has 16 authorities relating to “direction and coordination” of the SSUMP (including approval of the headquarters structure, appointments and dismissals of heads and deputy heads of independent units, approval of a work plan of the agency; issue of orders and instructions that are mandatory for the SSUMP etc.). While the approval of priorities for the SSUMP’s operations be MoH raises no concerns, the interference in the operational issues looks unjustified (for example, approval of the appointments and dismissals in SSUMP) is in our opinion excessive, since the Minister of Health is not accountable for SSUMP’s performance.

5. There is a duplication of functions of different regulatory agencies. The SEC conducts an expertise and prepares a resolution on the registration dossier of medicinal products. However, the final decision is made by the MoH which formally confirms the resolution of the SEC. Thus, actually the same regulatory function (examination and approval of the decision based on examination results) is artificially divided between the two agencies: the SEC and the MoH. Another example of duplications of functions is a formal approval by MoH the SEC’s resolution on clinical trial program. This needs changes. The both functions to examine registration dossiers and make decisions to register/re-register medicinal products should be assigned to the same agency that is fully responsible for the final decisions. Such agency can’t act as a commercial entity since this may cause a conflict of public and commercial interests.

6. The absence of a clear list of grounds for requesting additional information or conducting additional tests and raises administrative costs for business. There is no clear list of grounds on which an expert or a representative of the regulatory agencies might demand additional information/clarification (e.g. during the restriction procedure) from the applicant or request making additional test/examinations. The time for conducting additional examinations or providing additional information is not included in the total timeframe set for the regulatory procedure. Besides, any prolongation of the regulatory procedure often is associated with additional costs which are covered by business.

7. There is no efficient mechanism of liability of the regulatory authorities for the delays in making regulatory decisions or requiring additional information/tests from business while conducting the regulatory procedures. There are two possible ways to resolve this problem:

- One way is to reduce the payment for the administrative services (e.g. registration) in case there is a delay in its provision, or impose fines upon the regulatory agency/expert institution for the failure to meet the deadlines or follow standard procedures.
Another way is to employ the declarative principle for certain regulatory procedures. This allows shifting the primary responsibility on the market agent, at the same time reducing regulatory barriers for business. The declarative principle means that after applying for a permit business can immediately start its operations. The response from the regulatory authorities is expected within the standard timeframe. Only a negative decision of the regulatory authority can stop business operations.

The declarative mechanism was used in Georgia. Once the applicant submits the application, he/she starts operations. If the regulatory authority misses the deadline, it automatically means approval of the application. Implementation of the declarative approach needs transparency in the information flow concerning the status of the application and regulatory decisions.

8. There are problems in the area of expertise (as a part of regulations in the pharma market)

- The absence of an electronic document flow between the SEC, the MoH and the SAUMP results in delayed examinations and long queues.
- Criteria and selection procedures of SEC’s expects need an improvement. Unlike the European practice, there is almost no rotation of experts in SEC which slows down coming of the new professionals. The training of the existing pool of experts is limited due to the SEC’s hard budget constraints. Consequently, expertise takes more time, and its quality is sometimes questioned.
- There is unnecessary procedure of confirmation of individual experts’ resolutions at the meeting of the advisory bodies of SEC. This prolongs the time for issuing resolutions( the advisory bodies of SEC have their meetings once a month) without contributing to the quality of expertise.

9. There are significant problems in financing of the regulatory agencies (Table 6.2).

Table 6.2. Expenditures of the state budget on the regulatory agencies in pharma market (Table 6.2) (UAH / USD, thousands)

<table>
<thead>
<tr>
<th></th>
<th>2010</th>
<th>2011</th>
<th>2012</th>
<th>2013</th>
<th>2014</th>
<th>2015</th>
</tr>
</thead>
<tbody>
<tr>
<td>MoH</td>
<td>27,369.9</td>
<td>22,505.3</td>
<td>28,438.7</td>
<td>28,721.2</td>
<td>25,507.3</td>
<td>24,812.3</td>
</tr>
<tr>
<td></td>
<td>$3,449.0</td>
<td>$2,824.6</td>
<td>$3,558.8</td>
<td>$3,593.3</td>
<td>$2,145.9</td>
<td>$1,143.3</td>
</tr>
<tr>
<td>SAUMP</td>
<td>93,503.6</td>
<td>136,089.9</td>
<td>86,134.3</td>
<td>92,704.0</td>
<td>40,588.8</td>
<td>13,610.6</td>
</tr>
<tr>
<td></td>
<td>$11,782.8</td>
<td>$17,080.4</td>
<td>$10,778.9</td>
<td>$11,598.1</td>
<td>$3,414.6</td>
<td>$627.1 th</td>
</tr>
<tr>
<td>Average</td>
<td>7,9356</td>
<td>7,9676</td>
<td>7,9910</td>
<td>7,9930</td>
<td>11,8867</td>
<td>21,7025</td>
</tr>
<tr>
<td>exchange</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>rate $/Grv</td>
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<td></td>
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</tbody>
</table>

$63 The SOE “State Expert Center” is not financed from the state budget, being maintained out of revenues from its operational activity.
Over the recent years, the financing of the regulatory agencies in pharma market has been decreased without a significant reviewing of their functions. This had negatively impacted the efficiency of the regulatory agencies. Besides, it raised their motivation to search for funds by imposing additional costs on business via official (e.g., requesting additional paid examinations or inspections with fines imposed) and unofficial means (“corruption tax” for avoiding or speeding up different examinations/inspections).

At the same time, the stamp duty for the registration/re-registration of medicinal products remains low in Ukraine (100 euros), while in the other countries it constitutes an important source of financing the activities of regulatory authorities on the pharmaceutical market (e.g. in Poland, the registration duty is 5.2-18 thousand euros). As a result, there is a vicious circle: low state registration fees do not allow for an adequate financing of the regulatory. The latter raises incentives for an introduction of various paid services and corruption taxes.

**Recommendations**

<table>
<thead>
<tr>
<th>Action</th>
<th>Agency responsible</th>
<th>Timeframe</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Remove the artificial division of the registration/re-registration functions of medicinal products between two agencies.</td>
<td>CMU</td>
<td>2016</td>
<td>High</td>
</tr>
<tr>
<td>a) transfer the authority of making final decisions to register medicinal products to the State Expert Center;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>b) Increase the transparency of the decision-making on registration of medicinal products by canceling the function of SEC’s advisory bodies (Scientific Expert Council, Science and Technology Council of the State Expert Center) to confirm the reports of individual experts.</td>
<td>MoH</td>
<td>2016</td>
<td>High</td>
</tr>
<tr>
<td>c) Improve the selection procedure for the experts in SEC who are responsible for the examination of registration dossiers. The selection procedure should become more competitive and focus on professional criteria. Introduce a regular expert rotation arrangement.</td>
<td>SEC, MoH</td>
<td>2016</td>
<td>high</td>
</tr>
</tbody>
</table>
2. Introduce an exhaustive list of criteria for requesting additional information / making tests from business during the regulatory procedures. Develop an efficient liability mechanism of the regulatory agencies for missing the deadlines of the regulatory procedures or requesting additional unjustified information/ making additional tests for business within the regulatory procedures.

3. Ensure the electronic submission of applications, and electronic flow of all the documents related to the regulation of pharmaceutical market between the regulatory agencies.

4. Implement the one-stop-shop principle on the *interdepartmental basis* for receiving any type of regulatory permit for business in the pharma market. This may be, for example, an interdepartmental state institution “Center of Administrative Services in Healthcare” which will cooperate with all regulatory agencies and provide a complete package of services concerning:
   - marketing authorizations for medicinal products;
   - decisions to conduct clinical trials;
   - licenses for production of medicinal products in pharmacies, medicinal products retail/wholesale facilities;
   - licenses for importing medicinal products (except for API),

<p>| | | |</p>
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<tbody>
<tr>
<td>2. Introduce an exhaustive list of criteria for requesting additional information / making tests from business during the regulatory procedures. Develop an efficient liability mechanism of the regulatory agencies for missing the deadlines of the regulatory procedures or requesting additional unjustified information/ making additional tests for business within the regulatory procedures.</td>
<td>CMU, Verhovna Rada</td>
<td>2016</td>
</tr>
<tr>
<td>3. Ensure the electronic submission of applications, and electronic flow of all the documents related to the regulation of pharmaceutical market between the regulatory agencies.</td>
<td>MoH, CMU</td>
<td>2016</td>
</tr>
<tr>
<td>4. Implement the one-stop-shop principle on the <em>interdepartmental basis</em> for receiving any type of regulatory permit for business in the pharma market. This may be, for example, an interdepartmental state institution “Center of Administrative Services in Healthcare” which will cooperate with all regulatory agencies and provide a complete package of services concerning: marketing authorizations for medicinal products; decisions to conduct clinical trials; licenses for production of medicinal products in pharmacies, medicinal products retail/wholesale facilities; licenses for importing medicinal products (except for API),</td>
<td>MoH, CMU</td>
<td>2016</td>
</tr>
</tbody>
</table>
In the medium run, it is necessary to optimize the functions and improve the coordination between the authorities that are responsible for regulation of the pharmaceutical market. A careful audit of functions should be done in all the regulatory agencies of pharma market. Then, a two agency (two central executive authorities) model might be considered with one agency for regulating market access, and another one - for implementation and control). This requires a clear definition and distribution of functions to eliminate their duplication. The two-agency model could include:

- The National Medical Agency (responsible for medicinal products marketing authorization, registration, pharmacovigilance/adverse reactions, etc)
• The Medicines Quality Control Agency (a network of inspectorates and certified laboratories).

The MoH will concentrate on the overall healthcare policy (particularly, on health services delivery; quality, efficacy and safety of medicinal products). The state-owned enterprise (presently, SEC) should be relieved from the regulatory activities and perform only business functions (e.g. publish guidelines and methodological materials, ensure retraining of pharmaceutical specialists, provide various paid services etc.).

After reorganization the institutional framework itself should be protected against permanent changes for 5 years. In the future, it can be complimented by the professional associations, which could exercise certain delegated functions (e.g. certification of independent experts, verification of qualifications of distributors and pharmacists) and become a powerful instrument of public control of the government agencies. The government should assist in strengthening the capacity of non-governmental professional organizations.

Regardless of the institutional model, an adequate financing of the regulatory agencies in the pharma market should be ensured. This problem might be partly resolved by an increase in the registration fee for medicinal products (in line with the registration rates effective in the neighboring EU countries).
CHAPTER 7. ECONOMIC REGULATION OF THE PHARMACEUTICAL MARKET

Economic regulation of the pharmaceutical market is expected to promote affordability of medicinal products for the public, and create the incentives for development/ smooth market access of the innovative medicinal products. There is a wide range of tools for economic regulation, including price reimbursement schemes, direct price regulation, promotion of competition by ensuring equal market access, particularly to public procurements.

In the EU countries, economic regulation is mainly focused on price reimbursement and promotion of competition. In Ukraine, economic regulation is mainly focused on the direct and indirect price control.

Direct Regulatory Mechanisms for Fixing Prices

In Ukraine, two instruments are used for price regulation, namely mark-up regulation and price declaration. Maximum mark-ups are mandatory for the medicinal products that are on the List for procurement by the healthcare institutions when money from the state or local budgets are involved (CMU Resolution No. 1071 “On the Procedure for Procuring Medicinal Products by Budget-funded Healthcare Institutions” from September 5, 1996), as well as on the National list of the essential medicinal products and on the Mandatory minimum range of medicinal products 64.

<table>
<thead>
<tr>
<th>There are several lists of medicinal products which prices are under the state regulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>☐ the National List of the Essential Medicinal Products and Medical Supplies (215 International Nonproprietary Names (INNs)), approved by Resolution of the Cabinet of Ministers of Ukraine No. 333 of 25 March 2008;</td>
</tr>
<tr>
<td>☐ the Mandatory Minimum Range of (Social) Medicinal Products and Medical Supplies for Pharmacies (102 names of medicinal products and 15 names of medical supplies), approved by Order of the MoH No. 1000 of 29 December 2012;</td>
</tr>
<tr>
<td>☐ the List of Medicinal Products Produced by National and Foreign Companies which Can Be Procured by Healthcare Institutions and Establishments Fully or Partly Funded from the State or Local Budgets (784 INNs), approved by Resolution of the Cabinet of Ministers of Ukraine No. 1071 of 5 September 1996;</td>
</tr>
<tr>
<td>☐ the Register of Insulin Drugs, particularly their procurement funded by local budgets is conducted upon declaration of changes in wholesale prices for such drugs, as approved by Resolution of the Cabinet of Ministers of Ukraine No. 73 of 5 March 2014.</td>
</tr>
</tbody>
</table>

The maximum wholesale mark-ups for the medicinal products included in the National List of the Essential Medicinal Products and Medical Supplies (except for drugs, psychotropic substances, precursors and medical gases) and the Mandatory Minimum

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64 Resolution of the Cabinet of Ministers of Ukraine No. 333 of 25 March 2009.
Range of (Social) Medicinal Products and Medical Supplies for Pharmacies should not exceed 10 % of the wholesale price (with taxes and duties included), and maximum retail mark-ups should not exceed 25 % of the procurement price with taxes included. A progressive scale of maximum retail mark-ups was applied till April 2015. Mark-ups are not applied to the medicinal products that are not included in the mentioned above lists and register. Original innovative drugs are subject to the same rules as generics.

Producers' prices are controlled by the requirement to declare changes in the wholesale prices. This applies solely to the medicinal products for procurement using public funds. Such medicinal products account for about 30% of all medicinal products registered in Ukraine. Declaring changes in the wholesale prices does not require any clarification of the reasons for these changes.

A significant regional variation in prices for the same medicinal products is used as a justification for price regulation. For example, the price for Nebilet, as of late March 2015, was UAH 253.00 in Kyiv, UAH 126.04 in Zhytomyr, UAH 164.50 in Poltava, UAH 140.00 in Khmelnytskyi, UAH 220.00 in Ternopil and 139.00 in Lviv.

In the EU countries, prices for medicinal products are also regulated (in accordance with Directive relating to the transparency of measures regulating the pricing of medicinal products No. 89/105/EEC of 1989). For example, direct price regulation is used in France, Austria and the UK. However, usually it focuses on generics. In France, the maximum price for a generic drug is based on the price of original drug with a regulated minimum discount. In Austria, the first generic on the market gets the lowest minimum discount (compared to the price of original drug), while the second and the following generics get higher discounts generics. Market pricing is applied only to the innovative medicinal products , and it works mainly in Great Britain, Germany and France (since 2003), while for the other medicinal products various price relation direct mechanisms are used.

**Taxation**

Setting a preferential VAT rate (which is usually lower than the general one) is the main tax instrument for impacting prices for medicinal products. In Ukraine, a 7 % VAT rate for medicinal products was introduced in March, 2014. This brought about UAH 1.4 bln of additional budget revenues and a rise in drug prices for the final consumer.

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66 http://www.lse.ac.uk/LSEHealthAndSocialCare/pdf/euroObserver/obsvol10no2.pdf


68 “As the result of introduction of 7% VAT on medicinal products and medical supplies the budget will receive UAH 1.4 bln every year”, Holos Ukrayiny newspaper, available at: <http://www.apteka.ua/article/299779>
Preferential VAT rates for medicinal products are widespread in the EU countries. According to EU Directive No. 2006/112/EC (Annex III), pharmaceutical products and certain medical supplies can be taxed at a lower VAT rate (but not less than 5%) set by national governments.

The EU member states were very cautious in introducing VAT on medicinal products and raising its rate. Some of the EU countries managed to get the right to apply VAT rates which are lower than 5%. For example, France applies 2.1% VAT for the prescribed medicinal products.

**Medicinal Product Reimbursement Schemes**

All the EU countries have various reimbursement schemes for the medicinal products as an instrument for ensuring their affordability for the patients. They work in the following way: A list of medicinal products for reimbursement is approved by the competent national regulatory authority responsible for financing the healthcare facilities. The size of reimbursement for each medicinal product on the list is determined using the reference/comparable price method. In order to include the medicinal product in the reimbursement list, one should prove its therapeutic efficacy, high quality and cost-effectiveness, and low application risks. Thus, medicinal products of low therapeutic efficacy and cost-efficiency, normally, are not covered by the reimbursement programs. The reimbursement rates can vary from 10 to 100% of the reference price of medicinal product. The patient gets a prescribed drug in the pharmacy with a “price discount” which is reimbursed for the pharmacy by a relevant institution (e.g. health insurance fund etc.).

The reimbursement system allows to increase affordability of medicinal products for the patients and promote price competition between the suppliers of medicinal products for the participation in the reimbursement programs.

Today, Ukraine is the only European country which does not offer wide reimbursement programs for medicinal goods for the public. So far, there were only pilot projects in this area. In 2012-2014, there was a successful pilot project of reimbursement for hypertension medicinal products (currently stopped). In the mid-2015, the insulin reimbursement program was piloted in 4 regions of Ukraine.

**Main developments in the economic regulation of pharmaceutical market**

During the last 5 years, economic regulation of pharmaceutical market in Ukraine was a subject of frequent changes which sometimes lacked consistency.

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Price Regulation

- **Registration and declaration of prices for public procurement of medicinal products**. In September 2011, the registration of wholesale prices for medicinal products and medical supplies included into the list for public procurement was introduced. The applicant was required to submit the calculation of the wholesale price for a medicinal product/medical device, the information on registered prices for medicinal products/medical supplies in the country of origin, also in CIS and EU countries with price regulations, and the copies of custom declaration and the invoice for medicinal products/medical supplies of foreign origin. However, in September 2012, the price registration procedure was abolished due to the difficulties in its administration. It was replaced by the price declaration procedure.

The next effort to increase affordability of medicinal products for public was undertaken in August 2014. A mandatory justification of prices for medicinal products procured with public funds was introduced together with the reference price mechanism for declaring changes of the wholesale prices. The declared wholesale price was calculated as an average of relevant prices in the countries from the reference list (a country of origin, Bulgaria, Moldova, Poland, Slovakia, Czech Republic, Latvia, Hungary, Serbia and Ukraine). However, due to the drawbacks in the selection of reference countries and numerous complaints from business this mechanism was abolished.

- **Maximum Trade Mark-Ups.** In October 2014, the maximum retail mark-up of 25% was established for the cheap medicinal products (with prices below UAH 12). Before, this group of medicinal products was not a subject for regulated retail (except for the cases of public procurement). The aim was to keep low prices on the essential medicinal products. However, this measure caused a risk of shortages of drugs from the cheapest segment, since under the new regulation the pharmacies could not fully cover their expenses.

- **The Mandatory Minimum Range of (Social) Medicinal Products Produced by Domestic Companies and Medical Supplies for Pharmacies.** The Order of the Ministry of Health of Ukraine from December 29, 2011, introduced the Mandatory Minimum Range of (Social) Medicinal Products Produced by Domestic Companies and Medical Supplies for Pharmacies. It was considered to be an instrument to lower the risks of replacement of cheap drugs by the expensive ones in the pharmacies. However, in 2015 this mechanism was proposed to be cancelled as outdated and inefficient. Under direct regulation of mark-ups, the absence of reimbursement schemes always causes risks of shortage of cheap medicinal products.

Taxation

- In 2014, 7% VAT was introduced for importing and distributing transactions with medicinal products and medical supplies. It was considered as a step forward in harmonizing Ukrainian legislation with the European standards. However, due to a
delay in adopting relevant by-laws, the imported medicinal products were subject to 20% taxation several months after the law was passed.

- The introduction of 7% VAT for importing medicinal products/ medical supplies for clinical trials reduced the costs of the latter and facilitated their development.
- In 2015, the import duty of 5% was introduced for a year on a wide range of products including the pharmaceutical ones. Together with a sharp devaluation of the national currency, this tax pushed up domestic prices of the imported drugs.

Reimbursement for Medicinal Products

The pilot project on reimbursement for anti-hypertension medicinal products was implemented in 2012-2014. Firstly, reference price mechanisms were used to regulate prices for anti-hypertension drugs. Then, partial reimbursement mechanism was introduced. The patients bought prescribed anti-hypertension medicinal products in the pharmacies at a discount price. At the end of the month, pharmacies were reimbursed from the local budgets based on the data from a special registers of the reimbursement transactions. This pilot project reduced the costs and improved the treatment of more than 12 million patients, since patients started taking their medications regularly under the supervision of their doctors. The Project was relatively inexpensive. The total cost was UAH 130 million (less than 0.25% of the consolidated annual healthcare budget).

The implementation of the project revealed administrative problems: The local authorities often delayed reimbursements to the pharmacies. It reduced incentives for pharmacies to participate in the Project. The drawbacks in registering and monitoring the data on the prescriptions in the pharmacies made it difficult to prevent some manipulations on the local level. In early 2015, the pilot reimbursement project was stopped for fiscal reasons.

Problems in economic regulation of pharmaceutical market

1. Price regulation
   - The abolishment of the reference price mechanism has weakened the wholesale price declaration arrangement, and consequently reduced the efficiency of state control over producers’ prices. The regulation of the wholesale - and retail mark-ups proved not to be sufficient for ensuring the affordability of medicinal products.
   - Presently, several regulatory documents (3 resolutions of the Cabinet of Ministers of Ukraine) address differently the same issues of public

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72 Under the project, the patient used a prescription provided by a physician to buy necessary medicinal products from the approved list at a discount and the pharmacies had the discount reimbursed from the State Budget according to the special methodology.
procurement of medicinal products\textsuperscript{73}. The absence of the unified regulatory rules causes much inconvenience for business.

- The regulation of prices is similar for original drugs and generics. As a result, generics sometimes cost more than the original drugs. It is a serious disincentive for bringing the innovative drugs to the Ukrainian market. Consequently, it restricts the access of patients to the innovative drugs.

- Setting maximum mark-ups in the segment of the cheapest medicinal products creates the risks of their crowding-out by more expensive medicinal products.

2. \textit{Taxation of medicinal products needs to be improved.}

- Law of Ukraine No. 1707-VII of 20 October 2014 “On Making Amendments to the Law of Ukraine “On Medicinal Products” allowed the circulation of the stock of finished medicinal products and utilization of finished preparations of APIs in the production process for which the validity term of marketing authorization has expired, till the expiration dates specified by the producer. This provision allowed to secure patients’ access to medicinal products and the rational use of drugs procured under the budget-financed programs. However, its implementation became problematic due to a legal conflict. The Tax Code allows applying 7\% VAT rate exclusively to the medicinal products included in the State Register of Medicinal Products. At the same time, the Order of MoH (No. 314 of May 8, 2014) a drug is removed from the State Register of Medicinal Products when its state registration expires. So, the circulation of medicinal products with the expired marketing authorization is allowed till the end of the shelf life. However, the expired market authorization causes the removal of medicinal products from the Register. Consequently, these products are taxed at 20\% VAT rate irrespectively of the reasons for removal (including delays in the re-registration procedure, or in receiving GMP certificate from the SSUMP).

On 4 June 2015, a draft resolution of the CMU appeared for public discussion on the official website of the MoH of Ukraine. It aims to amend the Regulation on the State Register of Medicinal Products (Resolution of the CMU No. 411 of 31 March 2004), and resolve this issue. However, this resolution is yet to be adopted.

- \textit{The possibility to manipulate VAT rates.} Customs authorities can inflate the customs value of medicinal products in order to increase the volume of

\textsuperscript{73} These are Resolution of the Cabinet of Ministers of Ukraine No. 955 of 17 October 2008 “On Measures Aimed to Stabilize Prices for Medicinal Products and Medical Supplies”; Resolution of the Cabinet of Ministers of Ukraine No. 333 of 25 March 2009 “On Some Issues Relating to Regulation of Prices for Medicinal Products and Medical Supplies”; and Resolution of the Cabinet of Ministers of Ukraine No. 240 of 2 July 2014 “On Procedures for Declaring Changes in Wholesale Prices for Medicinal Products and Medical Supplies”, as amended by Resolution of the Cabinet of Ministers of Ukraine No. 449 of 22 April 2015.
VAT on their import. Customs authorities have an exclusive right to decide to classify the products. For example, for customs clearance, a medicinal product can be classified as a dietary supplement with 20% VAT rate\textsuperscript{74}. Thus, medicinal products and medical supplies are often classified as categories subject to higher VAT rates\textsuperscript{74}.

- **The import duty.** The main effect of this duty is further increase in prices for the imported medicinal products. It is estimated that import duty imposed on the supply of medicinal products brought up to UAH 600 million in the first 6 months of 2015\textsuperscript{75}. Misclassification of the medicinal products during the customs clearance remains a crucial problem not only for VAT but also for the import duty calculation. The point is that medicinal products are subject to the reduced import duty rate of 5%, but the rate of 10% is applied to other categories of medical supplies. The example below demonstrates how reclassification of a medicinal product to a medical device increases its price by 25%.

**Table 7.2. Increase in the Price for an Imported Medicinal Product due to Taxation**

<table>
<thead>
<tr>
<th></th>
<th>Medicinal Product</th>
<th>Medical Device</th>
</tr>
</thead>
<tbody>
<tr>
<td>VAT for import</td>
<td>7%</td>
<td>20%</td>
</tr>
<tr>
<td>Import duty</td>
<td>5%</td>
<td>10%</td>
</tr>
<tr>
<td>Import fee</td>
<td>0%</td>
<td>6.5%</td>
</tr>
<tr>
<td>Total increase in the</td>
<td>12%</td>
<td>36.5%</td>
</tr>
<tr>
<td>price</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Such manipulations in drug classification promote corruption, and put an additional regulatory burden on business. In May 2015, the CMU has instructed the MoH to adopt a resolution on the list of medicinal products which are not subject to the additional import duty. This resolution has not been approved.

**Recommendations**

<table>
<thead>
<tr>
<th>Action</th>
<th>Responsible agency</th>
<th>Timeframe</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Price Regulation</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>- Unify rules for regulating prices for medicinal products procured with public funds;</td>
<td>MOH, CMU</td>
<td>2016</td>
<td>High</td>
</tr>
<tr>
<td>- Restore the mechanism of reference prices to control the</td>
<td>CMU</td>
<td>2016</td>
<td>high</td>
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</tbody>
</table>


\textsuperscript{75} Based on amount of sales of imported medicinal products in the first half of 2015 (UAH 12.5 billion) and the import duty rate of 5%.
wholesale prices for medicinal. Pay a special attention to the choice of reference countries. Make the reference price mechanism easy to use by business.

- Introduce the maximum price for generics with a fixed discount compared to the declared price of the original drug.

#### 2. Reimbursement for Medicinal Products

- Renew the reimbursement project for anti-hypertension medicinal products.
- Develop a step-by-step plan to extend the list of medicinal products covered by the reimbursement programs.
- Implement e-technologies for issuing and registering medical prescriptions.

<table>
<thead>
<tr>
<th>Agency</th>
<th>Year</th>
<th>Priority</th>
</tr>
</thead>
<tbody>
<tr>
<td>CMU</td>
<td>2017</td>
<td>high</td>
</tr>
<tr>
<td>MoH</td>
<td>2017</td>
<td>medium</td>
</tr>
<tr>
<td>MoH</td>
<td>2017</td>
<td>medium</td>
</tr>
<tr>
<td>CMU</td>
<td>2017</td>
<td>medium</td>
</tr>
</tbody>
</table>

#### 3. Taxation

- Apply 7% VAT to medicinal products in circulation with the expired market authorizations until the expiration of the consumption date.
- Clarify the rules for classification of medicinal products for custom clearance concerning the VAT rates. Deprive customs authorities of the possibility to manipulate with different VAT rates for medicinal products.
- Refrain from further increases in the VAT rates for medicinal products in the short run.

<table>
<thead>
<tr>
<th>Agency</th>
<th>Year</th>
<th>Priority</th>
</tr>
</thead>
<tbody>
<tr>
<td>MoH, CMU</td>
<td>2016</td>
<td>High</td>
</tr>
<tr>
<td>MoH, CMU</td>
<td>2016</td>
<td>High</td>
</tr>
<tr>
<td>CMU</td>
<td>2016</td>
<td>High</td>
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</tbody>
</table>
## Key policy recommendations

<table>
<thead>
<tr>
<th>Area</th>
<th>Action</th>
<th>Responsible agency</th>
<th>Time frame</th>
<th>Priority</th>
<th>Ease of implementation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-registration procedures</td>
<td>1. Implement the one-stop-shop principle, creating the conditions for the applicant to submit the application materials and receive all the necessary permits for conducting clinical trials in one place. Establish transparent regulations for communication between the applicants and the experts during the assessment of clinical trial dossier.</td>
<td>MoH, SEC</td>
<td>2016</td>
<td>high</td>
<td>easy</td>
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<td></td>
<td>2. Cancel the function of SEC’s advisory bodies (Scientific Expert and Science and Technology Councils to confirm individual expert assessments of the clinical trial dossier. Implement best practices of EU countries when decisions on allowing the conduct of clinical trials are based on the individual expert assessments (with a high personal responsibility of an expert for the assessment results).</td>
<td>MoH</td>
<td>2016</td>
<td>high</td>
<td>easy</td>
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<td></td>
<td>3. Ensure the effective implementation of the current legislation concerning customs valuation and taxation of imports of medicinal products, medical supplies and/or medical equipment for clinical trials. Establish an electronic document flow between the governmental agencies (MoH, SEC and fiscal authorities), which will significantly accelerate all procedures</td>
<td>CMU, MoH</td>
<td>2016</td>
<td>high</td>
<td>medium</td>
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<tr>
<td></td>
<td>4. Enable an electronic submission of application materials of clinical trials</td>
<td>MoH</td>
<td>2016</td>
<td>high</td>
<td>easy</td>
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<tr>
<td></td>
<td>5. Create a full-fledged national register of clinical trials of medicinal products with the information on the completed projects and summary of their results, on-going projects, and all</td>
<td>MoH</td>
<td>2016</td>
<td>high</td>
<td>easy</td>
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<tr>
<td>Registration procedures</td>
<td></td>
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<tr>
<td>1. Ensure the issuing of permanent marketing authorizations for medicinal products that were re-registered after the Law No. 1707-VII (of November 5, 2014) was enacted. Make an automatic replacement already issued marketing certificates by the permanent ones after completion of this procedure.</td>
<td>MoH</td>
<td>2016</td>
<td>high easy</td>
<td></td>
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<tr>
<td>2. Abolish the requirement to have a GMP conformity confirmation from the national regulatory body for the foreign manufacturers that have GMP certificates issued by the competent authority of the PIC/S member. To cancel this requirement amend the following regulatory acts: - Resolution of the Cabinet of Ministers of Ukraine No. 902 of</td>
<td>CMU, MoH</td>
<td>2016</td>
<td>high easy</td>
<td></td>
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</table>
September 14, 2005 “On Approval of the Procedure for Carrying out State Control of the Quality of Medicinal Products Brought into the Customs Territory of Ukraine”,
- Order of the Ministry of Health of Ukraine No. 1130 of December 12, 2012 “On Approval of the Procedure for Confirmation of Medicinal Products Manufacturing Conditions Compliance with Good Manufacturing Practice Requirements”.

<p>| 3. Conclude intergovernmental agreements on the mutual recognition of GMP certificates | CMU, MoH | 2016-2018 | high | medium |
| 4. Ensure full implementation of the one-stop-shop principle in registration of drugs. The applicant should be able to submit all the requested materials and receive a positive or negative decision in one shop. Provide a regulatory framework for the interaction between the applicants and the experts during the expert reviewing of the registration dossier. | MoH | 2016 | high | easy |
| 5. Provide for an electronic document flow between the MoH, SEC and SSUMP to improve their coordination in the registration procedures. Provide for electronic submission of registration materials by the applicants. | CMU, MoH, SEC, SSUMP | 2016 | high | easy |
| 6. Introduce a simplified procedure for insignificant amendments of the registration dossier based on the declarative principle: do-tell principle - for minor changes of type IA, and tell-wait-make principle – for minor changes of type IB. | MoH | 2016 | high | easy |
| 7. Cancel the function of SEC’s advisory bodies (Scientific Expert and | MoH | 2016 | high | easy |</p>
<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Initiator</th>
<th>Year</th>
<th>Priority</th>
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<tbody>
<tr>
<td>Science and Technology Councils) to confirm individual expert assessments of the registration dossiers. Implement best practices of EU countries when decisions on drug registration are based on the individual expert assessments (with a high personal responsibility of an expert for the assessment results). This will make the decision-making process shorter and more transparent.</td>
<td>CMU, MoH</td>
<td>2016</td>
<td>high, medium</td>
</tr>
<tr>
<td>8. Develop and introduce a transparent mechanism for appealing the resolutions of MoH and SEC concerning the drug registration. Introduce the liability of MoH and SEC for the delays (over the official deadlines) in expert reviews of the registration dossier and making decisions on drug registration.</td>
<td>CMU, MoH</td>
<td>2016</td>
<td>high</td>
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<tr>
<td>9. Clarify the responsibilities of MoH and SEC in protecting the exclusivity of the registration dossier. Introduce the liability of the regulatory authorities for breaching the privacy of the registration dossier</td>
<td>CMU, MoH</td>
<td>2016</td>
<td>high, easy</td>
</tr>
<tr>
<td>10. For strengthening the protection of intellectual property rights consider the introduction of a patent protection system based on the US model.</td>
<td>MoH, CMU, Verhovna Rada</td>
<td>2018</td>
<td>medium</td>
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<tr>
<td>11. Consider the introduction of Bolar provision for enhancing the access of new international or domestically-produced generics to the Ukrainian market.</td>
<td>MoH, CMU, Verhovna Rada</td>
<td>2018</td>
<td>medium</td>
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<tr>
<td>12. Abolish mandatory registration of API and products in bulk (respective changes need to be made to the Law of Ukraine “On Medicinal Products” and corresponding by-laws). It will reduce the level of regulatory burden on business entities and increase their flexibility in choosing appropriate suppliers. Ensure that 7% VAT rate is</td>
<td>CMU, Verhovna Rada</td>
<td>2016</td>
<td>high, medium</td>
</tr>
<tr>
<td>Licensing of Economic Activities</td>
<td>1. Complete the restructuring and ensure full operations of the newly established State Service on Medicinal Products and Drugs Control with clear and transparent functions.</td>
<td>CMU, MoH</td>
<td>2016</td>
</tr>
<tr>
<td>2. Adopt new licensing terms with a clear and exhaustive list of requirements for businesses.</td>
<td>CMU, MoH</td>
<td>2016</td>
<td>High</td>
</tr>
<tr>
<td>3. Cancel import licensing for medicinal products for business entities from countries with a strict regulatory system (EU member states and PIC/S members).</td>
<td>CMU, MoH</td>
<td>2016</td>
<td>High</td>
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<tr>
<td>4. Cancel the confirmation of GMP certificate by the SSUMP for foreign companies that hold GMP certificate issued by the competent authority of a PIC/S member state.</td>
<td>CMU, MoH</td>
<td>2016</td>
<td>High</td>
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<tr>
<td>5. Consider allowing the institutions other than pharmacies to distribute certain types of popular non-prescription medicinal products that do not require special storage and dispense conditions.</td>
<td>CMU, Verhovna Rada</td>
<td>2017</td>
<td>Medium</td>
</tr>
<tr>
<td>Post-Registration control of quality and circulation of Medicinal Products</td>
<td>1. Enhance the transparency of quality control procedure for the imported medicinal products by improving criteria for sending medicinal products for the laboratory tests. The list of criteria should be clear, unambiguous and exhaustive in order to minimize the risks of an arbitrary decision by control agencies and reduce the “regulatory costs” for business</td>
<td>CMU, MoH</td>
<td>2016</td>
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<td>2. Define and implement the liability mechanism (including financial liability) for the state control agencies for unjustified sending of the medicinal products</td>
<td>CMU, MoH</td>
<td>2016</td>
<td>high</td>
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</table>
to the laboratory tests during the import quality control procedures.

<table>
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<tr>
<th>3.</th>
<th>Adopt by-laws to regulate the termination of marketing authorizations for medicinal products (based on requirements of the Directive 2001/83/EC) for a clearly defined list of cases.</th>
<th>CMU, MoH</th>
<th>2016</th>
<th>High</th>
<th>easy</th>
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<tr>
<td>4.</td>
<td>Replace the incoming quality control in pharmacies by an introduction of the GPP quality management system</td>
<td>CMU, MoH</td>
<td>2016</td>
<td>Medium</td>
<td>medium</td>
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<tr>
<td>5.</td>
<td>Replace the quality control of pharmacies by the quality control of medicinal goods focusing on manufacturer’s responsibility (including fines). Implement the European approach of taking samples of medicinal products in pharmacies for quality control according to the regular plans of inspections that are publicly available</td>
<td>CMU, MoH, SSUMP</td>
<td>2016</td>
<td>Medium</td>
<td>medium</td>
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<tr>
<td>6.</td>
<td>Refrain from the ban on quality control inspections of manufacturers and traders of medicinal products.</td>
<td>CMU, Verkhovna Rada</td>
<td>2016</td>
<td>Medium</td>
<td>easy</td>
</tr>
<tr>
<td>7.</td>
<td>Reconsider the “warning” requirement while conducting scheduled inspections of the medicinal products in circulation. The scope and frequency of the inspections should be risk-related, and the mandatory warning of business before the inspection might be cancelled.</td>
<td>CMU, MoH</td>
<td>2017</td>
<td>Medium</td>
<td>medium</td>
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<tr>
<td>8.</td>
<td>Make an audit of SSUMP’s activities and functions.</td>
<td>CMU, MoH</td>
<td>2016</td>
<td>High</td>
<td>medium</td>
</tr>
<tr>
<td>9.</td>
<td>Make sure that control functions of the SAUMP are covered by sufficient financial resources. In case of necessity, reconsider both functions and financing. Use the outsourcing of tests of medicinal products to the certified laboratories on the basis of transparent tariffs for services. Consider raise in registration and re-registration fees for medicinal products as a source of additional finance for the system of quality control.</td>
<td>CMU, MoH</td>
<td>2016</td>
<td>High</td>
<td>medium</td>
</tr>
<tr>
<td>11.</td>
<td>Develop the assessment criteria for public monitoring the efficiency of quality control system for medicinal products. These criteria should be result-oriented and show among others the results in fighting against the low-quality and counterfeit drugs. Ensure public access to the information on performance indicators of the control agencies. It will enhance the transparency of quality control system for medicinal products</td>
<td>CMU, MoH, Professional Pharmaceutical Associations</td>
<td>2016</td>
<td>High</td>
<td>medium</td>
</tr>
<tr>
<td>12.</td>
<td>Conclude the bilateral agreements with the governments of PIC/S member states on the</td>
<td>CMU, MoH</td>
<td>2016-2017</td>
<td>high</td>
<td>medium</td>
</tr>
</tbody>
</table>
mutual recognition of GMP certificates. Introduce the indicator of signed bilateral agreements as one of the success indicators of the CMU’s performance.

<table>
<thead>
<tr>
<th>The institutional framework for regulating production and distribution of medicinal products</th>
<th>1. Remove the artificial division of the registration/re-registration functions of medicinal products between two agencies.</th>
<th>CMU, MoH</th>
<th>2016</th>
<th>High</th>
<th>Medium</th>
</tr>
</thead>
<tbody>
<tr>
<td>a) transfer the authority of making final decisions to register medicinal products to the State Expert Center;</td>
<td>MoH</td>
<td>2016</td>
<td>High</td>
<td>Medium</td>
<td></td>
</tr>
<tr>
<td>b) Increase the transparency of the decision-making on registration of medicinal products by canceling the function of SEC’s advisory bodies (Scientific Expert Council, Science and Technology Council of the State Expert Center) to confirm the reports of individual experts.</td>
<td>SEC, MoH</td>
<td>2016</td>
<td>High</td>
<td>Easy</td>
<td></td>
</tr>
<tr>
<td>c) Improve the selection procedure for the experts in SEC who are responsible for the examination of registration dossiers. The selection procedure should become more competitive and focus on professional criteria. Introduce a regular expert rotation arrangement.</td>
<td>SEC, MoH</td>
<td>2016</td>
<td>high</td>
<td>medium</td>
<td></td>
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<tr>
<td>2. Introduce an exhaustive list of criteria for requesting additional information / making tests from business during the regulatory</td>
<td>CMU, Verhovna Rada</td>
<td>2016</td>
<td>High</td>
<td>easy</td>
<td></td>
</tr>
<tr>
<td>13. Consider the implementation of labelling of prescription medicinal products that enter the Ukrainian market in order to facilitate detection of counterfeit medicinal products and fight corruption in public procurements of medicinal products.</td>
<td>CMU, MoH, Verhovna Rada</td>
<td>2019</td>
<td>Medium</td>
<td>medium</td>
<td></td>
</tr>
</tbody>
</table>
Develop an efficient liability mechanism of the regulatory agencies for missing the deadlines of the regulatory procedures or requesting additional unjustified information/making additional tests for business within the regulatory procedures.

3. Ensure the electronic submission of applications, and electronic flow of all the documents related to the regulation of pharmaceutical market between the regulatory agencies.

4. Implement the one-stop-shop principle on the interdepartmental basis for receiving any type of regulatory permit for business in the pharma market. This may be, for example, an interdepartmental state institution “Center of Administrative Services in Healthcare” which will cooperate with all regulatory agencies and provide a complete package of services concerning:
- marketing authorizations for medicinal products;
- decisions to conduct clinical trials;
- licenses for production of medicinal products in pharmacies, medicinal products retail/wholesale facilities;
- licenses for importing medicinal products (except for API);
- licenses for cultivating plants included in the list of drugs, psychotropic substances and precursors, approved by the Cabinet of Ministers of Ukraine;
- licenses for developing, producing, manufacturing, storing,
transporting, procuring, selling importing/exporting, using and destroying the drugs, psychotropic substances and precursors included in the abovementioned list;
- permits for importing unregistered medicinal products;
- GLP, GCP, GDP and GPP certificates;
- GMP certificates and opinions as to conformity with GMP requirements

5. Consider using the declarative principle for some of the regulatory procedures (e.g. re-licensing, expanding business activities subject to licensing, entering data on the licensee’s places of business subject to licensing in the Unified State Register of Legal Entities and Sole Proprietors, amending registration materials)

| MoH, CMU | 2016 | high | easy |

6. Enhance the institutional capacity of regulatory agencies by clear allocation of their functions after conducting a thorough audit of functions; eliminate duplications of functions and provide an adequate functions-related financing. Consider raise in the registration fee and as an additional source of financing.

| MoH, CMU | 2016-2017 | high | medium |

**Economic Regulation of the Pharmaceutical Market**

1. Price Regulation
   - Unify rules for regulating prices for medicinal products procured with public funds;
   - Restore the mechanism of reference prices to control the wholesale prices for medicinal. Pay special attention to the

| MOH, CMU | 2016 | High | Easy |
| CMU | 2016 | High | Medium |
choice of reference countries. Make the reference price mechanism easy to use by business.

- Introduce the maximum price for generics with a fixed discount compared to the declared price of the original drug.

<table>
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<tr>
<th>2. Reimbursement for Medicinal Products</th>
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<tr>
<td>• Renew the reimbursement project for anti-hypertension medicinal products.</td>
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<td>• Develop a step-by-step plan to extend the list of medicinal products covered by the reimbursement programs.</td>
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<tr>
<td>• Implement e-technologies for issuing and registering medical prescriptions</td>
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<th>3. Taxation</th>
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<tr>
<td>• Apply 7% VAT to medicinal products in circulation with the expired market authorizations until the expiration of the consumption date.</td>
</tr>
<tr>
<td>• Clarify the rules for classification of medicinal products for custom clearance concerning the VAT rates. Deprive customs authorities of the possibility to manipulate with different VAT rates for medicinal products.</td>
</tr>
</tbody>
</table>
Refrain from further increases in the VAT rates for medicinal products in the short-run.

List of Referenced Legislative and Regulatory Acts


4. Law of Ukraine No. 269-VIII dated 19 March 2015 “On Making Amendments to Some Laws of Ukraine with regard to Ensuring Timely Access of Patients to Required Medicinal Products and Medical Supplies through the Carrying-out of Public Procurements with Involvement of Specialized Procuring Institutions”.

the Circulation of Medicinal Products and State Control of the Quality of Medicinal Products Brought into the Customs Territory of Ukraine”.


10. Resolution of the Cabinet of Ministers of Ukraine dated 26 May 2005 No. 376 “On Approval of the Procedure for State Registration (Re-registration) of Medicinal Products and Amounts of the Duty for their State Registration (Re-registration)”.


Control of the Quality of Medicinal Products Brought into the Customs Territory of Ukraine”.


18. Resolution of the Cabinet of Ministers of Ukraine No. 333 dated 25 March 2009 “On Some Issues Relating to Regulation of Prices for Medicinal Products and Medical Supplies”.


20. Order of the Ministry of Health of Ukraine No. 441 dated 01 November 2001 “On Approval of the Procedure for Carrying out the Preclinical Investigation of Medicinal Products, the Procedure for Identification of Entities that Carry out the Preclinical Investigation of Medicinal Products”.

21. Order of the Ministry of Health of Ukraine No. 95 dated 16 February 2009 “On Approval of Documents on Ensuring the Quality of Medicinal Products”.


27. Order of the Ministry of Health of Ukraine No. 245 dated 17 May 2007 “On Approval of the Procedure for Identification of Specialized Healthcare Facilities where Clinical Trials on Medicinal Products May Be Conducted”.


32. Order of the Ministry of Health of Ukraine dated 26 April 2011 No. 237 “On Approval of the Procedure for Bringing into the Territory of Ukraine Unregistered Medicinal Products, Standard Samples and Reagents”.

33. Order of the Ministry of Health of Ukraine dated 09 September 2014 No. 635 “On Approval of the Record-keeping Guidelines for Medicinal Products and Medical Supplies in Health Facilities”

34. Order of the USSR Ministry of Health No. 747 dated 02 June 1987 "On Approval of the Instruction on Record-keeping on Medicinal Products, Bondages and Medical Supplies in Healthcare Facilities Funded by the USSR State Budget".
35. Order of the Ministry of Health of Ukraine No. 1130 dated 27 December 2012 “On Approval of the Procedure for Confirmation of Medicinal Products Manufacturing Conditions Compliance with Good Manufacturing Practice Requirements”.


39. Guidelines ST-N of the Ministry of Health of Ukraine 424.0:2015 “Medicinal Products. Good Manufacturing Practice” which introduced amendments to the section “Premise and Equipment”, “Technological Process”, “Quality Control” and other (as brought into effect in the EU starting September and October 2014 and march 2015).

40. Order of the Ministry of Health of Ukraine No. 677 dated 29 September 2014 “On Approval of the Procedure for Quality Control of Medicinal Products in Wholesale and Retail Trade”.

41. Resolution of the Cabinet of Ministers of Ukraine No. 260 dated 3 February 2010 “Some Issues of State Control of the Quality of Medicinal Products”

42. Order of the Ministry of Health of Ukraine dated No. 809 dated 22 November 2011 “On Approval of the Procedure for Establishment of Prohibition (Temporary Prohibition) and Renewal of the Circulation of Medicinal Products within the Territory of Ukraine”.

43. Order of the Ministry of Health of Ukraine dated No. 677 dated 29 September 2014 “On Approval of the Procedure for Quality Control of Medicinal Products in Wholesale and Retail Trade”.

44. Order of the Ministry of Health of Ukraine dated No. 584 dated 16 December 2003 “On Approval of the Rules for Storage and Quality Control of Medicinal Products in Healthcare Facilities”.
45. Order of the Ministry of Health of Ukraine dated 26 December 2006 No. 898 “On Approval of the Surveillance over Adverse Reactions to Medicinal Products Permitted for Medical Use”.


47. DIRECTIVE 2001/20/EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medical supplies for human use.


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Annexes

Annex 1
ASSESSMENT OF THE REGULATORY PROBLEMS ON THE UKRAINIAN MARKET FOR MEDICINAL PRODUCTS

Findings of Expert Interviews with Representatives of Pharmaceutical Companies

The Survey was conducted upon request from the Analytical Centre “New Social and Economic Policy” within the framework of preparation of the analytical report “Regulatory Reforms on the Ukrainian Pharmaceutical Market” under Contract No. 7175729 by the Ukrainian office of the international research agency “IFAK Institute” in October 2015.

Empirical data was collected through expert interviews with 32 representatives of Ukrainian pharmaceutical market players.

The surveyed group included:
- Foreign manufacturers of medicines – 6 experts;
- Domestic manufacturers of medicines – 10 experts;
- Distributors / importers of medicines – 8 experts;
- Retail distributors – representatives of large pharmacy chains – 5 experts;
- Medicine wholesalers – 3 experts.

The surveyed representatives come from large (53%, 17 companies), middle-size (38%, 12 companies) and small (9%, 3 companies) businesses.

The surveyed representatives come from businesses that have been active on the Ukrainian pharmaceutical market for less than 3 years (3%, 1 company), 5 to 10 years (19%, 6 companies) and more than 10 years (78%, 25 companies).

Ranking regulatory barriers: According to those polled, the companies most often face regulatory problems while undertaking registration of drug and facing quality control of marketed medicines (81% of the respondents); and in the field of price regulation (75% of the respondents), taxation and licensing (72% and 69% respectively). Most significant were considered the problems related to economic regulation of the market: 65% of the experts who faced problems in taxation considered them very significant/rather significant. The same applies to 50% of those who faced problems in price regulation. 58% of the experts whose companies faced problems in registration considered them very or rather significant. Two thirds of the companies that faced problems in clinical or pre-clinical trials considered them very significant and rather significant.

Assessing the changes in regulatory arrangements of the Ukrainian pharmaceutical sector over the last 5 years, the experts pointed out that, in general, there were sound changes in regulations of the pharma market. Most positive developments, in their opinion, occurred in registration procedures (46% of those who replied). In some areas
the situation worsened. It concerns taxation and price regulation (78% and 63% of the responding experts correspondingly).

A serious problem is a delay in timely passing by-laws that are necessary for the implementation of the adopted legislative decisions. This concerns changes in registration procedures (68% of those who replied replied perceive them very / rather significant), licensing (62%) and quality control the of marketed medicines (60%).

**Pre-registration procedures:** 40% of the companies that faced problems in pre-clinical and clinical trials relate them to non-transparency in expert review, non-compliance with the expert review deadlines, and out-of-pocket payments. In addition, 35% of the companies that faced problems in pre-clinical and clinical trials pointed at the insufficient qualifications of experts who conducted the reviews.

In order to improve the pre-registration procedures, the experts proposed the simplification of the procedures regulating pre-clinical / clinical trials.

**Registration procedures:** The most widespread problems turned to be violations of deadlines for expert review, non-compliance with legal deadlines for decision-making on registration/re-registration of medicines, the need to duplicate GMP confirmation in Ukraine (for foreign companies with GMP certificate from PICs members). These problems were mentioned by 67% of respondents.

Among the most significant problems there were the need to duplicate GMP confirmation in Ukraine (79%), a violation of the deadlines for re-registration of a medicine (72%) and a violation of the expert review deadlines (70%).

Being asked about recommendations, the respondents proposed to cancel the confirmation of individual expert reports by the Scientific Expert Council of the State Expert Center, and recognize the registrations already made in the EU countries and US.

**Licensing:** The most often mentioned problems were the lack of a declarative principle in licensing (71% of the respondents), non-transparency in refusals of licences (62%), and the arbitrariness in making decisions on licensing in regulatory authorities (57% respectively). 67% of the respondents consider licensing of imports to be a redundant procedure which does not make sense from the perspective of securing the quality of drugs.

The experts’ proposals on the improvement of the licensing procedure included the need to start full operations of the licensing authority; follow the European standards in licensing; and enhance the qualifications of staff in licensing bodies.

**Post-registration quality control:** In this area the most significant problems were the lack of clear-cut criteria for taking medicines for laboratory testing and extra costs incurred by business when the quality of medicines is checked (76% of the respondents). A long procedure for quality control of medicines, the impact of subjective factors on quality control results, the lack of well-equipped laboratories for testing drugs quality – these problems were mentioned by 72% of the respondents.

The most significant problem was insufficient number of well-equipped laboratories to perform drugs quality tests (71% of the respondents).

In order to improve the procedures for quality control, the respondents propose to improve the capcacity of the laboratories for quality tests.

**Institutions of state regulation:** According to the experts, a one-stop-shop approach would simplify all regulatory procedures, provided this arrangement is transparent. An
introduction of one-stop-shop approach in registration was accepted most positively by 85% of those who replied to the question. The opinion on the establishment of a single regulatory body was not unanimous. The single regulatory body was favored by 50% of the polled who considered it beneficial for a further simplification of the regulatory procedures in the future. Another part of the experts (40%) stood against the single regulatory body fearing that it would elevate the risks of corruption. More than half of the polled (56%) believed that the lack of well-coordinated changes in the regulations for pharmaceutical market impeded business operations.