Performance Audit of Regulatory System of Drugs and Pharmaceutical Activities

PERFORMANCE AUDIT REPORT

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The presence of high quality, efficient and safe drugs is essential for the healthcare system in the country. Advanced system and standardized procedures that regulate drug activities are on high level in the world's leading countries due to the purpose that pharmaceutical activities, authorization and circulation of pharmaceutical product on the market should meet the acceptable standards and the response to the identified risks shall be prompt.

For us, it is one of the priorities to have accessible, high quality, safe and effective drugs for consumers of Georgia. Based on this, it is possible to create an appropriate model by developing a regulatory system based on international standards that ensures high quality of the drugs on the market, which should ease financial accessibility of pharmaceutical products and jeopardize open market.

In order to protect consumers from the alarming and grave results, it is important to ensure measures that eliminate the risks and problems and will enable the Agency to identify hazardous, counterfeit, substandard drugs or ineffective use of the products on time and increase efficiency.

The present audit report discusses the problems related to drug and pharmaceutical regulatory system, their causes and issues corresponding recommendations.

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Performance Audit Report

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Add: 0144, Tbilisi: N96, Saint Queen Ketevan Ave.

Contents

Glossary:

CPP - Certificate of the Pharmaceutical Product

EMA - European Medicines Agency

FDA - Food and Drug Administration

FIP - The International Pharmaceutical Federation

GCP - Good Clinical Practice

GDP - Good Distribution Practice

GLP - Good Laboratory Practice

GMP - Good Manufacturing Practice

GPP - Good Pharmaceutical Practice

GPVP - Good Pharmacovigilance Practice

MHRA - Medicines and Healthcare products Regulatory Agency

NCDC - National Center for Disease Control and Public Health

OECD - The Organization for Economic Co-operation and Development

OTC - Over-the-Counter drugs

PIC/S - The Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme

PV - Pharmacovigilance

WHO – The World Health Organization

WTO - World Trade Organization

Regulatory Agency - LEPL State Regulation Agency for Medical Activities, or state regulatory agencies of drugs and pharmaceutical activities of other countries.

Executive Summary

Due to global challenges, the role of pharmaceutical products intended for human use is huge in the modern world, as the risk of low quality, ineffective and hazardous pharmaceutical products are increased. The risk is especially high for low and middle-income countries, where the regulatory instruments and the quality control system does not ensure risk prevention and timely response.

Efficient, timely and accessible treatment using pharmaceutical products depends on a number of factors: defining drug regulatory policy, quality, efficacy and safety of the pharmaceutical product in the country, the price of the drugs, qualified medical personnel, and improving health system efficiency.

The quality and accessibility of the pharmaceutical products are closely related concepts since they can have the same influence on health.

The relationship between the regulatory system and the influence of the pharmaceutical product on public health is the following: pharmaceutical product is less beneficial and more harmful to public health when environment is not regulated, at the same time in over-regulated environment the accessibility to pharmaceutical product is lower and accordingly less beneficial. Accordingly, both quality and accessibility of the pharmaceutical products are optimal to ensure healthy population. This indicates that optimality and balance are the key components of the system.

Timely treatment with high quality, effective and safe pharmaceutical products may improve the health condition and reduce the costs of expensive medical services, such as emergency care, inpatient hospital care costs – surgery and long-term healthcare.

Unified regulatory system covers following pharmaceutical activity – manufacturing, clinical trial, the activity related to drug realization, promoting authorization of pharmaceutical products and its further monitoring

In 2009, amendments in Georgian pharmaceutical regulatory system removed the imposed barriers and gave wider import opportunities to companies, which resulted in increase of imports of pharmaceutical products.

Legislation amendments that promoted simplified regulatory mechanisms facilitated access to pharmaceutical market. However, it is important to implement such control mechanisms that on one hand will not impose artificial barriers for the pharmaceutical market accessibility and on the other hand will become the guarantee for the protection of the quality, efficacy and safety of the pharmaceutical product.

In Georgia the drugs and pharmaceutical activities are regulated by LEPL state regulation agency (the agency) for medical activities under the Ministry of Labor, Health and Social Affairs of Georgia.

The State Audit Office of Georgia showed interest in country's drug regulatory system, in order to appraise the quality, efficacy and safety of the pharmaceutical products.

For this purpose, the State Audit Office of Georgia examined issues related to regulatory system – existing legislation and the activities implemented by the agency.

The audit revealed that the drug regulatory policy and activities implemented by the agency does not ensure the quality, efficacy and safety of the pharmaceutical products.

The main purpose of pharmaceutical regulation, which is delivering high quality service to public is realized by three main functions:

- Developing standards;
- Developing and implementing effective regulatory instruments to ensure the adherence of standards;
- Monitoring and evaluating standards.

The audit revealed that regulatory system in Georgia falls significantly behind the recognized standards and best practices.

According to the existing law and legislation, permission conditions does not guarantee appropriate manufacturing and circulation of drugs. It appears to be easy to start pharmaceutical business while the control mechanisms are weak.

The scope of the drug authorization is restricted by legislation. There are shortcomings in national and recognition authorization procedures that have impact on proper quality control of pharmaceutical product.

Activities implemented by the agency do not ensure the monitoring of adverse reactions, side effects and risk-benefit balance of drugs. Accordingly, there is no evaluation system set in order to determine the efficacy and safety of the drug in cooperation with interested parties – patients, physicians, NCDC and other organizations.

As there are shortcomings in regulations, the resources of the agency are spent on the control of the pharmaceutical activities that does not lead to appropriate results.

There are some impediments for the agency to have timely, accurate information about the circulation of pharmaceutical product, about subjects involved in pharmaceutical activities and based on this to identify the risks in a proper way:

- Permission conditions under the existing regulations are incomplete; accordingly, there is narrow scope of pharmaceutical activities that are under the permission conditions. Permission issued for certain activities are unlimited;

- Regulatory system does not provide the methodological aspects of the inspection such as re-inspection, routine inspection mechanism, inspectorate resource planning in relation to inspection coverage and their differentiation according to activities. In addition, risk assessment criteria is incomplete;
- Pharmacovigilance system is not implemented; information about side effects and adverse drug reaction is not recorded.

This report discusses the regulatory system of the drugs and pharmaceutical activities. Based on analysis and conclusions, appropriate recommendations are issued. State audit office believes that the implementation of the recommendations will assist the Ministry and the Agency for solving problems and improve existing conditions in the system.

1. Introduction

1.1 Audit Motivation

Performance audit topic - Regulatory system of drugs[1] and pharmaceutical activities was selected as an area of concern and high public interest. The World Health Organization (WHO) considers the regulation of the drugs and pharmaceutical activities as a major challenge for developing countries and urges countries to ensure the efficient regulation of this sector by determining and improving deficiencies in regulations.

By the end of 2009, Georgia significantly amended regulation system of the drugs and pharmaceutical activities.

In recent period, various studies have been published by public sector in terms of quality of pharmaceutical products. [2]

Based on the reports published by various non-governmental organizations, the media actively discuss the effectiveness of the regulation of pharmaceutical activities, as well as the efficiency of quality management and control systems of the pharmaceutical product in the country.

The circumstances revealed during the study will help the ministry to form better regulation system and to promote its further development.

1.2 Audit Objective and Audit Questions

Audit objective is to study the efficiency of the regulatory system (existing regulations and activities are carried out by regulatory entity – LEPL State Regulation Agency for Medical Activities under the Ministry of Labor, Health and Social Affairs of Georgia) of the drugs and pharmaceutical activities, to prepare a report based on it and to issue relevant recommendations.

The recommendations given to the auditee will be based on the results obtained by the audit team. These recommendations will be directed to improve the activities of regulatory agency and to eliminate the shortcomings of the regulatory system revealed during the study.

[1] Pharmaceutical product (medicinal product) – drug or physiologically active, naturally or synthetically derived substance, or their combination, which are allowed for medical use, including complementary, biologically active additive and paramedical drugs which are voluntarily authorized by national procedure. For the purpose of audit, medicinal product for human use will be used as drug, medicinal product or pharmaceutical product.

[2] Transparency International Georgia – Georgian pharmaceutical market, International Foundation CURATIO – price changes of drugs in 2009-2011, NNLE Human Law Freedom – analysis and recommendations from the information about violations of established rules of circulation of pharmaceutical products under special control and drugs equalized with them.

By using audit procedures designated to achieve the objective of the audit, the State Audit Office of Georgia responded to the following main question:

› To what extent is ensured the quality, efficacy and safety of pharmaceutical products by the regulatory system of drugs and pharmaceutical activities? [3]

To answer this question audit team studied the legislative and procedural mechanisms of the pre-market and the post-market control of the pharmaceutical products, activities implemented by LEPL State Regulation Agency for Medical Activities.

1.3 Audit Scope and Methodology

Performance audit of the drugs and pharmaceutical activities encompasses 2012-2013 years. For the purposes of the audit, the audit period has also been used (Q1 through Q3 of 2014).

Auditee is the LEPL State Regulation Agency for Medical Activities under the Ministry of Labor, Health and Social Affairs of Georgia.

To obtain answers to main audit questions, the audit procedures have been developed, using which the regulatory system of the drugs and pharmaceutical activity and state program management of quality control of pharmaceutical products were studied.

Audit team used various methods to study the regulatory system and driving factors of the current trends:

› Introduction and analysis of the available and internationally accepted practices, guidelines and standards;
› Analysis of the legislation and norms regulating drugs and pharmaceutical activities;
› Database analysis;
› Analysis of financial documents;
› Interviews with the auditee (with relevant responsible officials).

[3] Quality, efficacy and safety of pharmaceutical activities – 3 main components of identifying the qualitative indicator of drug – recognized by the World Health Organization, international drug regulatory agencies (EMEA -Europe, FDA – The USA)

1.4 Audit Limitations

Pharmacovigilance system, which is related to gathering, detecting, assessing, monitoring and preventing the adverse drug reaction and side effects of pharmaceutical product, is not introduced in Georgia.

Data regarding side effects of drugs and adverse drug reaction[4] is not available. In monthly reports from stationaries, submitted by National Center for Disease Control and Public Health (NCDC), the number of drug intoxication is presented, however, the reasons of intoxication is not provided - over dosage, side effects, adverse effect.

There is no data on treatment of outpatients, who had adverse drug reaction or side effects due to treatment of pharmaceutical product. Accordingly, audit team does not have opportunity to receive, analyze and assess the safety indicators of the pharmaceutical product in the country.

1.5 Assessment Criteria

Audit Team has used the following documents and information in determining assessment criteria:

Pre-market control of pharmaceutical product:

- The current legislative, regulatory acts;
- Acts and Resolutions of the European Commission;
- World Health Organization, European Medicines Agency - international guidelines (GMP, GCP, GLP, GPVP);
- World Health Organization – surveys;
- Best practice determined by local regulatory agencies of European countries and the United States.

Post-market control of pharmaceutical product:

- The current legislative acts, regulatory acts;
- Best practices of national regulatory agencies of European countries and the USA;
- The Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation;
- OECD – surveys and reviews;
- World Health Organization, European Medicines Agency - international guidelines of GLP, GPVP, GCP, GMP.

[4] The difference between the side effects and adverse drug reaction is the following: generally, symptoms of side effects are revealed in patients after the treatment and it is provided in instructions of the pharmaceutical product, while the adverse drug reaction is the side effect, which holds serious risks to health and is dangerous for the patients' life.

2. General Information

The government supports circulation of effective, safe and high quality pharmaceutical products in Georgia.

Efficacy of the pharmaceutical product is related to its benefit[5], safety is related to non-existence of adverse drug reaction, while the quality means ensuring identity, strength, quantitative composition, purity, chemical and biological components with pharmacopeia standard[6].

The policy of the drugs and pharmaceutical activity is implemented by LEPL State Regulation Agency for Medical Activities structured under the Ministry of Labor Health and Social Affairs of Georgia.

The agency, according to its activities represents the main regulatory body.

According to the Georgian legislation, throughout the country the agency with its competence is responsible for regulation of drugs and pharmaceutical activities, medical-social expertise of individuals and legal entities, as well as other activities stipulated by Georgian legislative and subordinated acts.

According to international standards and the best practice there are 6 main principles affecting the quality, safety and efficacy of the pharmaceutical products and pharmacy service:

- **Good manufacturing practice (GMP)** – ensures that pharmaceutical products are produced and production quality is controlled according to the standards. GMP is designed to minimize the risks, which cannot be eliminated through testing the final pharmaceutical products;
- **Good clinical practice (GCP)** – after designing new pharmaceutical product it should pass clinical trial on patients. GCP is an international ethical and scientific quality standard for designing, conducting, recording and reporting clinical trials. Compliance with this standard provides assurance that the rights and safety of patients are protected and that the clinical trial data are credible;
- **Good laboratory practice (GLP)** – quality management control system of research laboratory;
- **Good distribution practice (GDP)** – ensures that products are consistently stored, transported and handled under suitable conditions as required by product specification;
- **Good Pharmacovigilance practice (GPVP)** – standard for monitoring the safety of pharmaceutical product;

[5] Quality characteristic, established by scientific methods, about the positive effect of the pharmaceutical product on the course of disease.

[6] Pharmacopeia standard (specification, articles, monographs, temporary pharmacopoeia articles, technical conditions) – the document reflecting the quality characteristics of the pharmaceutical product and its defined methods of analysis, which is the base of quality assessment.

› **Good Pharmacy Practice (GPP)** – standards for pharmacists for quality of pharmacy services.

Each of these guidelines is used for pre or post-market controls of pharmaceutical product:

GMP (Good Manufacturing Practice), GLP (Good Laboratory Practice), GCP (Good Clinical Practice) guidelines are used *before the pharmaceutical products are marketed*.

GDP (Good Distribution Practice), GLP (Good Laboratory Practice), GPVP (Good Pharmacovigilance Practice), GPP (Good Pharmaceutical Practice) are related to the *realization and consumption of the pharmaceutical product*.

Out of these 6 main guidelines, Georgia has accepted and recognized only one guideline of the International Conference on Harmonization - Good Clinical Practice.

The table below shows the coverage of the internationally accepted best practice guidelines on 3 main functions of the regulation:

Table 2.1: Georgia's Coverage of the Internationally Accepted Best Practice Guidelines

Process	GMP	GCP	GDP	GLP	GPVP	GPP
Developing standards	🗎	✓	✘	✘	✘	✘
Developing regulatory instruments to ensure the adherence of standards	✘	✓	✘	✘	✘	✘
Monitoring the adherence of standards.	✘	✓/✘	✘	✘	✘	✘

🗎 - symbol denotes the standard, which is planned to be implemented from 2016 - Resolution of Government of Georgia №349, November 16, 2010;

✓ - symbol denotes the standard, which has been implemented;

✘ - symbol denotes the standard, which has not been implemented;

✓/✘ - symbol denotes the monitoring of the implemented standard after the issuance of the permission – low frequency of inspections and the absence of a risk assessment methodology.

2.1 Overview of the Legislation of Drugs and Pharmaceutical Activities

Georgian legislation about the drugs and pharmaceutical activities covers the constitution of Georgia, the international treaties and agreements, Law of Georgia on Drug and Pharmaceutical Activities and other legislative and normative.

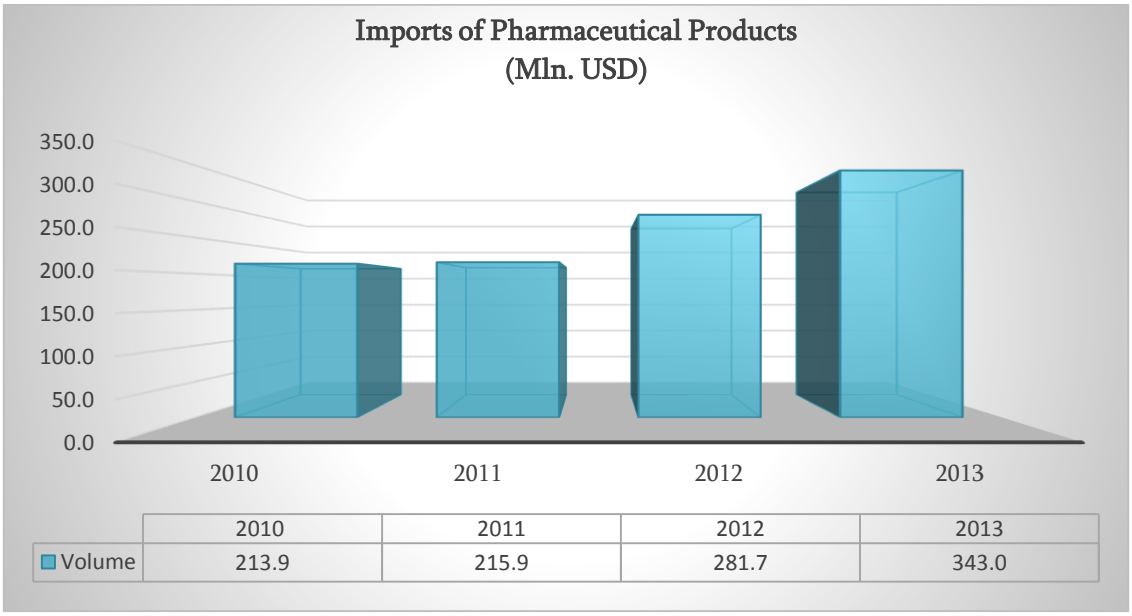
In 2009 the government adopted amendments in the Law of Georgia on Drug and Pharmaceutical Activities which aimed increasing competition on the market.

In previous legislation obstacles were reduced to 2 directions:

- To simplify the imports of the pharmaceutical product by introducing new regimes and simplifying the marketing authorization procedures;
- To simplify the starting of pharmaceutical activity.

Changes removed the barriers for imports of pharmaceutical product (access to the quality certificate) and gave wider opportunities to companies for import. Legislative amendments regulated problems related to imports of drugs, and as a result imports of pharmaceutical product increased, as it is shown on the chart below:

Chart 2.1.1: Imports of the Pharmaceutical Product in 2010-2013 (Million, USD)



	2010	2011	2012	2013
Volume	213.9	215.9	281.7	343.0

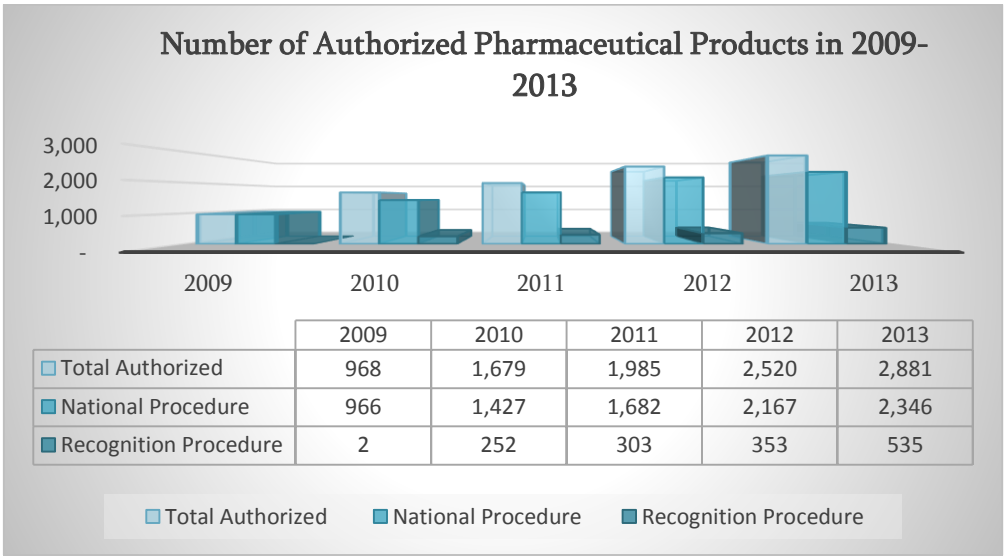
Opportunities of imports were increased as a result of drug marketing authorization by recognition procedure and allowing parallel import of drugs.

In Georgia, the recognition procedure is used for the pharmaceutical products, which are allowed on the market by regulatory agencies of other countries or by interstate regulatory agencies, defined by the resolution of the Government of Georgia[7].

These regulatory agencies include European Medicines Agency (EMA) and different EU member states, as well as The United States, Australia, New Zealand, Japan, Israel, Canada and South Korea. The recognition procedure means that the authorization of the pharmaceutical product is possible by prior recognition of the respective country and quality certificate issued by the producer is not needed.

In addition, amendment in the legislation allowed parallel imports and gave opportunity to suppliers to import drugs, which were authorized by the initial importer.

Chart 2.1.2:[8] Number of Authorized Pharmaceutical Products in 2009-2013



	2009	2010	2011	2012	2013
Total Authorized	968	1,679	1,985	2,520	2,881
National Procedure	966	1,427	1,682	2,167	2,346
Recognition Procedure	2	252	303	353	535

Simplification of import opportunities is related to simplification of state quality control system: before 2009, according to the order "Regulation of Quality Assurance of Medicinal Product[9]" different course of quality control were defined in Georgia: pre-approval control, mandatory serial control, further selective control and arbitral control.

At Present, in accordance with the current legislation, the agency is entitled to carry out the selective control of pharmaceutical products.

[7] Resolution of the government of Georgia №188 (22.10.2009)

[8] The chart shows the number of pharmaceutical products that were authorized in respective years and their authorization was valid until July 1, 2014. Accordingly, in this data there are no pharmaceutical products that were authorized in respective years but whose authorization was revoked or suspended as of July 1, 2014.

[9] Order №141/n of the minister of Labor, Health and Social Affairs of Georgia

The charts below represent information about the imported drugs according to manufacturer and importer countries:

Chart 2.1.3: Imports of Pharmaceutical Products by Manufacturer Countries in 2012-2013 (Private Purchases)

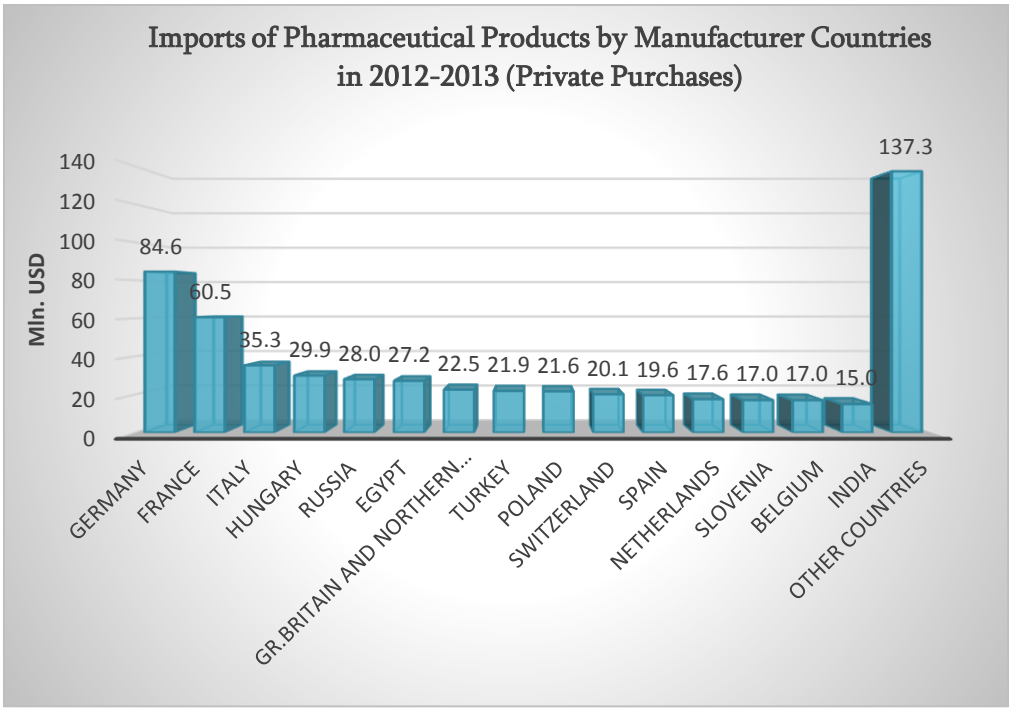
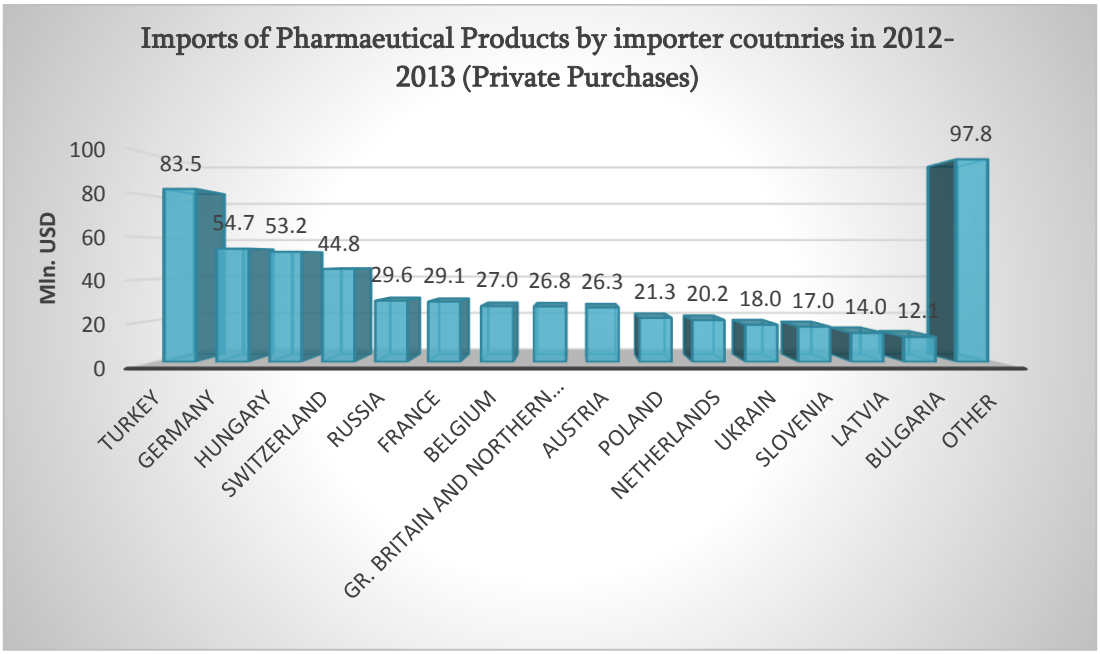


Chart 2.1.4: Imports of Pharmaceutical Products by Importer Countries (Private Purchases)



In addition to the improvement of import operation procedures as well as starting of pharmaceutical activities has simplified. According to the Law of Georgia on Licenses and Permits, manufacturing of pharmaceutical products, clinical trials, authorized pharmacy, imports-exports of pharmaceutical products under special control, need permission.[10] The agency implements the permission conditions through the selective control.

The aim of current legislation of drugs and pharmaceutical activities is to promote public accessibility to *reliable* pharmaceutical product. For this purpose, the legal basis of pharmaceutical product circulation and the rights and obligations of individuals and legal entities in this field are stipulated.

2.2 Overview of the Functions of LEPL State Regulation Agency for Medical Activities

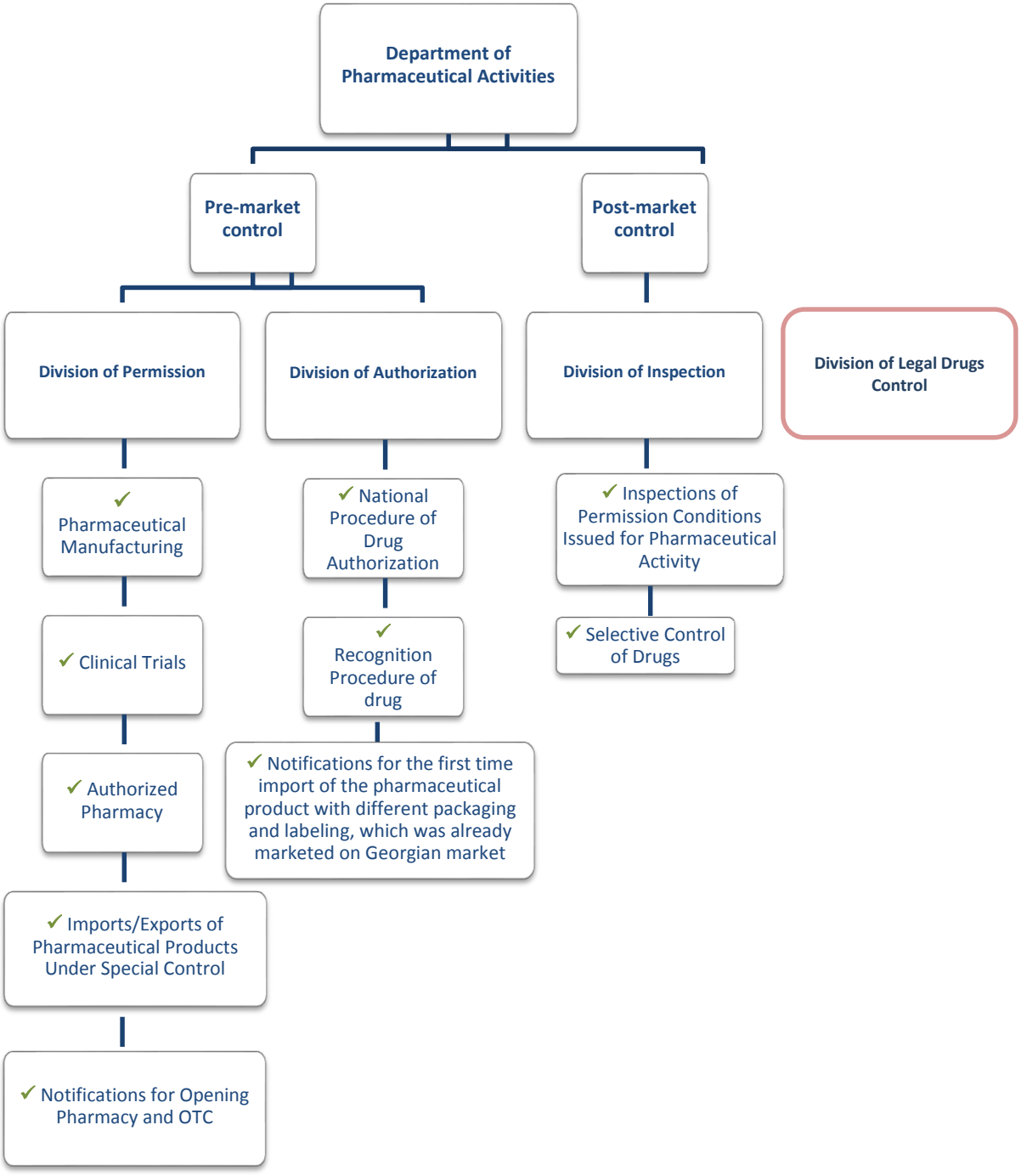
Regulation of drugs and pharmaceutical activities in compliance with legislation is executed by the Department of Pharmaceutical Activity under LEPL State Regulation Agency for Medical Activities.

The total budget of the agency in 2012 and 2013 amounted to 3,254,000 and 2,905,000, GEL respectively. 80% of the budget was salary and the amount allocated for quality control of pharmaceutical product totaled 70,000 GEL.

The Department of Pharmaceutical Activity provides pre and post-market control of pharmaceutical products.

[10] Resolution of the government of Georgia №176 about the rules and conditions of issuance of permits for clinical trials of pharmacological products, pharmaceutical manufacturing, pharmacies, import/export of pharmaceutical products under special control.

Scheme 2.2.1: Structure of the Department of Pharmaceutical Activities by Pre and Post Market Control Activities:[11]



[11] Division for legal circulation of drugs is out of the scope of the audit, because its goals and missions are not connected directly to the regulations of ordinary pharmaceutical products. However audit team used some information provided by this division.

Pre-market control

Pre-market control of pharmaceutical products is related to the following:

- Permits of pharmaceutical activities;
- Marketing authorization of the pharmaceutical product.

Divisions of permission and authorization provide the pre-market control of drugs and pharmaceutical activities:

Permissions of pharmaceutical Activities

In accordance with Law of Georgia on the *Licenses and Permits* permission division issues permits for pharmaceutical manufacturing, clinical trials, imports or exports of pharmaceutical products under special control and in authorized pharmacy.

Manufacturing of pharmaceutical product – a serial manufacturing of the pharmaceutical products according to the appropriate standards.

Currently, **75** manufacturing permissions are issued in Georgia.

Clinical trials of pharmacological products - after manufacturing, the pharmaceutical product goes through the stages of clinical trial. This activity needs permission. To obtain permission for clinical trial, applicant should submit pre-clinical[12] study results.

Currently, there are **45** permissions issued on clinical trials in Georgia.

Imports-exports of pharmaceutical products under special control [13]– imports-exports of such pharmaceutical products need permission because of their specifications.

Permits for authorized pharmacy – authorized pharmacy is subject to permit control, obtains right to sell first, second and third group pharmaceutical products and prepare pharmaceutical products by recipe (intended for individual patient or/and according to pharmacopeia).

In addition to the authorized pharmacy, Georgia has a general pharmacy and over-the-counter stores.

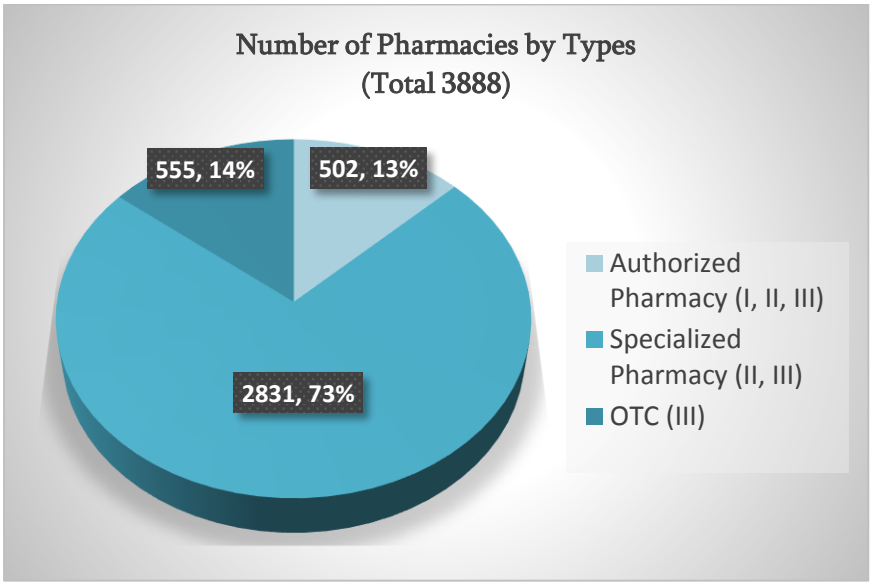
[12] It is pharmacological, toxicological and other scientific study of the pharmacological product to determine its impact on specific activity and on physiological system. Drug testing procedure, which is conducted on animals before clinical trial.

[13] Order №331/n of the minister of Labor, Health and Social Affairs of Georgia about determining the list of pharmaceutical products for I and III group. According to Georgian legislation, precursors, narcotics, psychotropic drugs belongs to I group.

A General pharmacy has the right to sell second and third group pharmaceutical products (prescription and nonprescription drugs). This pharmaceutical activity does not require permission.

Over-the-counter centers have the right to sell only third group pharmaceutical products (nonprescription drugs) and this pharmaceutical activity does not require permission.

Chart 2.2.1: Number of Pharmacies by Types (total - 3888)



Market authorization of the pharmaceutical product

In Georgia, pharmaceutical products are authorized through national and recognition procedure.

- Marketing authorization of the pharmaceutical product by **recognition procedure** can be used for the pharmaceutical products, which are allowed on the market by regulatory agencies of other certain countries or by interstate regulatory agencies. The list of these countries is defined by the Government resolution.
- ***National marketing authorization*** of the pharmaceutical product is used when the product is not authorized in "recognized" country and in interstate regulatory agency. If the applicant prefers, it is also possible to authorize pharmaceutical product through national procedure, which has authorization in recognized country.

In addition, the law allows the imports of pharmaceutical products with different packaging and labeling based on the notification – so called parallel import.

In case of approving the imports of pharmaceutical products with different packaging and labeling for the first time (mainly include parallel import), the agency is obliged to record information in the registry within 5 working days after the notification.

Pharmaceutical products imported in order to re-export, active substances and unpacked pharmaceuticals intended for domestic production (bulks) are not subject to marketing authorization.

As of July 1, 2014, **10 541** authorized pharmaceutical products were registered**,** out of which:

- 8 981 pharmaceutical products are authorized by national procedure;
- 1 560 pharmaceutical products are authorized by recognition procedure.

Post-market control

Post-market control of the drugs and pharmaceutical activities is related to the inspections held by division of inspection and pharmacovigilance of pharmaceutical products existing on the market.

Division of Inspection under the Department of Pharmaceutical Activity carries out:

Inspections of permission conditions issued on pharmaceutical activity

Selective control of Pharmaceutical Product

According to the Law of Georgia on Drug and Pharmaceutical Activities, pharmaceutical products are inspected only through the selective control.

The agency uses Guideline of Selective Control Based on Risk Assessment[14] which aims to define the control procedures, based on which wholesalers of the pharmaceutical products must be controlled.

Selective control based on risk assessment is subject to:

Authorized pharmacy, general pharmacy, and over-the-counter centers where pharmaceutical products are sold. Also retailers, who have the right to sell the pharmaceutical products in rural and village areas according to legislation and importers of pharmaceutical product.

[14] Order №380/n of the minister of Labor, Health and Social Affairs of Georgia

3. Pre-Market Control of the Drugs and Pharmaceutical Activities

3.1 Permits of Pharmaceutical Activities

Following pharmaceutical activities require permission in Georgia:

- Manufacturing of pharmaceutical products;
- Clinical Trials of pharmacological products;
- Imports-Exports of pharmaceutical products under special control;
- Authorized pharmacy.

Permission conditions of pharmaceutical activities are approved by the resolution of Government of Georgia[15]. Main function of Division of Permission under the Department of Pharmaceutical Activity is to issue the permits and control the permission conditions. In order to receive the permits for pharmaceutical activities, applicant should submit specific documentation related to the activity in addition to documentation defined by the Law of Georgia on Licenses and Permits [16].

3.1.1 Manufacturing of the Pharmaceutical Products – Undefined Strategy

Manufacturing of the pharmaceutical product is the serial production of pharmaceutical product consistent with appropriate standards.

In order to obtain a permit for manufacturing of the pharmaceutical product applicant should submit to the regulatory agency a plan of premises (building) indicating storage, information about responsible personnel and technological act of pharmaceutical product prior to the approving GMP standards, that will be valid from 2016 according to the resolution[17] of Government of Georgia.

During the transition period (until 2016), the agency follows technological instruction regulated by the Government, however, the articles, which formed the basis of the order №141/n, is removed or amended in the Law of Georgia on Licenses and Permits. Consequently, technological instructions, which could determine the technological process (technical facilities used in manufacturing process, raw materials, work safety and sanitary-hygienic standards), has no legal ground. Accordingly, there is no valid regulation with respect to technological process.

Pharmaceutical companies can voluntarily implement and adopt international, regional or national GMP standard recognized by the resolution before January 1, 2016.

[15] Resolution of Government of Georgia № 176.
[16] Law of Georgia on Licenses and Permits – chapter 25. List of Documents for getting permission
[17] Resolution of Government of Georgia № 349, November 16, 2010

Some of the Georgian large manufacturers obtained GMP certificates from other relevant European organizations. However, as GMP standards are not established in Georgia, agency has not trained GMP inspectors who could verify the compliance of local manufacturing process with GMP standards.

As of July 1, 2014, 75 permits are issued for manufacturing, of which 13 permits were issued in 2013-2014.

In recent years, regulatory agency has not inspected any permission condition of manufacturing in accordance with technological instruction, which was the reason for granting permission for manufacturing[18]. However, in case of adoption of a new form permission conditions of the pharmaceutical product are still inspected by the agency. More specifically, 8 manufacturing companies were inspected in 2012-2013 by the agency as a result of adding new pharmaceutical activities.

The transition process to GMP standards has not started yet by the agency, whilst the implementation process of the transition should start reasonably earlier and it should include trainings for manufacturer as well as for inspectors. There is no strategy defined in the agency on how and by who the standard should be implemented and what challenges the country faces in this direction. Existing technological instruction, which is valid during the transition period has deprived of the legal ground, is obsoleted and is significantly behind the best manufacturing practice. Accordingly, there are no standardized norms with respect to local manufacturing. In addition, strategic vision and action plan is not developed for implementing a good manufacturing practice.

3.1.2 Clinical Trial of Pharmacological Product – Shortcomings in Permission Conditions and Lack of Monitoring Methodology

Clinical trials of pharmacological products (testing, examining) are studies that are intended to verify adverse reaction, efficacy and safety of pharmacological products on trial subjects. Clinical trials are carried out according to the standards.

According to European practice, clinical trials are carried out in compliance with standards; the term for issuing permission is 30-90 days and depends on research object and its features[19]. European

[18] According to agency, order №141/n, which defines the technological act does not comply with the Law on Drug and Pharmaceutical Activities and needs modification. As the articles in Law on Drug and Pharmaceutical Activities is modified or revoked, that were the base of the order №141/n of the minister of Labor, Health and Social Affairs of Georgia (May 3, 2002), the above mentioned order is not valid according to the article 25, paragraph 4 of the Law on Normative Acts.

[19] For example: 60 days - gene therapy and somatic cell therapy, 90 days –for pharmaceutical products that contain genetically modified organisms.

regulatory authorities and UK regulatory agency of the pharmaceutical product have developed 3 types of inspection of clinical trials[20]:

- Risk based routine inspections;
- Ad hoc (specialized) inspection;
- Inspections made based on the information about the clinical trials, obtained at the time of marketing authorization of the pharmaceutical product.

According to the order[21] of Minister of Labor Health and Social Affairs, Good Clinical Practice (GCP) of International Conference on Harmonization and Nonclinical Safety Studies of International Conference on Harmonization (ICH) are defined as guidelines for preclinical and clinical trials of the pharmacological products.

Clinical trial is one of the significant quality measures of pharmaceutical products. Clinical trial should comply with ethical principles set out in guideline, as it involves trials on humans. The sponsors of the clinical trials are responsible for implementing and maintaining quality assurance and control systems to ensure that clinical trials are conducted in compliance with established standards.

As of July 1st, 2014, there are 71 permissions issued on clinical trials. Georgian company is a sponsor[22] of 7 clinical trials.

According to Georgian legislation, issuance of permission does not depend on type of trial or the number of applicants. Thus, according to the agency, in some cases pre - inspections of clinical trial are problematic.

According to legislation, term for issuing permission for any type of clinical trial is 20 days, whilst clinical trial is high-risk activity and its examination needs sufficient and reasonable period of time.

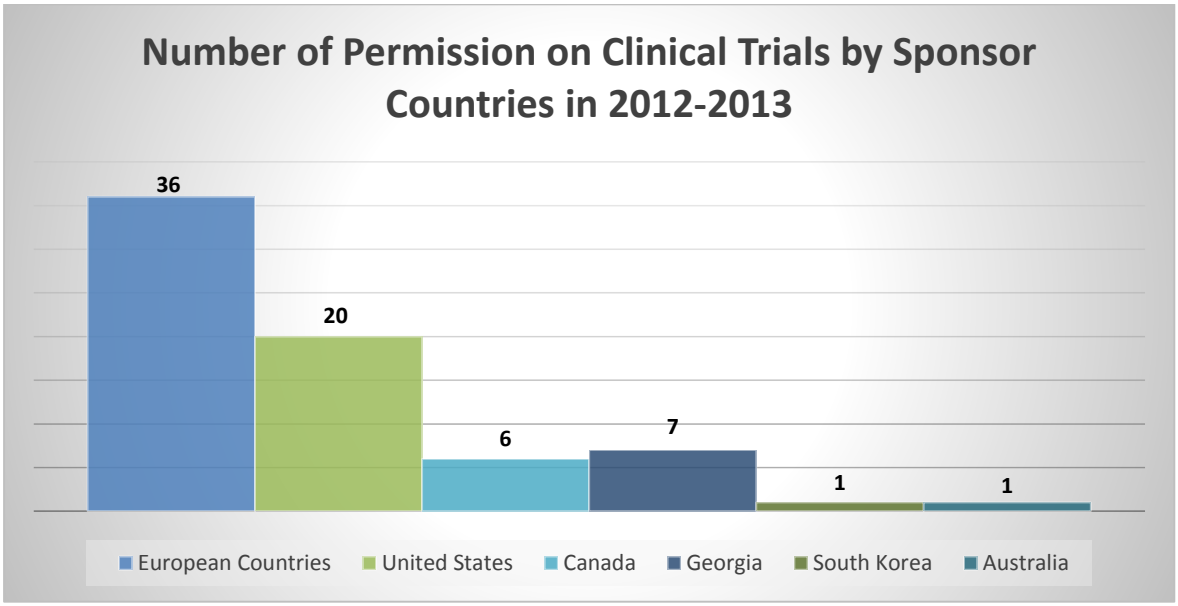
The chart below shows the number of issued permissions on clinical trials by sponsor countries in 2012-2013.

[20] MHRA.GOV.UK

[21] Order № 223/o, about the recognition of guidance (guidelines) of preclinical and clinical trials (valid from August 15, 2010)

[22] An individual, company, institution, or organization that takes responsibility for the initiation, management, and/or financing of a clinical trial.

Chart 3.1.2.1: Permissions Issued on Clinical Trials in 2012-2013



The guideline of clinical trial is essential as it helps regulatory agencies to monitor the process of clinical trial and gives opportunity to inspect the permission conditions according to the guideline. However, in some cases the terms of guideline are very general, and these issues are not presented in legislation.

Guideline states that regulatory agency should determine insurance of subject of clinical trial, the ethical committee members and their competences; however, in legislation there is no definition about abovementioned issues. Accordingly, agency cannot require all these from organization that carries out the clinical trial.

In 2012, two ongoing, international clinical trials were inspected in one medical institution,[23] also 5 finished clinical trials of pharmacological products were inspected[24]. In 2013 one multi-central clinical trial was inspected, which has been conducting in 8 medical institutions since 2010. [25]

[23] Ltd. "Clinical Medical Research Institute"

[24] The survey was conducted by:

a) Ltd. "V. Sanikidze's War Veterans Clinical Hospital". Reliability issues of the clinical study results of the drugs "Domentol" and "Gagenol".

b) Ltd. „Tbilisi endocrinology center". Reliability issues of the clinical study results of the drug "N Medea"(manufacturer Ltd. "Geopol")

c) Ltd. "N3 prophylactic treatment center of Tbilisi". Reliability issues of the clinical study results of the ointment "Uebari"(manufacturer Ltd. "Biopharm L")

d) LEPL TSMU "Al. Aladashvili University Clinic". Reliability issues of the clinical study results of the drug "Ferd"

[25] 8 medical institutions participating in the study:

Ltd. "Diabetes Research Center", Ltd. "Medelit", Ltd. "David Metreveli Medical Center", Ltd. "National Institute of Endocrinology", Ltd. "Medulla-Chemotherapy and Immunotherapy Clinic", Ltd. "i. Jordania Human Reproduction Research Institute", Ltd. clinic "LJ" Jiqia, Ltd. "Unimed Adjara (Batumi Referral Hospital) "

It is worth mentioning that after issuance of the permission inspection of ongoing and completed clinical trials is very rare. In addition, the risk assessment methodology, the coverage indicators for the inspection is not defined.

The reason for these rare inspections after the issuance of permissions is that division of inspection of the agency has other type of challenges which appears to have higher priorities. Accordingly, the agency uses its resources in this direction.

Based on the above-mentioned, despite the fact that activities of clinical trials are standardized, the term of issuing permission is not based on specifications of the clinical trial. Current legislation is not in compliance with internationally accepted standards. After the permission is issued, the inspections are not carried out based on defined methodology, risks assessment and coverage criteria.

3.1.3 Permission Conditions on Pharmacy Activities – Shortcomings in Regulations

In EU countries[26] any type of pharmacy that sells prescription drugs needs special permission.

The permission term of pharmaceutical activity is limited in most countries. For example, in Estonia[27], Latvia[28] the term for license is 5 years, at least two months before the expiration of 5 years term, the license holder can apply for renewal of license (along with a renewal fee). In case of issuance or renewal for the license, the regulatory agency should inspect submitted documentation and permission conditions. Renewal of permission condition ensures the systematic control of the permission, which is the prerequisite of the safe storage and reduces the risks of deterioration.

According to the Law of Georgia on Drug and Pharmaceutical Activities, [29] following entities are allowed to retail and wholesale pharmaceutical product:

Authorized Pharmacy - first[30], second[31] and third[32] groups of pharmaceutical products are sold. They also prepare pharmaceutical products by recipe (intended for individual patient or/and according to pharmacopeia).

General Pharmacy - second and third group pharmaceutical products are sold.

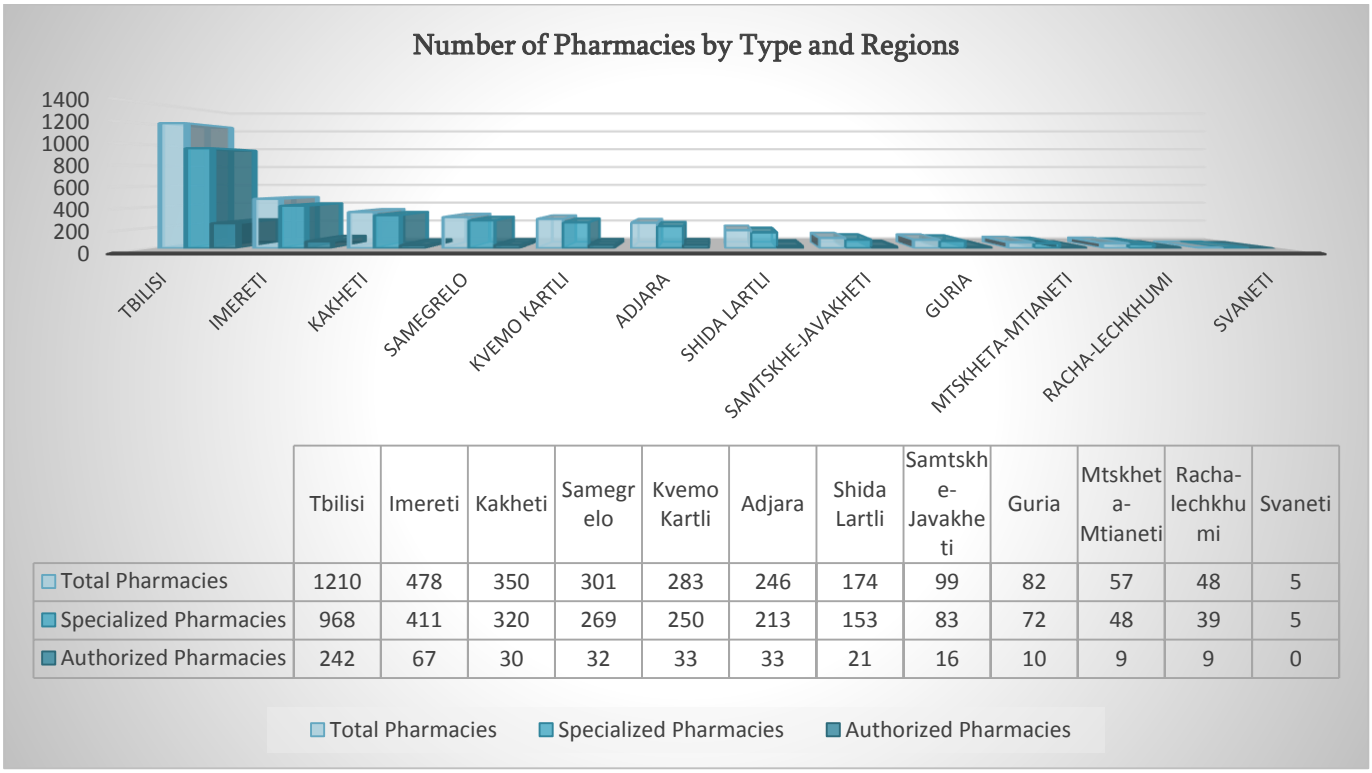
Over-the-Counter centers - third group pharmaceutical products are sold.

[26] Estonia, Medicinal products act
[27] Estonia, Medicinal products act
[28] Law on pharmacy – state agency of medicines of the republic of Latvia
[29] Law of Georgia on Drug and Pharmaceutical Activities
[30] Pharmaceutical products under special control or drugs equalized with them
[31] Prescription drugs – pharmaceutical product, misuse of which can harm the health and life of a person or/and which cannot be used only by instruction, without prescription of the doctor and which can be bought by prescription
[32] OTC drugs – pharmaceutical product which can be bought and used without prescription of the doctor

Person with medical background or independent medical practitioner – has the right to retail pharmaceutical products (except pharmaceutical products under special control) in rural and village areas in order to improve the population accessibility to pharmaceutical products.

The chart below shows the number of different types of pharmacies as of July 1, 2014: [33]

Chart 3.1.3.1: Number of Authorized Pharmacies



	Tbilisi	Imereti	Kakheti	Samegrelo	Kvemo Kartli	Adjara	Shida Lartli	Samtskhe-Javakheti	Guria	Mtskheta-Mtianeti	Racha-lechkhumi	Svaneti
Total Pharmacies	1210	478	350	301	283	246	174	99	82	57	48	5
Specialized Pharmacies	968	411	320	269	250	213	153	83	72	48	39	5
Authorized Pharmacies	242	67	30	32	33	33	21	16	10	9	9	0

In Georgia, only **authorized pharmacy** needs permission that has the right to sell all pharmaceutical products including drugs under special control.

Special conditions for the permission of **authorized pharmacy** are defined by the resolution[34] of Government of Georgia. Conditions include the criteria about the office space, personnel, safety and material-technological environment. But the criteria are general and do not contain details about technical base, obligatory equipment, room temperature range, protecting the safety from negative impacts of environmental factors that are important for pharmaceutical activity and safety according to international standards.

In addition, permission for pharmacy does not take into account criteria for geographical locations.

[33] The data include all type of pharmacies except OTC where III group pharmaceutical products are sold
[34] Resolution of Government of Georgia about №176

Permission for authorized pharmacy does not expire. This causes problems when recording pharmacies in registry.

Namely, it was identified cases where instead of authorized pharmacy, other company with different business activity is functioning in the same address, and the information of the primary permission holder is unknown.

The current legislation does not provide any response mechanism for such cases, as the permission does not expire there is no right to abolish or suspend the permit for the permission holder.

Division of Legal Circulation of Narcotics receives information from the entities about the turnover of pharmaceutical products that are under special control, these entities have right to sell first grout pharmaceutical products (authorized pharmacy and equivalent to authorized pharmacy).

The agency receives information monthly – In 2013, they received data from only ***300*** institutions[35], while according to database of regulatory agency, as of January 1, 2013, 539 entities have permits to sell pharmaceutical products under special control. Consequently, the agency does not have precise data about the number of currently *functioning* authorized pharmacies.

Unlike authorized pharmacy opening **general pharmacy** is not subject to permissions. Applicant should only send the notification to the agency. Applicant should meet the sanitary-hygienic/technical conditions[36] defined by the order of Minister. The conditions are inspected only in case of selective control of pharmaceutical products at post-market control level.

As an applicant sends a notification to the agency, sanitary-hygienic/technical conditions are not inspected prior to the opening ordinary pharmacy. Also according to the legislation, sanctions are not set in case of violation of the sanitary-hygienic/technical conditions while the number of general pharmacies amounts to 72 % (2831 units) of all pharmacies and they have the permit to sell prescription drugs.

[35] It is possible that the pharmacy operates, but do not report to the agency, in some cases the pharmacy may be abolished without any notification to agency.
[36] Order №387/n of the minister of Labor, Health and Social Affairs of Georgia

Table 3.1.3.1: Pharmacies Subject to Permission

	Prescription Drugs	Permission for Pharmaceutical Activity
General pharmacy	✓	x
Authorized pharmacy	✓	✓

Issuance of permissions for pharmacies is not based on prescription drug criteria. In particular, according to Georgian legislation general pharmacies, which sell prescription drugs, are not under the permission conditions, whilst the number of such pharmacies, as it was mentioned above, is high and amounts to 72% (2831 pharmacy) of all pharmacies. In addition to this, sellers must carry out activities in some protected environment, which is essential, as prescription drugs require handling and storage in protected conditions. This would be the reason why these kinds of pharmacies are under the permissions in the United States and in most European countries.

According to the legislation, permission issued for authorized pharmacies does not expire, which does not allow agency to monitor the activities of pharmacies, to possess accurate and updated information about currently functioning pharmacies and about the protection of the permission conditions.

3.1.4 Undetermined Permission Conditions for Drug Storage, Handling and Transportation

In Georgia, pharmacy has right to exercise retail and wholesale activities simultaneously.

For retailers and wholesalers drug storage and realization conditions are defined, which include the space for drug realization (with the possibility of product delivery and consultation with user) and storage.

According to current legislation permission is needed from the agency only when importing or exporting pharmaceutical products under special control.

Resolution of the government about permission does not take into account permits issued dependently for retailers and wholesalers. Also, it does not provide permission for drug distribution. Accordingly, the permission criteria of the distribution conditions are not defined. Legislation does not define the protection mechanisms from the high risk of deterioration; also material-technical base and range of temperature are not indicated.

Retail and wholesale of pharmaceutical products are separated activities in most EU countries[37]. Activities of retailers as well as wholesalers are under the permission conditions. In addition to this, different permission conditions exist for retailers and wholesalers to store and transport pharmaceutical product and to document realization related issues. Standards define the list of institutions, legal and private person to whom wholesaler sells pharmaceutical product in details. They can be other wholesalers, retailers, clinics and persons, who have permission for such activity. Separation of drug realization activities promotes the quality control of distribution chain – protection of the standards of storage, handling, transportation and realization of the pharmaceutical product.

Georgia has not implemented standards of Good Distribution Practice (GDP) recognized by the World Health Organization and European Medicines Agency, which is one of the most important levels of quality assurance of pharmaceutical product.

GDP standard provides the conditions not only for wholesaling and retailing, but also criteria for realization area, storage, distribution, transportation, environmental conditions and material-technical base.

GDP ensures the control of the supply chain and therefore promotes reduction of high risks of deterioration, as it includes all stages of the supply chain from manufacturer to the pharmacy or person. Implementing and fulfilling the right practice at each level is the guarantee of the quality of the pharmaceutical product.

According to GDP guideline, all obligations and interested parties related to possessing, distribution, supply and storage apply as wholesale distribution, whilst retail distribution implies selling pharmaceutical product to final consumer, by protecting appropriate rules.

Protection of GDP guidelines ensures supervision of pharmaceutical activities and improves/maintains the quality of pharmaceutical products, which consists of the following topics:

- **Quality Management** (organizational structure, processes that ensures that product, while transported and stored, maintains its quality);
- **Competent personnel** (appointment of responsible person with pharmaceutical educational background, all personnel involved in wholesale distribution activities should be trained according to the requirements of GDP);
- **Building and Equipment** (adequate equipment for storage and distribution of pharmaceutical products, temperature and environment control, key equipment: refrigerators, temperature and humidity recording devices, ventilation units, etc.);
- **Documentation** (written procedures, instructions, contracts, records and data, name and quantity of the product, information about supplier, etc.);
- **Operations** (qualification of suppliers and customers, storage, destruction of obsolete goods);

[37] Medicinal Products in Human Medicine Act Bulgaria; Medicinal Products Act. Estonia. Medicinal Products Act. Slovenia.

- **Complaints, returned and falsified pharmaceutical products** (conditions, about returning pharmaceutical product, notifications from wholesale distributors to competent authorities and the marketing authorization holder about falsified or doubtful pharmaceutical product);
- **Self-inspections** (compliance with GDP standards, identifying the gaps and finding the ways to solve them);
- **Transportation** (protecting of temperature conditions which is defined by the manufacturer or is on the outer packaging, recording all vehicles that are used to distribute the pharmaceutical product, in case of transit storage particular attention should be paid to temperature monitoring, cleanliness and the security, providing transport facilities, which will ensure the quality of the pharmaceutical product, in case of narcotic and psychotropic drugs ensure providing information about the transportation conditions to the consumer if it is demanded).

According to current international standards, all wholesalers must own authorization/license for wholesale and must satisfy GDP standards for the purpose that their activities were controlled and protected following from the high risks of drugs. Also manufacturers, who distribute their pharmaceutical products, must follow GDP standards.

The introduction of distribution practice will ensure the circulation of drug in safe environment. This standard is compulsory for all distributors, including sellers of parallel import.[38] Accordingly, protecting the relevant standards and documenting from whom and under what conditions was procurement made is mandatory. In case *of relevant risks*, regulatory agency with the traceability principle can check from which country was the parallel import made. Also, can check if the importer country had the permission for distribution and if the different packaging of the pharmaceutical product is relevant to manufacturing standard (whether the procedure has been agreed with the producer or the relevant license holder in the importing country). This can be achieved by the cooperation with the regulatory agency of the particular country.[39]

Nonexistence of good distribution practice puts quality of circulated pharmaceutical product at the risk. Especially in the circumstances, when during transportation it is important to protect cold chain conditions according to instruction[40]. Standardized procedures promote control and strengthening of the quality of pharmaceutical product.

[38] Parallel import – pharmaceutical product that is produced by manufacturer and is imported in particular country without permission of holder of intellectual property right (manufacturer, trade license holder). According to WHO, parallel import is sometimes referred to as "grey market" imports. The Trade-Related Aspects of Intellectual Property Rights (TRIPS) agreement explicitly states that this practice cannot be challenged under the World Trade Organization (WTO) dispute settlement system and so is effectively a matter of national discretion.

[39] Form for Notification of parallel distribution of a centrally authorized medicinal product 24 EMEA-Ho-2368-04-Rev 1 EMEA Post-Authorization Guidance on Parallel Distribution;

[40] The temperature is fully controlled during drug supply and transportation when cold chain conditions are met.

Due to abovementioned factors and the shortcomings in the regulations, the safe environment for the drug circulation is not guaranteed during drug storage, handling and transportation. Permission conditions and standards are behind the internationally accepted practice and standards; furthermore, it does not ensure its further monitoring opportunities.

Recommendations:

In order to ensure the quality, efficacy and safety of the pharmaceutical product, it is important that ministry, with the agency verify developing conditions for manufacturing, its further trial, distribution, storage, handling and realization, promote activities for improving current conditions by initiating internal organizational and legislative changes:

- → Develop strategic view, action plan for the implementation of GMP standards and its further monitoring, control;
- → Depending on the specifics of the clinical trial, review the permission issuance procedure and term with respect to types of the clinical trial, number of organizations, subjects involved in the study. Improve legislation in conformity with recognized clinical trial guidance and develop methodology for further monitoring of the clinical trial;
- → To ensure safe and controlled environment for storage and realization of prescription drugs in ordinary pharmacies, it is important to set the conditions that correspond to current international standards, related to realization of the pharmaceutical product – permission conditions, terms of permissions and their further controls;
- → To develop and set distribution standards for pharmaceutical products, that is related to transportation of the pharmaceutical product in safe environment, quality management issues and control of distribution.

3.2 Marketing Authorization of the Pharmaceutical Product

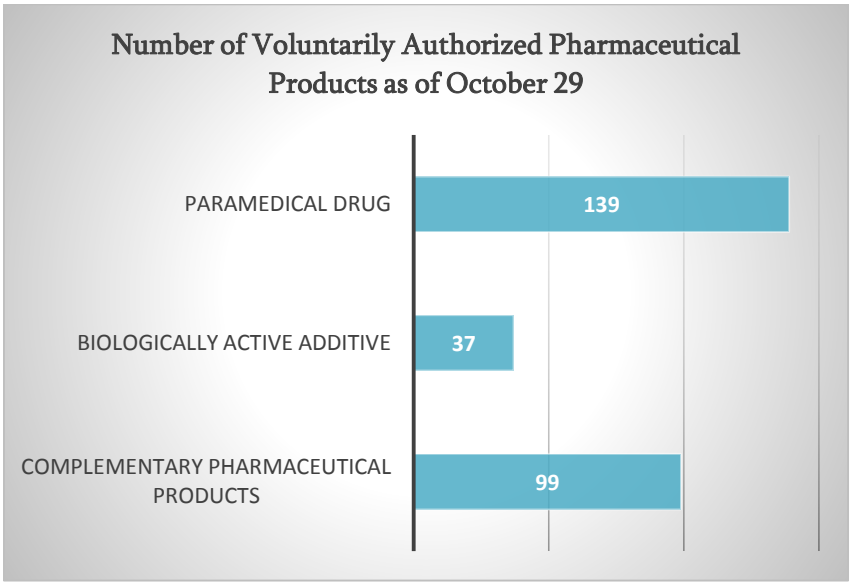
3.2.1 Scope Limitation of Marketing Authorization

Marketing authorization of the pharmaceutical product is a pre-market control mechanism, which ensures that only the products that meet defined standards of quality, safety and efficacy, are released on the market. During the marketing authorization procedure, the protection of standards is carefully reviewed by experts, which protects consumers from poor quality, ineffective and unsafe pharmaceutical products.

According to the Law of Georgia on Drug and Pharmaceutical Activities, there are pharmaceutical products, for which marketing authorization is mandatory and those products for which marketing authorization is voluntary (Annex 1 and 2).

The number of voluntarily authorized pharmaceutical products as of October 29, 2014 is the following:

Chart 3.2.1.1: Number of Voluntarily Authorized Pharmaceutical Products as of October 29, 2014



In case of voluntary marketing authorization of complementary pharmaceutical products[41], biologically active additive[42] or paramedical drugs[43], the applicant should submit relatively less documents unlike other pharmaceutical products.

According to the agency, applicant may want to authorize pharmaceutical products voluntarily from the marketing point of view, or to increase the credibility of the product. For example, insurance companies compensate only for authorized pharmaceutical product by the agency.

The agency has no information about the number of unauthorized pharmaceutical products (that are under voluntary authorization) circulating on the market. Thus, the quality, composition and effect of these products are unknown (doubtful).

The basis of limitation of the authorization scope is to simplify import. In addition to this, these kind of pharmaceutical products (complementary pharmaceutical products, biologically active additives and paramedical drugs) under voluntary authorization scheme are considered to have less threat.

In the United States and in member states of the European Union, marketing authorization of all these abovementioned products are mandatory. In addition, there are two types of marketing authorization: ordinary authorization and simplified authorization. If the product is realized as the completed pharmaceutical product (with therapeutical and side effects), it must be authorized by ordinary authorization. Whereas, if the drug:

- Is intended for external use and,
- Has not indicated therapeutical effects or such information on the package and instruction

Than this drug can be marketed by simplified authorization, which is simpler procedure than ordinary authorization.

The general basis for the authorization of all kind of drugs is derived from the risks of pharmaceutical products. According to regulatory agencies of European countries it is extremely important to authorize any type of pharmaceutical product and monitor them after the authorization procedure. Unlike other pharmaceutical products, the authorization procedure of complementary pharmaceutical products, biologically active additive and paramedical drugs is simpler, one-time procedure with the minimal authorization fee.

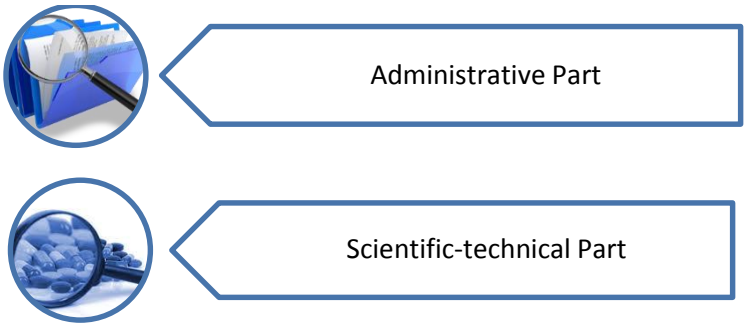
[41] Complementary (homeopathic, anthroposophic, homitoxicological) pharmaceutical product – products made by the substances or by the sum of the substances from the natural origin (mineral, vegetable, animal), whose action and standardization is confirmed by the objective evidence.
[42] Biologically active additive – product preserving physiological condition
[43] Paramedical drugs – products from the natural origin (mineral, vegetable, animal), which has some therapeutical effects and contains the specific substance with such form and quantity, that it can be considered as the form of drug.

3.2.2 Shortcomings in National Marketing Authorization Procedure

According to the Georgian legislation, the pharmaceutical products can be authorized by national or recognition procedure.

Applicant of the authorization of the pharmaceutical product can be any person – manufacturer, owner of the trade license, importer or any individual and legal person.

To get marketing authorization by national procedure, the applicant should submit an extensive list of documents, which is divided into two parts:



After receiving complete documents of administrative and scientific-technical parts, the drug regulatory agency is obliged to examine the documents and accept or reject requirement of the applicant[44].

Administrative part of the National Marketing Authorization

Administrative part consists of the application, the certificates of the pharmaceutical products, instructions, the sample of packaging and labeling, etc.

According to the Georgian legislation, the following documents **are not** required for the authorization procedure:

- **Summary of product characteristics** – this is almost the same as the instruction of the pharmaceutical product, but more detailed and comprehensive;
- **Information about experts** – applicant should submit to the agency the information about the experts, who confirm the safety issue of the pharmaceutical products;
- **Preliminary system for developing pharmacovigilance** – this is about the system of how applicant is going to collect and transmit the information to the agency about the side effects of the pharmaceutical product.

In EU Member States, there are several marketing authorization regimes, and one of them is national authorization. Unlike the Georgian legislation, in these countries authorization

[44] Law of Georgia on Drug and Pharmaceutical Activities

documentation of national marketing authorization is more comprehensive and detailed. In addition, all EU member States, the United States and Japan have the same (if not identical) authorization procedures after the harmonization process[45].

One of the most important from the abovementioned authorization documents is the developing pharmacovigilance system.

Pharmacovigilance system ensures the safety monitoring of the pharmaceutical product by collecting information about the side effects of the drugs from the applicant and other regulatory authorities. It must be mentioned that in EU Member States the pharmacovigilance system is well-planned and well-organized process, because applicant is usually manufacturer or owner of the trade license. Accordingly, the applicant is responsible for developing the pharmacovigilance system, whilst the regulatory agency is responsible to monitor this system.

The supervision of the side effects of the drug is time-consuming process, but it is the essential as it ensures the monitoring of the efficacy and safety of the pharmaceutical product. In addition, it may become a reason of withdrawal of the pharmaceutical product from the market if substantial side effects reveals.

Submitting administrative part of the dossier by applicant ensures that the information about the quality, safety and efficacy is reliable. These documents are also the guarantee of the permanent monitoring of the pharmaceutical product after granting the marketing authorization.

Scientific-technical part of the National Marketing Authorization

According to the Georgian legislation, the scientific-technical part of the national authorization dossier must contain monographs of the methods of analysis and specifications of the active substances[46] and excipients[47], samples of the pharmaceutical product, reference standards[48], information about preclinical and clinical trials, about side effects, etc.

[45] Harmonization process – process, initiated by European Community (now the European Union) in 1980s, which aimed to harmonize and insert in the same frame the regulations in pharmaceutical industry. Later the USA and Japan joined this process.

[46] Active substance - Any substance or mixture of substances intended to be used in the manufacturing of a medicinal product and that, when used in its production, becomes an active ingredient of that product intended to exert a pharmacological, immunological or metabolic action with a view to restoring, correcting or modifying physiological functions or to make a medical diagnosis. (DIRECTIVE 2001/83/EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL)

[47] Excipients - Any constituent of a medicinal product other than the active substance and the packaging material. (DIRECTIVE 2001/83/EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL)

[48] Reference standards – given in pharmacopoeia, accurately determined ingredient or substance, with one or more feature, which is used for calibration of equipment, measurement and asses the quality of the substance, (Law of Georgia on Drug and Pharmaceutical Activity)

The scientific-technical part is different for innovative (new original), generic[49] - reproduced, paramedical drugs, complementary pharmaceutical product and biologically active additive.

The audit revealed that:

- According to the Georgian legislation, for granting marketing authorization, it is not required to submit information about the side effects of the generic pharmaceutical product;
- According to Georgian legislation, active substance and excipients should have information about methods of analysis and their specification; however, it is not required to submit information about the validity (relevance) of these methods, which could confirm that submitted methods of analysis are valid and gives opportunity to assess the quality of the substances completely;
- There is no laboratory control during the authorization procedure;
- Bio equivalency[50] of the generic pharmaceutical products, produced in Georgia is represented by in vitro[51] (laboratory) solubility, which is easier and less costly than in vivo[52] (living organism) method. As in Georgian legislation there is no guideline or regulation, which could define meaning and the list of required documents for bio equivalency, the applicants submit only limited number of analyses, which could be insufficient and irrelevant for all form of pharmaceutical product and active substance. Thus, the conclusion about the therapeutical equivalency of the generic product with the original may be unclear and unreliable. In-vivo bio equivalency study is unable to conduct for local generic products, because such kind of studies are not introduced in Georgia. In addition, subjects, who carry out the study, are not identified.

According to the directive of the European parliament, the scientific-technical part of the dossier, submitted for the marketing authorization is more comprehensive. It is divided into three parts:

- Pharmaceutical part;
- Non-clinical reports;
- Clinical study reports.

In EU Member States, while examining the pharmaceutical part of the dossier, the chemical, biological and microbiological study is conducted and at this stage, full cycle of the production is

[49] Generic pharmaceutical product - International nonproprietary reproduced pharmaceutical product(Law of Georgia on Drug and Pharmaceutical Activity)

[50] Bio equivalency - the property wherein two drugs with identical active ingredients (as a brand-name drug and its generic equivalent) or two different dosage forms (as tablet and oral suspension) of the same drug possess similar bioavailability and produce the same effect at the site of physiological activity.
bioavailability-the degree and rate at which a substance (as a drug) is absorbed into a living system or is made available at the site of physiological activity

[51] in vitro – study, which is conducted in artificial conditions

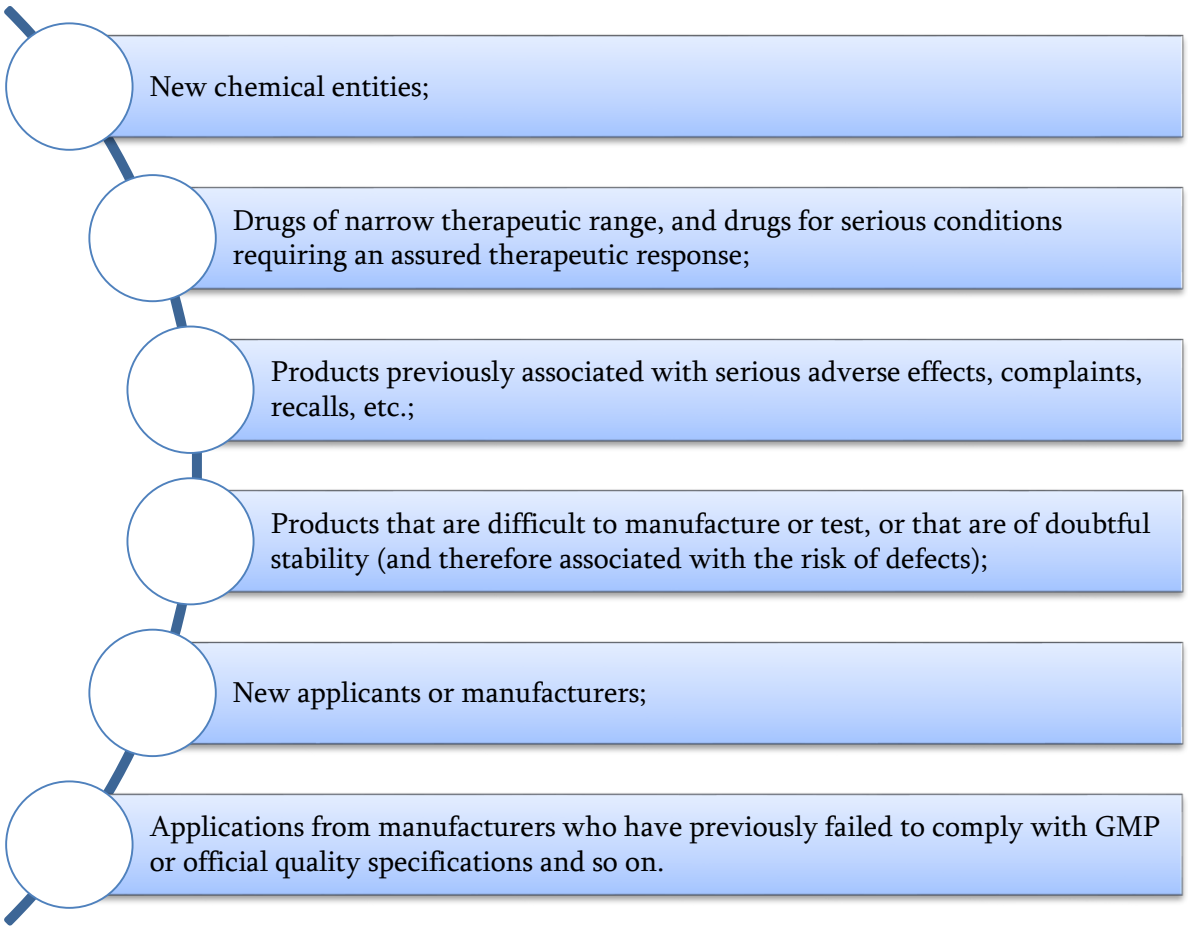
[52] in vivo – study, which is conducted on living conditions

checked – staring from the quality of initial substance, finished by control and inspection of the packaging material.

It is essential for the manufacturer of the pharmaceutical product to have a good manufacturing practice (GMP).

In some exceptional cases, the agencies may require to submit samples of initial and intermediate substances of the pharmaceutical product and make a laboratory analysis for quality control.

The importance of submitting methods of analysis and samples is conditioned due to pre-approval inspections, which is implemented by regulatory agencies in state or independent laboratories. This mechanism of control is not routine, so it is not mandatory to make laboratory analysis for all pharmaceutical products, which are willing to grant marketing authorization. However, WHO and FDA have developed priorities and criteria, according to which pre-approval inspection and laboratory controls are mandatory. These inspections are required for[53]:

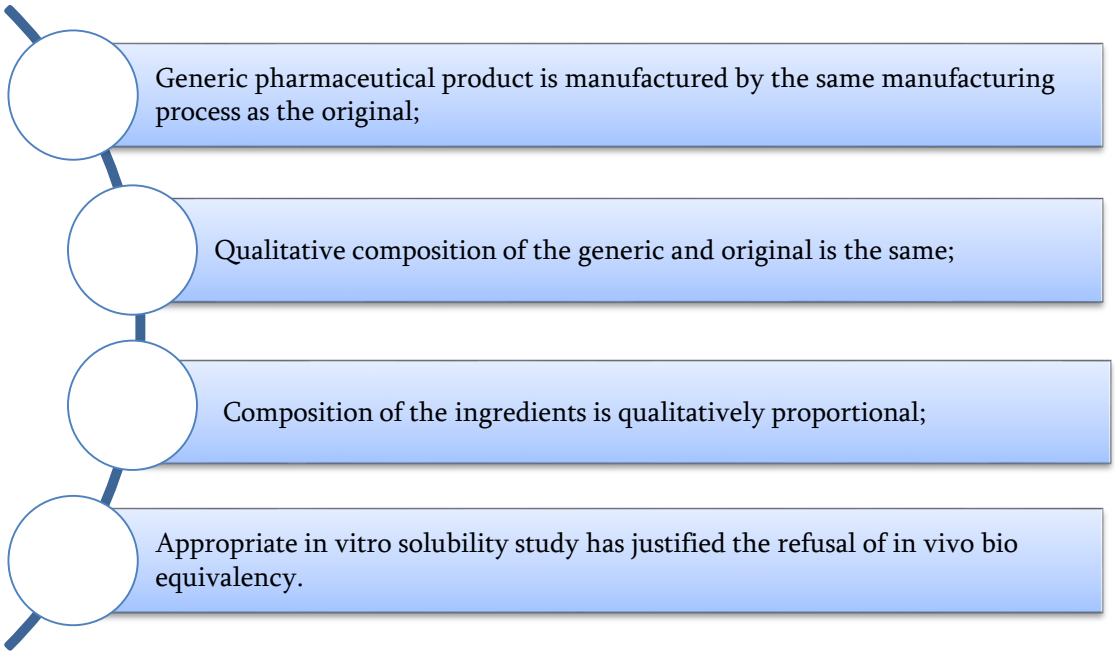


[53] WHO expert committee on specifications for pharmaceutical preparations, Thirty-sixth report, annex 7 Guidelines on pre-approval inspection Food and drug administrations, compliance guidance manual, pre-approval inspections.

Such control is essential as problems related to quality and identity must be revealed during the process of the marketing authorization.

According to the directive of European parliament, it is not required to submit non-clinical and clinical study reports for granting marketing authorization for generic pharmaceutical products, as it is required for innovative pharmaceutical products. However, the information about side effects of the drug is required to submit. This is because gathering information about side effects of the generic pharmaceutical products is easier, as its original product is already presented on the market for some period and this information is available from medical personnel and patients.

It is essential to submit a document, confirming the bio equivalency of the pharmaceutical product with its original product; the same is required for Georgia, however EMA has criteria, when it is recommended to submit in vitro bio equivalency solubility study.[54] Such kind of pharmaceutical products or active substances must have some specific properties, in order to justify the refusal of in vivo bio equivalency. These criteria are:



As it follows from the above, the existing regulatory framework of the national drug authorization procedure does not ensure examination of the quality, efficacy and safety of the pharmaceutical product by using the important mechanisms like submitting information about the side effects of the generic pharmaceutical products, laboratory control of the drugs, use of bio equivalency study, submitting information about the validity of the methods of analysis.

[54] Multisource (generic) pharmaceutical products: Guidelines on registration requirements to establish interchangeability, Annex 7, the World health Organization. WHO Technical report Series, No.937, 2006

3.2.3 Shortcomings in Recognition Marketing Authorization Procedure

In Georgia, the recognition procedure can be used for the pharmaceutical products, which have been granted market authorization by regulatory agencies of other countries or by interstate regulatory agencies, defined by Government resolution. These regulatory agencies include European Medicines Agency (EMA) and agencies of different EU member states, as well as The United States, Australia, New Zealand, Japan, Israel, Canada and Korea. The recognition procedure in Georgia is used for generic, as well as for innovative pharmaceutical products.

Compared to national marketing authorization, in Georgia the recognition procedure is much simpler due to small number of required documents for marketing authorization.

During the recognition procedure, regulatory agency of Georgia does not examine the scientific-technical part of the dossier, and grants authorization based on a few number of documents. The agency is obliged to expertise the submitted documents within one week after the completed submission, and this process itself implies to determine if the presented pharmaceutical product is really authorized in "recognized" country.

For this reason, it is essential to compare submitted documents with the agency of the "recognized" country; especially this applies to certificate of the pharmaceutical product[55] (CPP), authorization number[56] and term of marketing authorization.

Regulatory agencies of "recognized" countries do not have information that Georgia has recognized their pharmaceutical product, thus Georgian regulatory agency does not compare any documentation to these countries.

The agency collects the information about the pharmaceutical product, which has to be authorized, by using web sites. By this time applicant has already submitted certificate of the pharmaceutical product (CPP), authorization number and term of marketing authorization.

Checking documents only on web sites makes doubt on the authenticity and validity of the submitted documents. The "recognized" country may have suspended the authorization of pharmaceutical product for some reasons and this may not appear on the information, uploaded on the web site.

The main point of the recognition procedure is the high communication between regulatory agencies and exchange of authentic information, which must be performed continuously, even after the authorization of the pharmaceutical product.

[55] Certificate of the pharmaceutical product – the document that confirms that the pharmaceutical product is allowed on the market by regulatory agency of the "recognized" country or by interstate regulatory agency.
[56] Authorization number – the unique code, released when pharmaceutical product is allowed in the market

In September 17, 2012 Georgia has joined global surveillance and monitoring program for the drugs, which is implemented by the World Health Organization (WHO). Within this project, 57 member countries of program, receive “operative notifications” about the serious quality problems of pharmaceutical products, in particular, about circulation of substandard, spurious, falsely labeled, falsified and counterfeited pharmaceutical products.

The Georgian regulatory agency implements the appropriate measures based on “operative notifications”. For example, in July 11, 2013, Georgia suspended marketing authorization of the pharmaceutical products consisting "hydroxyethyl starch” based on notification received in June 14, 2013. Based on the clinical study, this pharmaceutical product increased the risk of renal dysfunction and led to an increase in lethality in critical patients and in patients with acute sepsis.

It must be mentioned, that agency does not receive notifications about the side effects of the pharmaceutical product or about the monitoring issues related to risk-benefit balance.

The agency is able to search such kind of information only on web sites of other regulatory agencies, frequent monitoring is not ensured, which results in delayed feedback from Georgian agency. This can be shown from the example below:

On October 11, 2013, the European Commission has decided to suspend the authorization of per oral[57] pharmaceutical products containing antifungal active substances "ketoconazole". The basis of the decision was the information, accumulated over the years about the side effects of these pharmaceutical products, containing "ketoconazole”. In particular, it was found that the benefit from treatment with these pharmaceutical products was less than the damage, resulting from the side effects ("ketoconazole" was characterized by acute hepatotoxicity [58]- hepatitis, cirrhosis of liver, liver failure or fatal conditions that required liver transplantation).

Despite the fact that European commission published the information about suspension straight after they made the decision (11.10.2013), Georgian regulatory agency issued an order on suspension of these pharmaceutical products 8 months later (17.06.2014). Lack of awareness of the regulatory agency and the delayed response on pharmacovigilance in case of "ketoconazole" is caused by two reasons:

- Applicant for marketing authorization by recognition procedure may be any natural person and not only manufacturer of the pharmaceutical product or owner of the trading license, who could have had enough information about the side effects and risk-benefit balance of the pharmaceutical product;

[57]Per oral – to receive a drug by using a mouth
[58] Hepatotoxicity – damaging or depleting liver cells

› The recognition procedure in Georgia is unilateral and as a result, regulatory agencies of "recognized" countries are unable to provide information about the side effects of the pharmaceutical products and about the changes in dossier to Georgian agency.

For these two reasons Georgian regulatory agency cannot receive information on time about the risk-benefit balance of the pharmaceutical product, authorized in Georgia, which puts the safety of the pharmaceutical product under question.

Applicant of marketing authorization by recognition procedure can be any interested party unlike national marketing authorization. If manufacturer or trade license holder of the recognized country changes the dossier of the pharmaceutical product (for example changes in therapeutical effects), Georgian agency may be unable to receive this information, because importer and distributor usually do not have access to such kind of information.

If the recognized country, whose reliability was the reason of authorization of pharmaceutical product in Georgia, removed authorized pharmaceutical product before the term, Georgian regulatory agency is obliged to remove the pharmaceutical product from the registry. However, the agency does not receive information about this on time.

As Georgia is not a member of the European Union, the principles of the bilateral recognition procedure cannot apply to it, however, even in case of unilateral recognition, the connection to the "recognized" country, whose pharmaceutical product is authorized in Georgia, is not established.

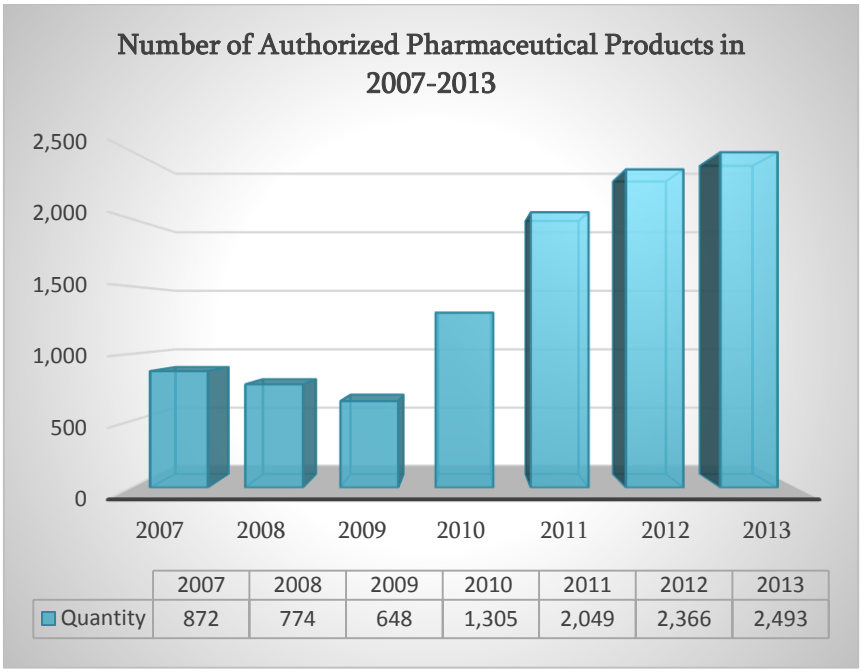
The partner countries of mutual recognition continuously exchange the information about the pharmacovigilance as well as about the risk-benefit balance and its change of the pharmaceutical product.

Communication related to pharmacovigilance in EU member states is essential, as partner countries of mutual recognition will continually have information about the efficacy, quality and safety of the authorized pharmaceutical products. In addition, one of the reasons of rejecting authorization or revocation of authorization of the authorized pharmaceutical product may become its inconsistency of risk-benefit balance with modern medicine[59].The chart below shows the number of authorized pharmaceutical products in Georgia in 2007-2013:[60]

[59] Medicinal Products Act. Estonia. Medicinal Products Act. Slovenia. Pharmaceutical Law. Poland.

[60] Number of pharmaceutical products in the chart does not include I and II order changes and re-authorizations. Also 2007-2009 years does not include authorization of dental materials, however contains diagnostic materials authorized by national procedure (it was not possible to separate them from the statistical data supplied by the agency). In 2010-2013 years, the data does not include diagnostic and dental materials authorized by recognition procedure, however it includes dental and diagnostic materials authorized by recognition procedure or imported by different packaging and labeling.

Chart 3.2.3.1: Number of Authorized Pharmaceutical Products in 2007-2013



	2007	2008	2009	2010	2011	2012	2013
Quantity	872	774	648	1,305	2,049	2,366	2,493

The audit revealed that after amendments in Georgian legislation in 2009, the number of annually authorized pharmaceutical products has tripled, however in 2011-2012 from 3884 pharmaceutical products that were authorized by national and recognition procedure (except local manufacturing), 35% was not imported in the country (1364). This confirms that the authorization procedure in Georgia is simplified.

According to Georgian regulatory agency, this happens frequently, because some applicants need authorization of the pharmaceutical product not for Georgian market. Regulatory agencies of some country require that pharmaceutical product, which has to be authorized in its country, should already had authorization in some other countries. And Georgia, with its lower authorization fees and simplified authorization procedure is the appropriate country for such cases.

The legislation does not take into consideration to resolve the issue, when authorized pharmaceutical product does not appear in Georgian market for several years.

To take an example of Estonia, the regulatory agency revokes the authorization of the pharmaceutical product, which has not appeared on the market for 3 years.

Due to above-mentioned circumstances, Georgian legislation does not ensure protection of the quality standards of the pharmaceutical product during authorization procedure. Marketing authorization is simple procedure. Applicant of marketing authorization by recognition procedure can be any interested party, who will not have information about the changes in authorization dossier in recognized country all time.

Marketing authorization by recognition procedure–unilateral recognition mechanism does not ensure the connection with regulatory agencies of recognized countries and elimination of the risks, which is possible to eliminate by mutual recognition by EU agencies. Considering this, after the authorization, the regulatory agency may also have delayed response on removing from the market unsafe and ineffective pharmaceutical products, which were removed by "recognized" country or by interstate regulatory agency.

The reason of this is the lack of communication with the "recognized" country. Georgia is not able to become a member of mutual recognition and is unable to receive information automatically about withdrawal of the pharmaceutical product because of side effects and risk-benefit balance. However, communication during authorization procedure, monitoring of the information on web sites after the authorization, in case of needs gathering additional information from other agencies is common and accepted process. Accordingly, interagency cooperation is not based only on mutual recognition procedure.

Recommendations:

Marketing authorization of pharmaceutical product and accompanying procedures that comply with internationally accepted standards are important pre-requisite for the safety, efficacy and quality of the pharmaceutical product, It is important that ministry with the agency reviewed regulatory standards and existing procedures by initiating the relevant changes in internal, external regulations:

- Review the authorization scope and harmonize the administrative and scientific-technical part of authorization with the international standards, which implies presenting information about the side effects of the generic pharmaceutical products during authorization procedure, drug laboratory control if relevant criteria exists, presenting information about the validity of methods of analysis by applicant.

- It is important that the drug authorization right was transferred to the manufacturer or trade license holder of the drug in order to provide the agency with relevant information permanently:
  - Changes related to pharmaceutical product
  - To ensure that pharmacovigilance implementation plan will be submitted by the applicant during the authorization procedure, which includes the monitoring plan of adverse and side reactions of the pharmaceutical product.

- It is important that the agency ensured permanent monitoring of the operative notifications and information published on web sites of the respective foreign regulatory agencies. If it is necessary, the agency should ensure gathering additional information from foreign regulatory agencies about the effectiveness (risk-benefit balance), safety of the pharmaceutical product authorized in Georgia to make certain that unsafe and inefficient pharmaceutical products are removed from the Georgian market promptly.

4. Post-Market Control of Drugs and Pharmaceutical Activities

4.1 Selective Control of Authorized Pharmacy – Defining Priorities and inefficiency of the results

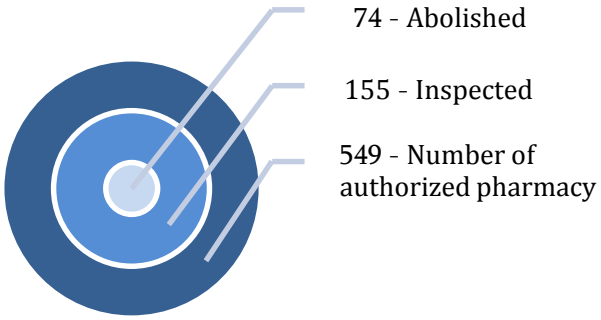
The agency uses selective control mechanism for the inspection of the permission of the pharmaceutical activities according to the Law of Georgia on Licenses and Permits and law on Drug and Pharmaceutical Activities.

Audit team studied the criteria and control of permission conditions of authorized pharmacy. Inspections show that revealing facts of violation of permission conditions, selling first group pharmaceutical products without prescription in Tbilisi, is the priority for the division of inspection. As the agency notes priority comes from the increase in "pharmacy drug addiction".

In 2012-2013, audit revealed that inspection division had a 244 inspection cases on permission conditions, which covered 155 authorized pharmacies at least once.

Out of inspected pharmacies, 47% (74 pharmacies) were abolished. Out of which 6 pharmacies were abolished on the basis of the explanatory note of the inspection division for the purpose of frequent violations (3 violations in one year), and other pharmacies were abolished by permission holder's various will.

Scheme 4.1.1: Number of Authorized, Inspected and Abolished Pharmacies in 2012-2013.[61]



In case of 54 pharmacies, permission conditions were controlled two, three or four times, which amounted to 143 cases - 60 %of total inspected permission conditions.

Audit revealed that in 2012-2013 out of all violations 80 % amounted to violations of permission conditions of authorized pharmacy.

[61] As for January 1, 2013 according to departmental-permission registry, 336 permissions were issued for authorized pharmacies and 203 for pharmacies equalized with authorized pharmacies (Total 539)
As for January 1, 2014 according to departmental-permission registry, 360 permissions were issued for authorized pharmacies and 189 for pharmacies equalized with authorized pharmacies (Total 549)

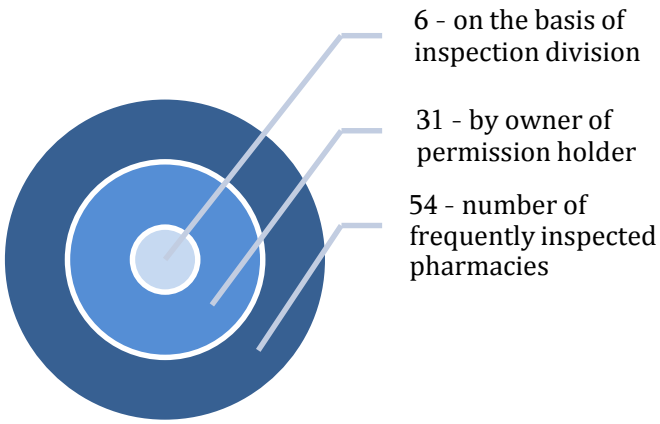
10,829,499 first group pharmaceutical products were sold without prescription in 2013 and 12,957,152 in 2014 (from January 1st to September 29).

Violating the rules of realization of the pharmaceutical products is the violation of proceedings, which is the same as violation of permission conditions. Violations were detected in all inspected authorized pharmacies.

Audit studied to what extent agency reaches its goal to fight against "pharmacy drug addiction" and selling the drugs without prescription. The results showed that out of 54 frequently inspected authorized pharmacies 37 were revoked for different reasons: 6 of them were abolished based on inspection division, rest of them by owner of permission holder.

The scheme below shows the number of abolished pharmaceutical products from frequently inspected pharmacies:

Scheme 4.1.2: Number of Abolished Frequently Inspected Pharmacies by reasons:



Business register revealed that abolished pharmacies start pharmaceutical activity again. In 8 cases (16 participator)[62] pharmacies were abolished based on its own request after the violations revealed by the inspection. After certain period, the same permit holder at the same or different address started the activity by the name of another legal entity.

In 3 cases, after revealing violations[63] by the inspection division pharmacy renewed functioning at the same address as different legal entity with different director of the pharmacy.

Abovementioned cases are caused by the existing shortcomings and problems in regulation. There are simple procedures for opening new pharmacy. Permission conditions are not detailed. Instead of paying the fine for repeated violations, permission holders prefer to start activity with different legal entity and manager.

[62] The number may not be precise as there may be other similar cases that cannot be revealed by business register.
[63] 3 violations detected during the calendar year

In 2012-2013, inspection division took 70 days to examine abovementioned entities for several times each.

In 2012-2013 the agency conducted selective inspections of permission conditions. 80% - 188 inspections were conducted in Tbilisi (50% of authorized and equivalent to authorized pharmacies are located in Tbilisi).

Other 56 inspections were regional, in 23 municipalities or self-governing cities. In majority (43 out of 63) of municipalities inspections were not conducted (Annex 3).

As follows from the abovementioned circumstances, geographical coverage is not ensured by selective inspection.

This is connected to several issues:

- There is only selective control, routine inspection is not established;
- Revealing violations in selling of first group pharmaceutical products without prescription and eradication of "pharmacy drug addiction" is priority for the agency which is related to large amount of resources and time. Inspections are conducted where the high risk of "pharmacy drug addiction" and selling of first group pharmaceutical products without prescription is high;
- The agency does not employ regional inspectors.

WHO, inspectorate of UK[64], Sweden[65] and other European countries have different approach to inspection. Inspections are divided into several categories:

- Routine inspections (manufacturers are controlled 2-3 times per year, wholesale distributors 3-4 times);
- Ad hoc (specialized) inspection;
- Inspections for revealing certain risks.

According to best practice of WHO and other regulatory agencies, risk based assessment system may not cover all wholesalers and retailers, while the coverage of the whole country is significant. Risk and priority based inspection should have relevant impact – eradicate the cause of the problem. This is not ensured in case of the agency inspections because of legislative shortcomings and lack of resources.

The table below shows the number of authorized pharmaceutical products and activities relative to number of inspectors:

[64] MHRA.GOV.UK
[65] http://www.lakemedelsverket.se/english/

Table 4.1.1: Number of Pharmaceutical Activities and Authorized Pharmaceutical Products Relative to Number of Inspectors

Pharmaceutical Activity and Authorized Pharmaceutical Products	Quantity	Number of Inspectors
Authorized pharmaceutical products	10,541	13 inspectors
All pharmacies	3,333	
All manufacturing	75	
All clinical trials	45	

On the one hand, inspections based on priorities do not have instant results, since infringers still continue authorization activities because of simple procedures of starting a business. Accordingly, huge resources of inspection division are spent on control of activities that cannot be prevented under the current regulations. In addition, inspectors participate in supervision of pharmaceutical activities in medical institutions[66]. On the other hand, number of authorized drugs, pharmacies, manufacturing, clinical trials is huge because of simple procedures and is related to human resources. Together with this, the agency does not have regional inspectors and the work undertaken by the inspector is not differentiated by the type of pharmaceutical activity. In particular, the same inspectors make selective control of pharmaceutical products, and controlling of the permission for manufacturing, pharmacy and clinical trial, whilst in European countries and US regulatory agencies, inspectors are differentiated and trained depending on the type of activity[67].

[66] Ltd. "Clinical Hospital of Infectious Diseases of Children in Tbilisi" (order №02-114/m);
Ltd. "The National Cancer Center of Georgia" (order №02-343/m);
Ltd. "Archimedes Clinic" (order №02-405/m);
Ltd. "Shalva (David) Koridze Maternity House (order №02-263/m);
Ltd. "Elite Clinic" (order №02-72/m);
NNLE "National Academy of Palliative Care - practical, educational and scientific resource center" (order №02-393/m);
Ltd. "Heart Disease Center" (order №02-238/m);
LEPL Emergency Medical Center (order №02-498/m);
N19 Tuberculosis Treatment and Rehabilitation Center of Georgian (order №02-524/m);
Ltd. "Referral Hospital" (order №02-24/m);
JSC "K. Eristavi Experimental and Clinical Surgery National Center (order №02-222/m);
JSC "Rustavi Central Hospital" (order №02-330/m);
Ltd. "Mental Health and Prevention of Addiction" (order №02-503/m).
9 specialists from inspection division of the pharmaceutical department were involved in inspections.

[67] EMEA, MHRA, FDA

4.2 Selective Control of the Pharmaceutical Product–Lack of Information Schemes and Methodological Criteria for Risk Assessment

Agency uses selective control guidelines for selective control of pharmaceutical products.

Guideline aims to define control procedures, which should be the base for risk-assessment based selective control of drug sellers.

The main goal of the selective control is to protect Georgian market from falsified, damaged, obsolete, outdated and not authorized pharmaceutical products.

Agency uses laboratory and distribution chain administrative control mechanisms for risk assessment based selective control of pharmaceutical products. Agency has the agreement with LEPL "Levan Samkharauli National Forensics Bureau" (Forensics Bureau) for laboratory control.

Criteria of high risks of falsification and counterfeit are the base of selective inspection of pharmaceutical products.

During selective control, the agency prioritizes locally manufactured pharmaceutical products to eliminate the gaps in unstandardized monitoring and control procedures.

Criteria of the agency for the selective control of wholesale and retail of pharmaceutical products are:

- wholesalers and retailers that were not inspected for a year;
- wholesalers and retailers that were inspected and the violations were revealed in recent 2 years, and the violations were regular;
- Inspection may be conducted in case of visual doubt that the pharmaceutical product is falsified, counterfeited, obsolete, damaged, outdated and/or sanitary-hygienic/technical conditions of storage and handling are not protected;
- In case of information/notification that imported medicine is damaged, falsified, counterfeited or damaged in importer country;
- In case of information/notification about the sellers, that there is high risk that product is low quality.

Based on one of these criteria, while making risk based selective control, the agency purchases the sample of the pharmaceutical product from the sellers.

Agency purchases pharmaceutical products from retail chain. In all critical zones, where the quality change risk is high or if there is a doubt about the origin (at the custom, during transportation or marketing) of the pharmaceutical products, inspection division takes samples.

Audit revealed that 95 % of selective control was conducted in ordinary pharmacies and not in authorized one.

While the majority of inspection activities (70%) are control of permission conditions, 95 % of the inspection of pharmaceutical products is conducted in the ordinary pharmacies that are out of scope of permission. This can be considered as a positive occurrence.

1125 pharmaceutical products from 218 sellers were inspected in 2012-2013.

- 130 sellers – 2012
- 88 sellers – 2013

The following violations were revealed during administrative traceability and the study of different packaging and labeling.

Table 4.2.1: Revealed Violations

Type of Violation	2012	2013
Circulation of the pharmaceutical products with different packaging and labeling	25	6
Circulation of the substandard pharmaceutical products	8	1

The agency made laboratory analyses. This mechanism was used for the authorized pharmaceutical products (by recognition or national procedure), in case of high risks of falsification and deterioration.

250 pharmaceutical products were sent to LEPL "Levan Samkharauli National Forensics Bureau" for laboratory control in 2012-2013, 9 of which were inconsistent with normative-technical requirements.

The cases of falsifications were not revealed in mentioned years, while in other countries in strictly defined quality control systems, several falsification facts are recorded by regulatory agencies.

With respect to falsification, only in 2014, in one pharmaceutical manufacturing 5 brand named falsified products were detected (consisting of 170 312 unit of pharmaceutical product) by the agency, which was sealed and confiscated.

Audit revealed that informative environment, which is essential for identifying risks and risk assessment criteria do not ensure adequate control of pharmaceutical products.

To control pharmaceutical products, the agency uses formal criteria for risk identification; however, the agency has not implemented risk assessment system, which is related to risk identification by risk assessment criteria in appropriate informational environment (risk ranking system).

Shortcomings in legislation and absence of risk ranking system are related to informational system failure, which is reflected in following:

- As the permission validity of opening new pharmacy is unlimited and the permission criteria are simple - inspection division does not have the real number of active sellers. Number of pharmacies is high for these simple procedures, also renewal of permissions, routine inspections are not established that can be the base for risk ranking system;
- Majority of pharmacies (72%) are not subject to permissions and start functioning according to notification. Accordingly, inspection is unable to define the risks during initial inspection for the selective control in the future;
- Geographical coverage of selective control is low. this is shown on the map below:

Map 4.2.1: Geographical Coverage of Selective Control

As it turns out, selective control of pharmaceutical products was not conducted in several regions in recent years.

- Pharmacovigilance system is not established in Georgia, which is one of the most important steps in assessing falsification risks during post-market control. Agency does not monitor side effects and adverse drug reaction. Complaints recorded by telephone, electronically or written from medical staff, patients, and other subjects involved in pharmaceutical activities is very small (13 calls in 2012-2013), which is the most important part of risk assessment system.

The audit revealed that according to NCDC, many cases of drug intoxication were reported in last year shown on the table below:

Table 4.2.2: Number of drug intoxication

Year	Patients who left the hospital	Of which died	Total mortality rate (%)
2009	2048	23	1.1
2010	2417	28	1.2
2011	1504	9	0.6
2012	1141	6	0.5
2013	1723	5	0.3

Consolidated information by NCDC is based only on the patients that were hospitalized. In case of drug intoxication, NCDC cannot obtain information about the causes of intoxication (overdose, adverse reaction, etc.). NCDC and Department of Pharmaceutical Activities do not communicate regarding these issues.

According to the agency, attempt to establish pharmacovigilance system was unsuccessful as the agency did not receive any information on side effects and adverse reaction of pharmaceutical products from medical staff. Accordingly, order of Minister that obligated medical staff to submit information to the agency about side effects was not successful, as the agency did not receive any reliable information from doctors[68] out of all such cases.

The agency has not received any complaints from patients while regulatory agency of Sweden receives up to 500 complaints per year.

The Georgian regulatory agency has not taken any significant steps for increasing public awareness about this issue. In European countries, the communication between the regulatory agency and doctors happens on regular basis. At the same time, the information system for patients is refined – there is contact information of regulatory agencies on packaging of drug -and there is warning that in case of side effects and adverse drug reactions they should communicate regulatory agency.

As it was mentioned above, agency has implemented guidelines of risk assessment criteria, however the most frequently used criteria indicated in documents are: *inspections of pharmaceutical products were not conducted for a year*, but as the agency notes criteria is certain information that is not documented. For developing risk assessment system it is very important to record inspection history (to record criteria that were used while inspection) of seller, which will be given the status in the system.

Significant criteria are defined in methodology but it lacks some other criteria that are recommended by Euro Commission directive[69]:

[68] Order №167/n of the minister of Labor, Health and Social Affairs of Georgia (August 7, 2003)
[69] Directive 2011/62 EU

- Price of pharmaceutical products – as low as well as high price. Low price of parallel import is used as risk assessment criteria;
- Specific pharmaceutical products – pharmaceutical products for orphan, rare diseases;
- Information received through local and foreign pharmacovigilance system.

From above mentioned follows that existing shortcomings in pre-market control affects post-market control – inspection and pharmacovigilance. Current inspection system does not provide public protection from drug falsification. There are shortcomings not only in methodology and geographical coverage, but also in resource planning and differentiation. Inspection system lacks the precise information about all subjects involved in pharmaceutical activities, the agency lacks information about risks, and there is no system ensuring information exchange between subjects involved in the system. This leads to the assumption that the pharmaceutical market is not protected from falsified and unsafe products.

4.3 Problems Related to Timely Response on Violations Related to Imports of Pharmaceutical Product with Different Packaging and Labeling

For imports of already marketed pharmaceutical product with different packaging and labeling re-authorization is not required. This kind of pharmaceutical products are released on the market based on notifications.

Change of packaging and labeling without authorization or without notification should be fined by 2000 GEL, with stopping the sale before the eradication of violation.

Inspectors reveal this kind of case during the selective purchase in the pharmaceutical centers. By that time wholesaler has already marketed the pharmaceutical product for the sale. According to legislation, review of the violation protocol and make the final decision of the administration violation lasts by certain period in City or District Court.

The table below shows the time interval for each violation from the writing of violation protocol until the resolution of the Court of Appeal:

Table 4.3.1: Time interval for each violation from the writing of violation protocol until the resolution of court of appeal

Date of writing the violation protocol	Resolution date of City court	Resolution date of Appeals Court
03.10.2013	16.10.2013	12.12.2014
01.08.2014	14.08.2014	21.10.2014
01.08.2014	13.08.2014	30.09.2014
22.09.2014	23.10.2014	28.11.2014

After the resolution of court, the subject of violation is under the suspension of the realization before the eradication of violation.

At that time, it may be the case that wholesaler does not possess a huge part of the pharmaceutical products, because it is already realized from the retailers.

According to the agency, infringer appeals Court to increase the period for circulation of the pharmaceutical product with violated different packaging and labeling until the court makes the decision. Before the decision of Appeals Court, the pharmaceutical product is fully realized.

Imports of the pharmaceutical product with different packaging and labeling based on the agency notification (based on simple mechanism) does not mean that the illegal circulation of the pharmaceutical product was possible after detecting the violation.

Recommendations:

In order to ensure the proper planning of post-market control Ministry with the agency should ensure implementing appropriate activities and changes related to organizational and legislative aspects:

- For the purpose, that conducted inspections to have real results, resources for the inspection division should not be wasted inefficiently, it is important to review and improve permission conditions of authorized pharmacies;

- *Improvement of methodology* of inspection, which will be focused on risk assessment and elimination. For that reason, it is important to improve methodological aspects of control activities: improving the risk assessment criteria, implementing routine (once in a few years) or risk-based control of pharmaceutical activities based on their peculiarity. It is important that during inspections the issue of geographic coverage was taken into account – this will give opportunity to the agency to have precise and updated information about all subjects involved in the pharmaceutical activity and about the protection of permission condition, to define risks and have its further responses;

- It is significant that timely responses were ensured when there is violation of the parallel import notification procedure. For this reason, it is important that adequate mechanisms were introduced in legislation, such that the violator does not have opportunity to sell violated pharmaceutical products as a result of prolonged procedures;

- It is important that control procedures were improved, human resources were planned carefully, during which the distribution of inspectors should be differentiated depending on the type of activity, which will increase the efficiency and will promote the increase of skills in particular direction;

- Pharmacovigilance system should be implemented by active communication with medical personnel, the NCDC, patients, manufacturers, trade license holders. Activities for raising awareness for the public and medical personnel were carried out to receive information about side effects and adverse drug reaction of the pharmaceutical products, which could give opportunity to agency to control drugs and pharmaceutical activities by implementing risk assessment system.

Summary Conclusions and Recommendations

Regulatory system analysis shows that quality, efficacy and safety of the pharmaceutical products is not a priority of the country.

Pharmacovigilance system - monitoring of adverse drug reaction and side effects of pharmaceutical products is not introduced, this indicates that evaluations of efficacy and safety of drugs does not exist.

Current regulatory system cannot ensure quality, efficacy and safety of pharmaceutical products that is revealed in the following:

Pre-market control of drugs and pharmaceutical activities:

Pharmaceutical activity

There are significant shortcomings in legislation and strategic planning in terms of pharmaceutical activities, namely: GMP standards are planned to be valid in 2016. The agency has not started the transition process to GMP standards, whilst the preparation process of the transition should start reasonably early and should include trainings and raising awareness not only for manufacturer, but for inspectors as well. In the agency there is no strategy defined on how standards should be implemented and what challenges the country has in this direction.

Despite the fact that activities of clinical trials are standardized, the term of issuing permission is not based on features of the clinical trial, which could influence issuance of permission for wider and challenged clinical trials. Current legislation is not in compliance with internationally accepted standards. After the permission is issued, the inspections are not carried out based on defined methodology, risks assessment and coverage criteria.

As for pharmaceutical activities, issuance of permissions for pharmacies is not based on prescription drug criteria. In particular, according to ongoing legislation general pharmacies, that sell prescription drugs, are not under the permission systems. While the number of such pharmacies is high and amounts to 72% (2831 units) of all pharmacies.

Despite the fact that these pharmacies sell prescription drugs, storage and handling conditions for pharmaceutical products and norms of pharmacy practices is not standardized for them. Sanctions are not defined for the pharmacies if the sanitary-hygienic norms are violated.

According to legislation, permissions issued for authorized pharmacies are unlimited, which does not allow agency to monitor the activities of pharmacies, to possess accurate and updated information about currently functioning pharmacies and the protection of the permission conditions.

Nonexistence of good distribution practice puts at the risk the quality of circulated pharmaceutical product. Especially in the circumstances, when during transportation it is important to protect cold chain conditions according to instruction. Standardized procedures promote control and strengthen the quality of pharmaceutical product.

Due to the abovementioned factors and the shortcomings in the regulations, the safe environment for the drug circulation is not guaranteed during drug storage, handling and transportation. Permission conditions and standards fall behind the internationally accepted practice and standards; furthermore, it does not ensure its further monitoring opportunities.

Authorization of the pharmaceutical product

According to Georgian legislation, protecting all types of quality standards is not considered. During national marketing authorization, control of quality, efficacy and safety of pharmaceutical products, is not ensured under the current regulations by the following mechanisms:

- Submitting the information about the side effects of the generic pharmaceutical products;
- Preliminary laboratory control of pharmaceutical products;
- Use of in vivo bioequivalence method;
- Submitting information about the validity of the methods of analysis.

Authorization of pharmaceutical product is simple procedure in Georgia. This is corroborated by the fact that the number of authorized pharmaceutical products is high (10 541) and 35% of authorized medicines (2011-2012) has not been imported in the country yet (the end of audit period). Accordingly the purpose of market authorization was not the realization of the pharmaceutical product in Georgian market.

Marketing authorization by recognition procedure – unilateral recognition mechanism does not ensure elimination of risks connected to pharmaceutical product by intercourse of recognized regulatory agencies.

The agency does not ensure the permanent monitoring of the web sites and if necessary connection with other regulatory agencies.

After the authorization, the regulatory agency may also have delayed reaction to remove from the market unsafe and ineffective pharmaceutical products, which were removed by “recognized” country or by interstate regulatory agency.

Post-market regulation of drugs and pharmaceutical activities

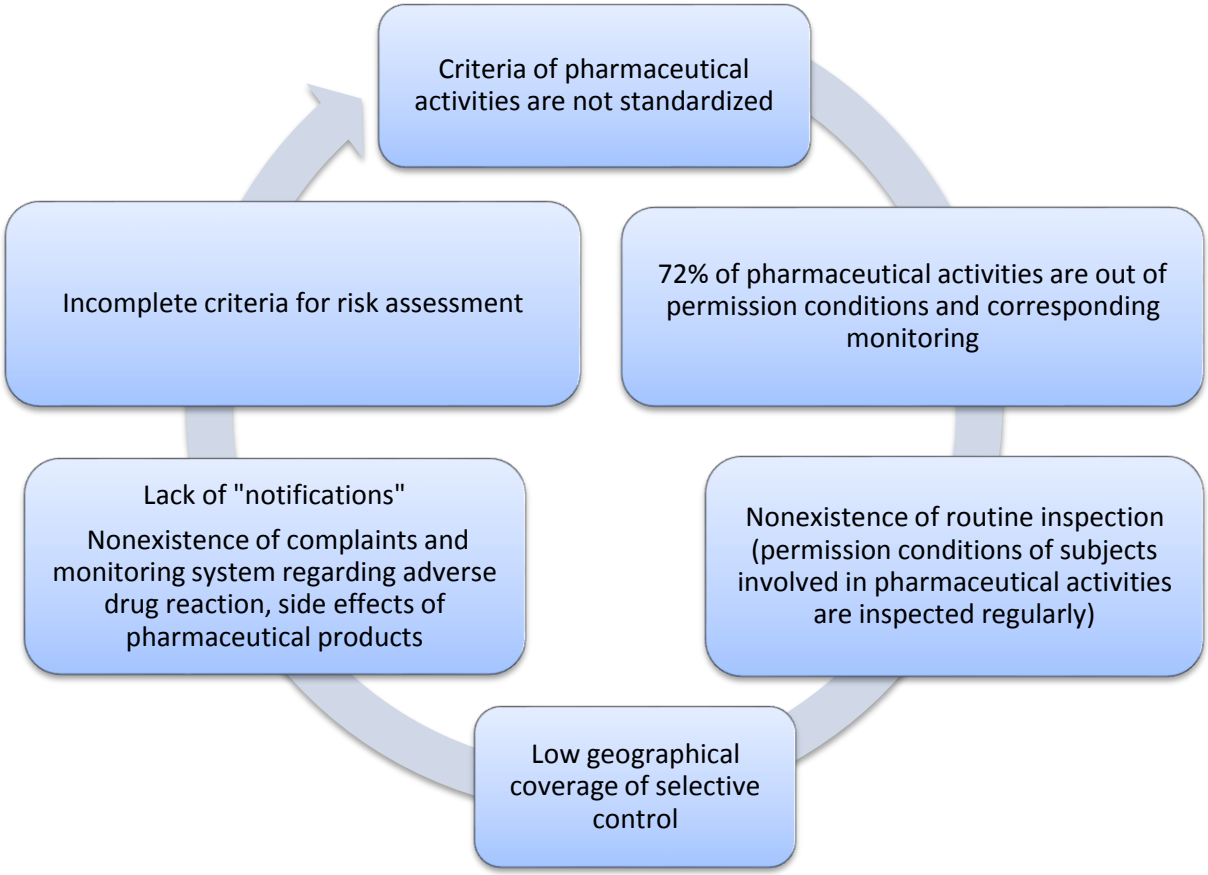
Inspection and pharmacovigilance

Agency ensures post-market control of pharmaceutical products by inspection of permission conditions and selective control of pharmaceutical product.

Permission conditions are mostly inspected in authorized pharmacies, which sell pharmaceutical products under special control. The purpose of frequent inspections is the high rate of realization of drugs without prescription and other existing violations, however despite frequent inspections, abolished pharmacies start pharmaceutical activity anyway because of simple legal basis.

Accordingly, huge resources of inspection division are spent on the control of activities that cannot be prevented under the current regulations.

Agency does not have full information about the number of subjects involved in pharmaceutical activities. Informational environment of the agency cannot ensure complete and precise identification of risks, which is stipulated by the following factors:



The number of authorized pharmaceutical products, and subjects involved in pharmaceutical activity is huge and is related to human resources. Together with this, the agency does not have regional inspectors and the work undertaken by the inspector is not differentiated by the type of pharmaceutical activity. In particular, the same inspectors make selective control of pharmaceutical products, and controlling of the permission for manufacturing, pharmacy and clinical trial, whilst in European countries and US regulatory agencies, inspectors are differentiated and trained depending on the type of activity.

Information sharing mechanisms with patients, medical personnel, organizations involved in pharmaceutical activities, NCDC are not established. These mechanisms are necessary for monitoring, eliminating and preventing adverse drug reaction and the side effects of pharmaceutical products.

Recommendations:

To Ministry of Labor Health and Social Affairs of Georgia, state regulation agency for medical activities:

Related to Pharmaceutical Activities:

In order to ensure the quality, efficacy and safety of the pharmaceutical product, it is important that ministry, with the agency verify developing conditions for manufacturing, its further trial, distribution, storage, handling and realization, promote activities for improving current conditions by initiating internal organizational and legislative changes:

- Develop strategic view, action plan for the implementation of GMP standards and its further monitoring, control;

- Depending on the specifics of the clinical trial, review the permission issuance procedure and term with respect to types of the clinical trial, number of organizations, subjects involved in the study. Improve legislation in conformity with recognized clinical trial guideline and develop methodology for further monitoring of the clinical trial;

- To ensure safe and controlled environment for storage and realization of prescription drugs in ordinary pharmacies, it is important to set the conditions that correspond to current international standards, related to realization of the pharmaceutical product – permission conditions, terms of permissions and their further controls;

- To develop and set distribution standards for pharmaceutical products, that is related to transportation of the pharmaceutical product in safe environment, quality management issues and control of distribution.

Related to Authorization of Pharmaceutical Products:

Marketing authorization of pharmaceutical product and accompanying procedures that comply with internationally accepted standards are important pre-requisite for the safety, efficacy and quality of the pharmaceutical product, It is important that ministry with the agency reviewed regulatory standards and existing procedures by initiating the relevant changes in internal, external regulations:

- Review the rules of the authorization scope and harmonize the administrative and scientific-technical part of authorization with the international standards, which implies presenting information about the side effects of the pharmaceutical products during authorization of the generic pharmaceutical product, drug laboratory control if relevant criteria exists, presenting information about the validity of methods of analysis by applicant;

- It is important that the drug authorization right was transferred to the manufacturer or trade license holder of the drug in order to provide the agency with relevant information permanently related to:
  - Changes related to pharmaceutical product
  - To ensure that pharmacovigilance implementation plan is submitted by the applicant during the authorization procedure. (Includes the monitoring plan of adverse drug reaction and side effects of the pharmaceutical product);

- It is important that the agency ensured permanent monitoring of the operative notifications and information published on web sites of the respective foreign regulatory agencies. If it is necessary, the agency should ensure gathering additional information from foreign regulatory agencies about the effectiveness (risk-benefit balance), safety of the pharmaceutical product authorized in Georgia to make certain that unsafe and inefficient pharmaceutical products are removed from the Georgian market promptly.

Related to Post-Market Monitoring, Inspections:

In order to ensure the proper planning of post-market control Ministry with the agency should ensure implementing appropriate activities and changes related to organizational and legislative aspects:

- For the purpose, that conducted inspections had real results and resources of the inspections division was not wasted inefficiently, it is important that permission conditions of authorized pharmacies were reviewed and improved;

- Improvement of methodology of inspection, which will be focused on risk assessment and elimination. For that reason, it is important to improve methodological aspects of control activities: improving the risk assessment criteria, implementing routine (once in few years) or risk-based control of pharmaceutical activities based on their peculiarity. It is important that during inspections the issue of geographic coverage was taken into account – this will give opportunity to the agency to have precise and updated information about all subjects involved in the pharmaceutical activity and about the protection of permission conditions, to define risks and have its further responses;

- It is important that timely responses were ensured when there is violation of the parallel import notification rules. For this reason, it is important that adequate mechanisms were introduced in legislation, such that the violator does not have opportunity to sell violated pharmaceutical products as a result of prolonged procedures;

- It is important that control procedures were improved, human resources were planned carefully, during which the distribution of inspectors should be differentiated depending on the type of activity, which will increase the efficiency and will promote the increase of skills in particular direction;

- Pharmacovigilance system should be implemented by active communication with medical personnel, the NCDC, patients, manufacturers, trade license holders. Activities for raising awareness for the public and medical personnel were carried out to receive information about side effects and adverse drug reaction, which could give opportunity to agency to control drugs and pharmaceutical activities by implementing risk assessment system.

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Annexes

Annex 1: Scope of Mandatory and Voluntary Authorization

Mandatory authorization	Voluntary authorization	No need for authorization
› pharmaceutical products (drugs) › Innovative/generic › First and second order of changes in authorization › Immunobiological drugs › Radiopharmaceutical drugs › Mechanical contraceptives › Diagnostic materials › Dental materials	› Complementary drugs › Biologically active additives › Paramedical drugs	› Pharmaceutical substance › Bulks › Pharmaceutical products prepared by recipe › Allergens for individual use › Non-invasive methods of contraception

Annex 2: The Number of Authorized Pharmaceutical Products in 2010-2013

	Pharmaceutical product	Number of authorized pharmaceutical products			
		2010	2011	2012	2013
1	Primary authorization of innovative drugs	12	12	35	22
2	Primary authorization of generic, blood, immunobiological, paramedic and radiopharmaceutical drugs	566	525	530	490
3	Primary authorization/register of biologically active additive	10	5	2	5
4	Primary authorization/register of complementary pharmaceutical products	4	4	5	0
5	Primary authorization/register of dental materials	0	25	10	2
6	Primary authorization/register of diagnostic materials	46	49	53	92
7	Re-authorization of innovative drugs	2	4	10	6
8	Re- authorization of generic, blood, immunobiological, and radiopharmaceutical drugs	428	440	792	759
9	Re- authorization of paramedic pharmaceutical products	35	16	39	45
10	Re- authorization/register of biologically active additive	0	2	4	3
11	Re- authorization/register of diagnostic materials	4	8	23	17
12	I order changes	1689	682	1729	2157
13	II order changes	436	489	452	500
14	Authorization by recognition procedure of pharmaceutical products, dental and diagnostic material	290	350	362	535
15	Imports of pharmaceutical products, dental and diagnostic materials with different packaging and labeling	423	1153	1432	1441
	Sum	**3945**	**3764**	**5478**	**6074**

Annex 3: Inspections Conducted in the Cities and Municipalities

Municipality/city	Quantity	Number of authorized pharmacy
Tbilisi	188	242
Batumi	10	19
Kutaisi	8	33
Rustavi	4	18
Gurjaani	3	5
Telavi	3	5
Chiatura	3	3
Zestafoni	2	6
Lagodexi	2	3
Mtskheta	2	4
Ozurgeti	2	3
Samtredia	2	5
Poti	2	6
Khashuri	2	6
Khelvachauri	2	4
Akhalcikhe	1	6
Bolnisi	1	3
Gardabani	1	5
Zugdidi	1	10
Kaspi	1	1
Senaki	1	7
Kareli	1	2
Kobuleti	1	6
Tsnori	1	5
Gori	×	13
Lanchkhuti	×	5
Ambrolauri	×	4
Dedoflistskaro	×	4
Marneuli	×	4
Tskaltubo	×	4
Akhmeta	×	3
Borjomi	×	3
Terjola	×	3
Martvili	×	3
Sachkhere	×	3
Khoni	×	3
Abasha	×	2
Adigeni	×	2
Akhalkalaki	×	2
Baghdati	×	2
Vani	×	2

Lentekhi	×	2
Ninotsminda	×	2
Oni	×	2
Sagarejo	×	2
Tkibuli	×	2
Kvareli	×	2
Chokhatauri	×	2
Chkhorotsku	×	2
Aspindza	×	1
Settlement Akhalgori	×	1
Settlement kazbegi	×	1
Dmanisi	×	1
Dusheti	×	1
Tetritskaro	×	1
Tianeti	×	1
Sighnaghi	×	1
Surami	×	1
Keda	×	1
Ksani	×	1
Shuakhevi	×	1
Tsageri	×	1
Tsalenjikha	×	1
Tsalka	×	1
Kharagauli	×	1
Khobi	×	1
Khulo	×	1

State Audit Office of Georgia
0144, Tbilisi: N96, Saint Queen Ketevan Ave.
Tel: +995 32 2438438