Clinical Trials in Ukraine
Orange Paper

1st Half of 2017

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Contents

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Executive Summary

According to statistical data there were 2,420 clinical trials approved to to be conducted in Ukraine for the period from 2007 to the 1st half of 2017.

The Ministry of Health of Ukraine (MoH) approved 106 new clinical trials during the 1st half of 2017. The largest contribution to the total number of studies was made by multinational multi-center clinical trials (MMCT) with 87 trials. The number of bioequivalence studies (BE) in the 1st half of 2017 amounted to two. The number of local clinical trials (LCT) in the 1st half of 2017 was 17 studies.

The share of MMCT was 82% of the total number of clinical trials in the 1st half of 2017, while the share of local clinical trials amounted to 16% and bioequivalence studies amounted to 2% respectively.

There were no approvals registered for Phase I MMCT in the 1st half of 2017. Phase II trials were approved 25 times and Phase III trials remain in the leading position with 61 respectively. There was only 1 Phase IV trial approved in 1st half 2017.

Among international clinical trial applicants *Quintiles Ukraine*, which holds 12% of the market, was on the top of the heap in the 1st half of 2017. Second and third stages hold companies *InnoPharm (PPD Ukraine)* and *PSI Ukraine* with 6% each, followed in the 4th-5th place by companies *Astra Zeneca Ukraine* and *INC Research Ukraine* with 5% each, and other 28 companies totaled 66%.

Among international sponsors the leading position was held by the following companies, *Gilead Sciences, Inc., USA* on the top with 6%, second is *AstraZeneca AB, Sweden* with 5%, and third-fourth places are followed by *Pfizer, Inc., USA* and *Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc. USA* with 3% each respectively. 43 other sponsors had 83% of the market.

The Ukrainian companies *PJSC "Farmak"* and *PJSC "Pharmaceutical company "Darnytsya"* held 24% of the market each and ranked number one among domestic pharmaceutical applicants in the 1st half of 2017. They are followed by *LLC "Pharmaceutical company "Zdorovye"* with 10%, other six companies made up the other 42%.

In the 1st half of 2017, the majority of MMCTs were initiated in seven leading therapeutic areas: the largest numbers of studies were initiated in Oncology (14) and Psychiatry and Neurology (12); followed by Rheumatology (10); Cardiology (eight); Pulmonology (five); Endocrinology (five) and Hematology (four).

During the 1st half of 2017, the State Expert Center of MoH of Ukraine granted 10 positive permissions for MMCT conducted in pediatrics, four more than in all of 2016. Only one Phase II clinical trial (10%) and nine Phase III trials (90%) were conducted in pediatric groups in the 1st half of 2017.

The Center for Drug Evaluation and Research (CDER) of the FDA approved 70 new drugs during the 1st half of 2017; 17 of them were new molecular entities (NME). Seven of the 70 new drugs were (or are being) studied in clinical trials conducted in Ukraine.

During the 1st half of 2017, the Committee for Medicinal Products for Human Use (CHMP) of the European Medicine Agency (EMA) gave positive recommendations on 26 new drug applications[1]. Negative opinions were adopted for three drugs. Twenty-one new drugs which received positive opinions were (or are being) tested in clinical trials in Ukraine.

The State Expert Center of MoH of Ukraine conducted 28 inspections (clinical audits) during the 1st half of 2017.

There were no significant Regulatory updates within the 1st half of 2017.

[1] Positive opinions on new generic, hybrid and biosimilar medicines are not included.

Clinical Trials by Type

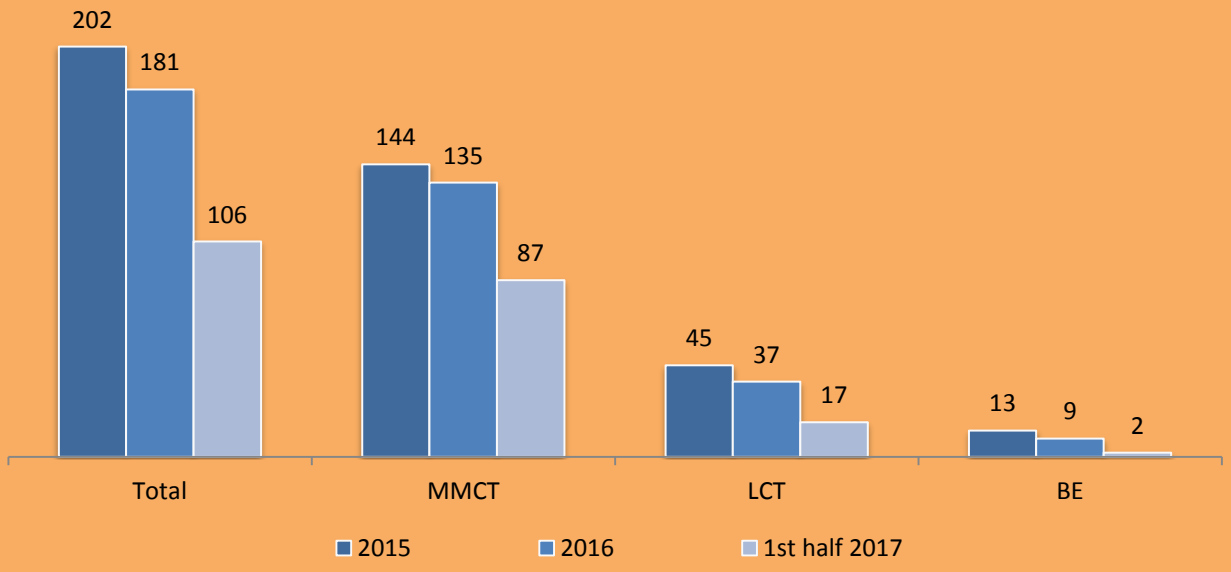
The MoH of Ukraine approved 106 new clinical trials of all types including local and bioequivalence studies during the 1st half of 2017, indicating a potentially significant increase for 2017 in comparison with the last year.

As shown in **Figure 1**, the main contribution into the total number of studies was made by multinational multi-center clinical trials (MMCT) and amounted to 87 studies in the 1st half of 2017 compared with 144 in 2015 and 135 in 2016.

The number of local clinical trials (LCT) decreased from 45 in 2015 to 37 clinical trials in 2016 and continue this tendency in the 1st half of 2017 with 17 clinical trials.

The number of bioequivalence studies (BE) decreased from 13 in 2015 to nine BE trials in 2016 and continue to decline in 2017 with two BE trials in the 1st half of 2017.

Figure 1. Clinical Trials in Ukraine in 2015 – 1st Half of 2017

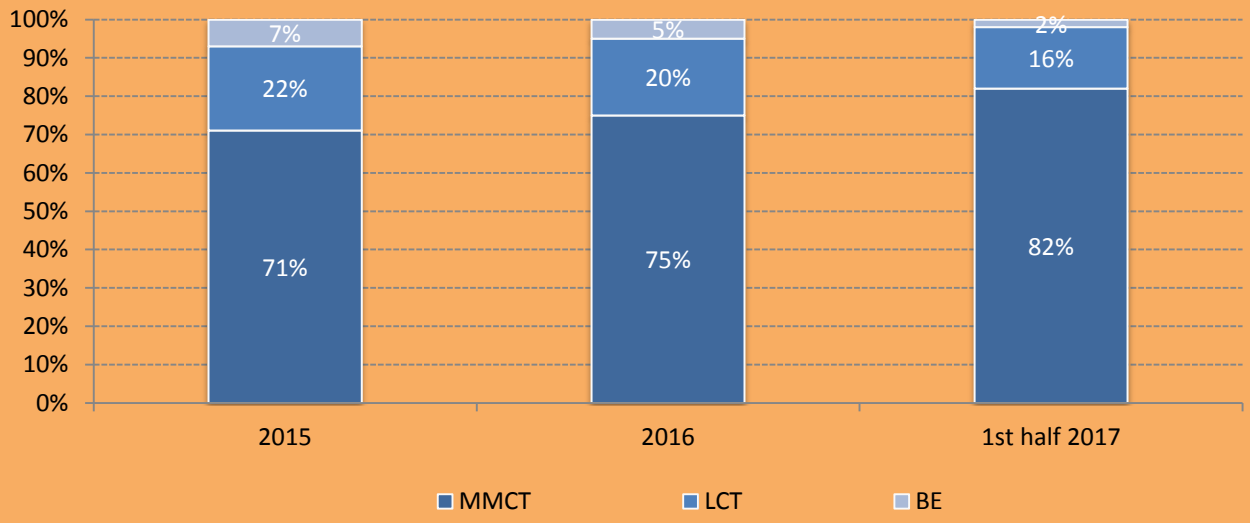


The proportions between different study types (multinational multi-center clinical trials and local studies) changed noticeably since 2015 year (see **Figure 2**).

In comparison with 2015, the share of bioequivalence studies decreased from 7% to 5% of the total number of clinical trials approved in 2016 and 2% in the 1st half of 2017.

The share of the local trials decreased from 22% in 2015 to 20% in 2016 and 16% in the 1st half of 2017. The share of multinational multi-center clinical trials increased from 71% in 2015 to 75% in 2016 and 82% of the total number of trials approved during the 1st half of 2017.

Figure 2. Clinical Trials by Type in 2015 – 1st Half of 2017

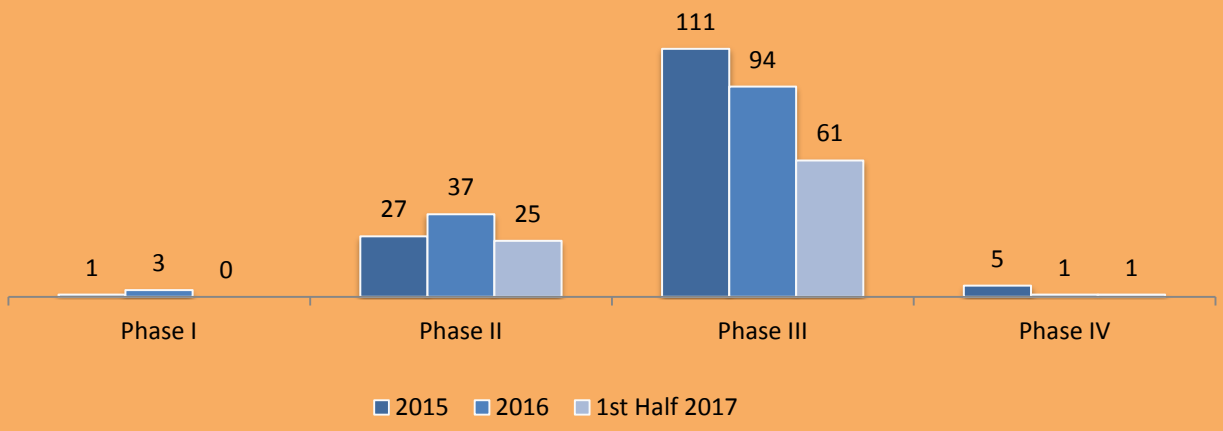


During the clinical trial, the applicant may submit to the State Expert Center of MoH of Ukraine (Center) the significant amendments to the clinical trial protocol (additions or changes of existing information) which are reviewed according to current local legislation. During the 1st half of 2017, the Center issued 613 positive conclusions for MMCT amendments, which is on track to reach the same levels of 2016 with 1,222 positive conclusions.

Multinational Multi-center Clinical Trials by Phase

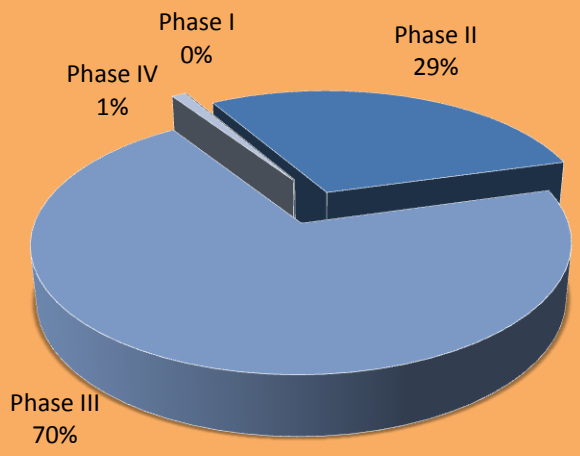
During the 1st half of 2017 there were no approved Phase I MMCT when 2016 saw three new Phase I MMCT and one study in 2015. Phase II trials were approved 25 times and Phase III trials remain in the leading position with 61 respectively. Phase IV trials reduced to one new study in the 1st half of 2017 that equal to amount in 2016 and four studies less that in 2015 (**Figure 3**).

Figure 3. Multinational Multi-center Clinical Trials in Ukraine in 2015 – 1st Half of 2017 by Phase[1]



[1] Studies indicated by sponsors as phase I-II in the applications submitted to MoH, are shown in phase II studies group; phase I-III, II-III and III-IV – in phase III group.

Figure 4. Percentage Breakdown of Ukrainian MMCT by Phase (1st Half of 2017)



Rating of International Applicants and Sponsors

Clinical trial applicants are indicated in **Table 1** and Sponsors in **Table 2**.

Table 1. Applicants of Multinational Multi-center Clinical Trials in Ukraine in 1st Half of 2017

№	Company Name	Market share
1	Quintiles Ukraine	12%
2-3	InnoPharm (PPD Ukraine)	6%
2-3	PSI Ukraine	6%
4-5	Astra Zeneca Ukraine	5%
4-5	INC Reseach Ukraine	5%
6	Other 28 applicants	66%

Table 2. Sponsors of Multinational Multi-center Clinical Trials in Ukraine in 1st Half of 2017

№	Company Name	Market share
1	Gilead Sciences, Inc., USA	6%
2	AstraZeneca AB, Sweden	5%
3-4	Pfizer, Inc., USA	3%

3-4	Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc. USA	3%
5	Other 43 sponsors	83%

Rating of Ukrainian Sponsors

Clinical trials applicants are indicated in **Table 3**.

Table 3. Applicants of Local Clinical Trials in Ukraine in 1st Half of 2017

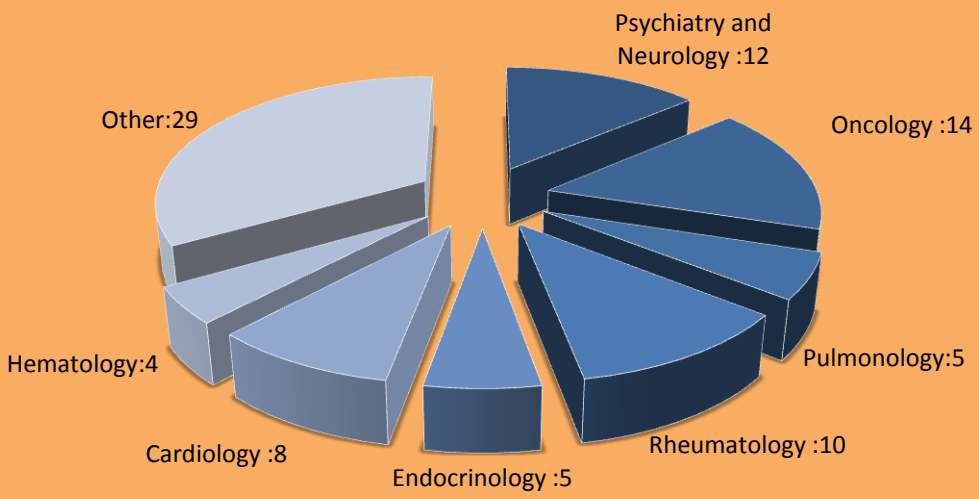
№	Company Name	Market share
1-2	PJSC "Farmak"	24%
1-2	PJSC "Pharmaceutical company "Darnytsya"	24%
3	LLC "Pharmaceutical company "Zdorovye"	10%
4	Other 9 applicants	42%

Therapeutic Areas of Multinational Multi-center Clinical Trials in 1st Half of 2017

In the 1st half of 2017, the majority of MMCTs were initiated in seven leading therapeutic areas: the largest number of studies was initiated in Oncology (14) and Psychiatry and Neurology (12); and are followed by Rheumatology (10); Cardiology (eight); Pulmonology (five); Endocrinology (five) and Hematology (four).

The breakdown of therapeutic areas is shown in **Figure 5**.

Figure 5. MMCT in Ukraine in 1st Half of 2017 by Therapeutic Area



Multinational Multi-center Clinical Trials in Pediatrics

During the 1st half of 2017, the State Expert Center of MoH of Ukraine granted 10 positive permissions for MMCT to be conducted in pediatrics. 90% of cases (nine trials) Phase III clinical trials were conducted in pediatric groups and 10% (one trial) were conducted in Phase II trials in pediatric patients. (**Figure 6**).

Figure 6. Positive Conclusions Regarding MMCT in Pediatrics (2015 – 1st Half of 2017 years)

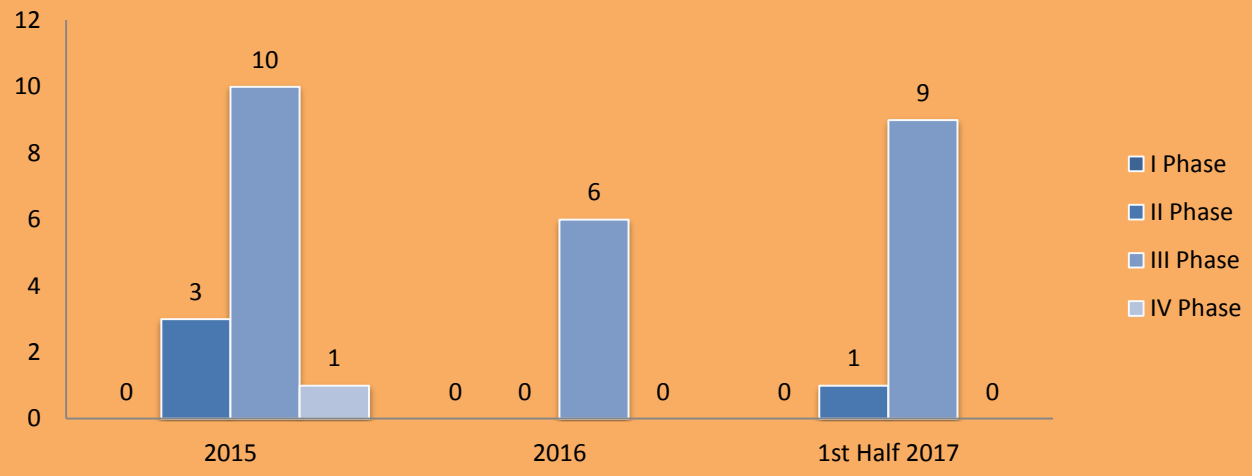


Table 4. Therapeutic Areas of MMCT in Pediatrics (Approved in 2015, 2016 and 1st Half of 2017)

Nosology	2015	2016	1st Half 2017
Psychiatry	3	1	0
Hematology	2	1	0
Infectious diseases	0	2	1
Endocrinology	1	2	1
Surgery	2	0	2
Neurology	1	0	0
Pulmonology	1	0	2
Oncology	2	0	0
Urology/Nephrology	1	0	0
Allergology	0	0	1
Immunology	0	0	1
Rheumatology	0	0	1
Dermatology	0	0	1

Clinical Trials Results

The Center for Drug Evaluation and Research (CDER) of the FDA approved 70 new drugs during the 1st half of 2017; 17 of them were new molecular entities (NME). Seven of 70 new drugs were (or are being) studied in clinical trials conducted in Ukraine.

Table 5 shows the drugs which were approved by the FDA in the 1st half of 2017 that were (or are being) tested in clinical trials in Ukraine.

Table 5. New Drugs Approved by FDA in 1st Half of 2017 and Tested in Ukrainian Sites

APPROVAL DATE	DRUG (ACTIVE INGREDIENT)	COMPANY
01/27/2017	AIRDUO RESPICLICK (FLUTICASONE PROPIONATE; SALMETEROL XINAFOATE)	TEVA PHARM
01/27/2017	ARMONAIR RESPICLICK (FLUTICASONE PROPIONATE)	TEVA PHARM
03/28/2017	DUPIXENT (DUPILUMAB)	REGENERON PHARMACEUTICALS
03/28/2017	OCREVUS (OCRELIZUMAB)	GENENTECH INC
05/01/2017	IMFINZI (DURVALUMAB)	ASTRAZENECA UK LTD
05/22/2017	KEVZARA (SARILUMAB)	SANOFI SYNTHELABO
06/23/2017	BEVYXXA (BETRIXABAN)	PORTOLA PHARMS INC
		Source: FDA

During the 1st half of 2017, the Committee for Medicinal Products for Human Use (CHMP) of the European Medicine Agency (EMA) gave positive recommendations on 26 new drug applications[1]. Negative opinions were adopted for three drugs. Twenty-one new drugs which received positive opinions were tested in clinical trials in Ukraine.

Table 6 shows the drugs which were approved by EMA in the 1st half of 2017 that were (or are being) tested in clinical trials in Ukraine.

Table 6. New Drugs Approved by EMA in 1st Half of 2017 and Tested in Ukrainian Sites

Approval date	Drug	Company
26/01/2017	XELJANZ	PFIZER LIMITED
26/01/2017	REVLIMID	CELGENE EUROPE LIMITED
26/01/2017	SYNJARDY	BOEHRINGER INGELHEIM GMBH
23/02/2017	DARZALEX	JANSSEN-CILAG

[1] Positive opinions on new generic, hybrid and biosimilar medicines are not included.

		INTERNATIONAL NV
23/02/2017	MEKINIST	NOVARTIS EUROPHARM LTD
23/02/2017	TAFINLAR	NOVARTIS EUROPHARM LTD
23/03/2017	KEYTRUDA	MERCK SHARP & DOHME LIMITED
23/03/2017	ZEBINIX	BIAL - PORTELA & Cª, S.A.
21/04/2017	BESPONSA	PFIZER LIMITED
21/04/2017	KEVZARA	SANOFI-AVENTIS GROUPE
21/04/2017	ERELZI	SANDOZ GMBH
21/04/2017	RIXATHON	SANDOZ GMBH
21/04/2017	RIXIMYO	SANDOZ GMBH
21/04/2017	AVASTIN	ROCHE REGISTRATION LIMITED
18/05/2017	REAGILA	GEDEON RICHTER
18/05/2017	KOMBOGLYZE	ASTRAZENECA AB
18/05/2017	ONGLYZA	ASTRAZENECA AB
22/06/2017	MAVENCLAD	MERCK SERONO EUROPE LIMITED
22/06/2017	FASLODEX	ASTRAZENECA UK LTD
22/06/2017	MIMPARA	AMGEN EUROPE B.V.
22/06/2017	VICTOZA	NOVO NORDISK A/S
		Source: EMA

Inspections

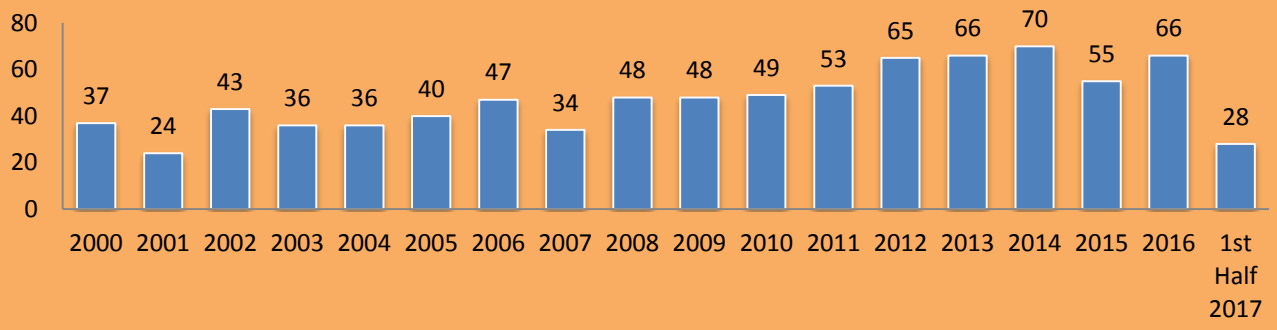
FDA Inspections

In the period from 2012 to the 1st half of 2017 there were six FDA inspections conducted in Ukraine together with representatives of the State Expert Center of Ministry of Health of Ukraine; two inspections of EMA and one of Japan PMDA (Pharmaceuticals and Medical Devices Agency).

State Expert Center Clinical Audits (Inspections)

One of the main constituents in quality assurance of clinical trials conduct is clinical audits, which are regularly held by the State Expert Center employees. Twenty-eight clinical audits were conducted in the 1st half of 2017. Sixteen audits had non-significant findings, nine audits found significant observations and one audit had critical findings.

Figure 7. State Expert Center Clinical Audits (Inspections) (2000 – 1st Half of 2017)



Regulatory Update

There were no changes in clinical trials regulations in Ukraine in the 1st half of 2017.

Clinical Trials in Ukraine are conducted in accordance with Order #690 MoH of Ukraine dated 23.09.2009 with changes stated in Orders MoH of Ukraine #523 dated 12.07.2012, #304 dated 06.05.2014, #966 dated 18.12.2014 and #639 dated 01.10.2015.

Summary

The statistical data of the 1st half of 2017 show a potential for 15-20% increase of yearly volume of the clinical trials market.

According to opinion of clinical trials market experts the potential of Ukraine is used only in 10-15% and an increase of number of conducted trials in Ukraine is expected because of step by step movement and harmonization of Ukrainian health system to EU standards.

The current situation in Ukraine is favorable to conduct clinical trials. Contributing factors to this favorable environment include country population, a well-developed and structured system of healthcare, highly qualified staff and a growing number of experienced investigative sites that contribute to the rapid recruitment of patients.

Compliance with regulatory requirements and GCP standards, the availability of local Ethics committees, as well as a system for pharmacovigilance and control, ensure the quality of the data received from studies conducted in Ukraine.

We would like to express special gratitude to the employees of the State Expert Center of MoH of Ukraine, for providing full and detailed data on the statistics of clinical trials in Ukraine.

The next issue is scheduled for April 2018 and will cover data for 2017.

About Synergy Research Group

Synergy Research Group is a contract research organization successfully operating since 2002. Synergy provides a full range of CRO services to help pharmaceutical and biotechnological companies conduct cost-effective clinical trials. Today, Synergy is represented in Moscow, Saint-Petersburg, Novosibirsk, Yekaterinburg, Perm, Krasnodar (in the Russian Federation); in Kyiv (Synergy Group Ukraine head office), Uzhhorod, Kharkiv and Odessa (in Ukraine); and also in Almaty and Astana (Kazakhstan). The company's headquarters are in Moscow. We have Synergy employees and staff in the USA, Canada, Lithuania (EU) and Georgia.