Clinical Trials in Ukraine
Orange Paper

2016 Annual Summary

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Contents

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Executive Summary

According to statistical data there were 2314 clinical trials approved to conduct in Ukraine for period from 2007 to 2016 years.

The Ministry of Health of Ukraine (MoH) approved 181 new clinical trials during 2016 (about 10% reductions in comparison with the 2015 figure).

The largest contribution to the total number of studies was made by multinational multi-center clinical trials (MMCT). The total number of these studies decreased from 144 in 2015 to 135 in 2015 (6% decrease). The number of bioequivalence studies (BE) reduced in 2016 to 9 studies and it is 4 studies less than in 2015. The number of local clinical trials (LCT) decreased from 45 to 37 clinical trials (representing about 18% less than in 2015).

The share of MMCT was 75% of the total number of clinical trials in 2016, while the share of local clinical trials amounted to 20% and bioequivalence studies amounted to 5% respectively.

The number of Phase I MMCT increased to 3 new studies in 2016, more than in 2015 with 1 study approved. The number of Phase II trials increased from 27 to 37 and the number of Phase III trials decreased from 111 to 94 respectively. The number of Phase IV trials decreased to 1 study in 2016 that is 4 less than in 2015.

Among international sponsors/CROs *Quintiles Ukraine*, which holds 19% of the market share, was on the top of the heap in 2016. Second stage holds *PPD (InnoPharm) Ukraine* which had 11%, third place is *Parexel Ukraine* with 6% followed by *Synergy Group Ukraine* with 5%, *PSI Ukraine* with 4%, other companies had totally 55%.

The Ukrainian company *PJSC "Farmak"* held 16% of the market and ranked number one among domestic pharmaceutical applicants in 2016. It is followed by *LLC "Biopharm"* with 14%, *PJSC "Kyiv Vitamin Factory"* with 11%, *PJSC "Kyivmedpreparat"* with 9% and *LLC "Zdorovya"* with 7% market share, other companies had remained 43%.

In 2016, the majority of MMCTs were initiated in seven leading therapeutic areas: the largest number of studies were initiated in Oncology (30) and Psychiatry and Neurology (26); followed by Pulmonology (14); Rheumatology (14); Endocrinology (6); Hematology (6) and Cardiology (5).

During 2016, the State Expert Center of MoH of Ukraine granted 6 positive permissions for MMCT conducted in pediatrics, 8 less than in 2015 and 13 less than 2014. Only Phase III clinical trials were conducted in pediatric groups. Phase III trials in pediatric patients held 100% in 2016 compared with 71% in 2015.

The Center for Drug Evaluation and Research (CDER) of the FDA approved 105 new drugs during 2016; 15 of them were new molecular entities (NME). 16 of 105 new drugs were (or are being) studied in clinical trials conducted in Ukraine.

During 2016, the Committee for Medicinal Products for Human Use (CHMP) of the European Medicine Agency (EMA) gave positive recommendations on 88 new drug applications[1]. Negative opinion was adopted for 2 drugs. 41 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 66 inspections (clinical audits) during 2016.

There were no significant Regulatory updates within 2016.

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

Clinical Trials by Type

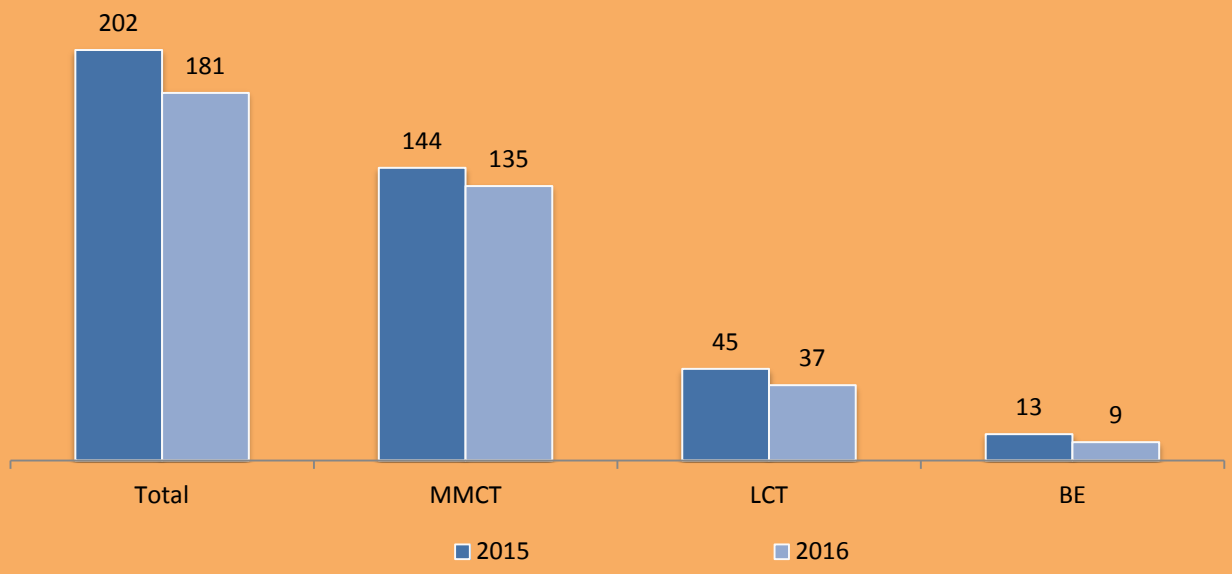
The MoH of Ukraine approved 181 new clinical trials of all types including local and bioequivalence studies during 2016, demonstrating 10% decrease in comparison with the last year.

As shown in **Figure 1**, the main contribution into the total number of studies was made by multinational multi-center clinical trials (MMCT), the number of these studies also decreased from 144 studies in 2015 to 135 in 2016.

The number of local clinical trials (LCT) decreased from 45 in 2015 to 37 clinical trials in 2016.

The number of bioequivalence studies (BE) decreased from 13 in 2015 to 9 clinical trials in 2016, about 30% decrease from last year's figure.

Figure 1. Clinical Trials in Ukraine in 2016

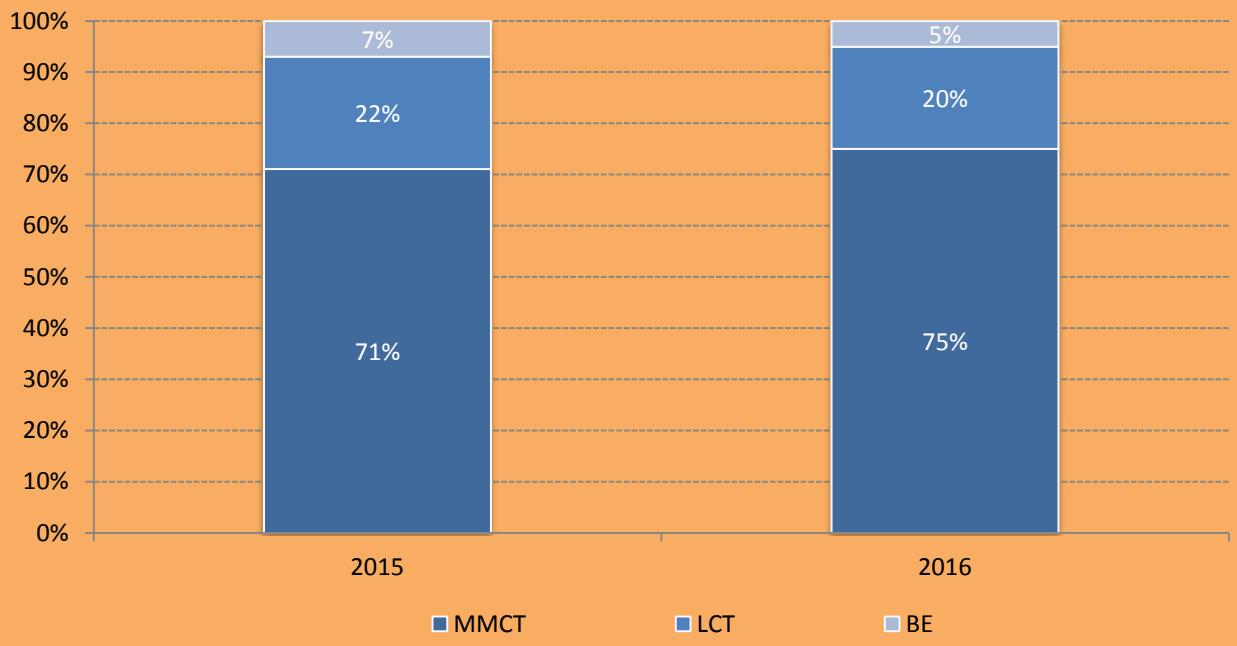


The proportions between different study types (multinational multi-center clinical trials and local studies) changed noticeably since last year (see **Figure 2**).

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

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

Figure 2. Clinical Trials by Type in 2016

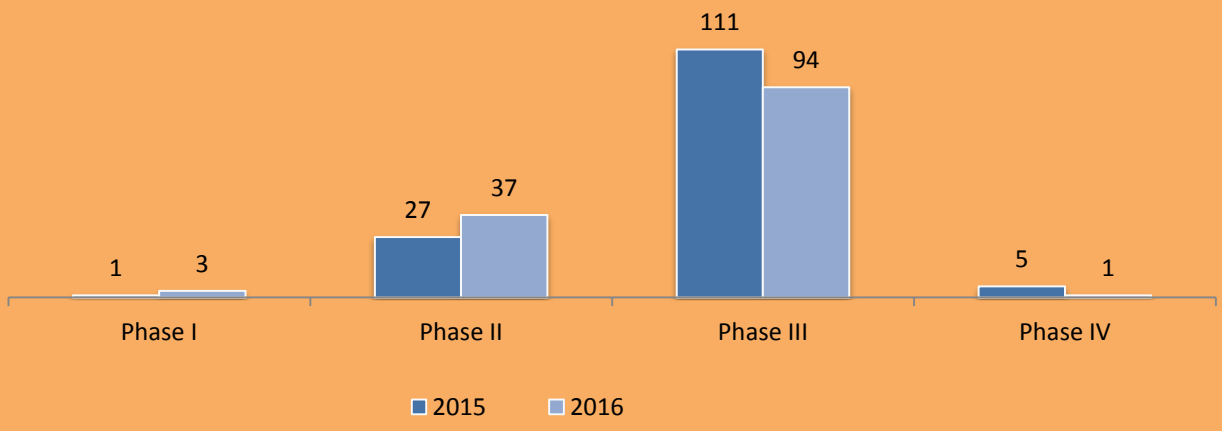


During the clinical trial, the applicant may submit to the State Expert Center of MoH of Ukraine (Center) the significant amendments to the clinical trial protocol (additions or changes of existing information) which are reviewed according to current local legislation. During 2016, the Center issued 1,222 positive conclusions for MMCT amendments that is about 15% more than in 2015 with 1,065 positive conclusions.

Multinational Multi-center Clinical Trials by Phase

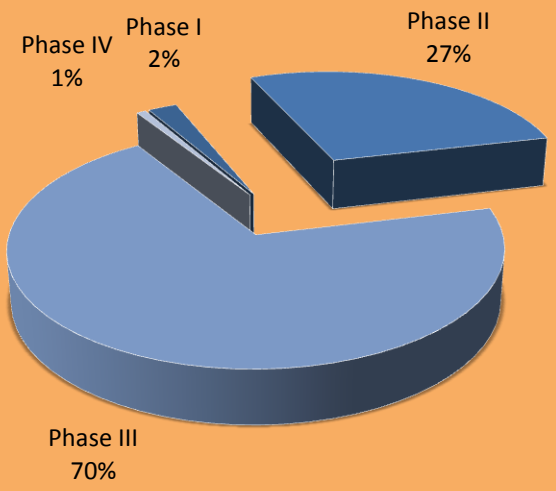
2016 saw 3 new Phase I MMCT and it is two studies more than in 2015. Phase IV trials reduced to one new study in 2016 that is 4 studies less that in 2015 (**Figure 3**).

Figure 3. Multinational Multi-center Clinical Trials in Ukraine in 2016 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



Rating of International Sponsors

Clinical trial applicants are indicated in Table 1.

Table 1. Applicants of Multinational Multi-center Clinical Trials in Ukraine in 2016

№	Company Name	Market share
1	Quintiles Ukraine	19%
2	PPD (InnoPharm) Ukraine	11%
3	Parexel	6%
4	Synergy Group Ukraine	5%
5	PSI Ukraine	4%
6	Other 31 applicants	55%

Rating of Ukrainian Sponsors

Clinical trial applicants are indicated in Table 2.

Table 2. Applicants of Local Clinical Trials in Ukraine in 2016

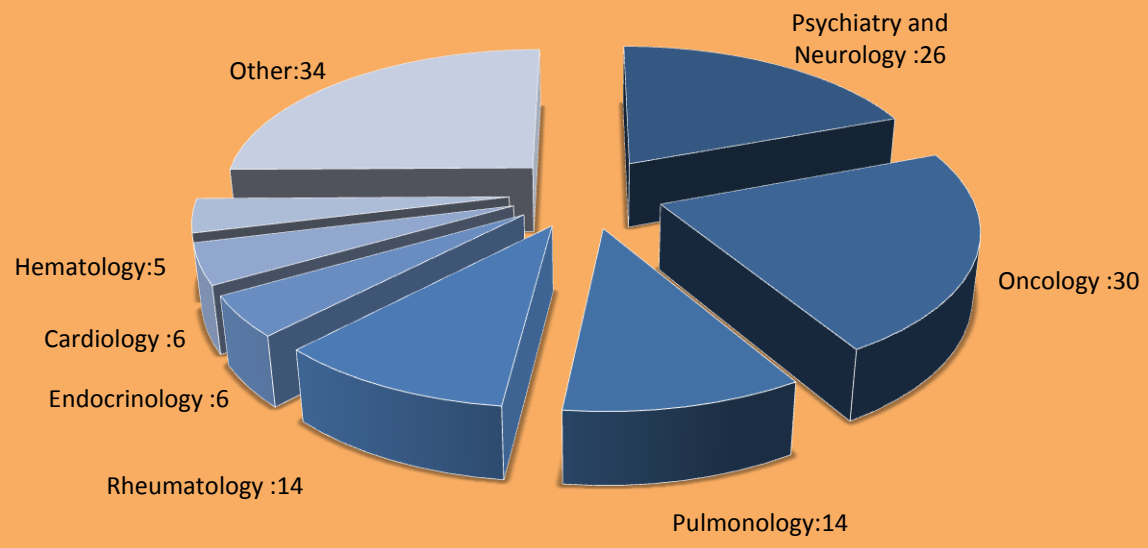
№	Company Name	Market share
1	PJSC “Farmak”	16%
2	LLC "Biopharm"	14%
3	PJSC “Kyiv Vitamin Factory”	11%
4	PJSC “Kyivmedpreparat”	9%
5	LLC “Zdorovya”	7%
6	Other 14 applicants	43%

Therapeutic Areas of Multinational Multi-center Clinical Trials in 2016

In 2016, the majority of MMCTs were initiated in seven leading therapeutic areas: the largest number of studies was initiated in Oncology (30) and Psychiatry and Neurology (26); and is followed by Pulmonology (14); Rheumatology (14); Endocrinology (6); Hematology (6) and Cardiology (5).

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

Figure 5. MMCT in Ukraine in 2016 by Therapeutic Area



Multinational Multi-center Clinical Trials in Pediatrics

During 2016, the State Expert Center of MoH of Ukraine granted 6 positive permissions for MMCT conduct in pediatrics, eight less than in 2015. In all cases, Phase III clinical trials were conducted in pediatric groups. Phase III trials in pediatric patients reached 100% in 2016 comparing with 71% in 2015 (**Figure 6**).

Figure 6. Positive Conclusions Regarding MMCT in Pediatrics (2015-2016 years)

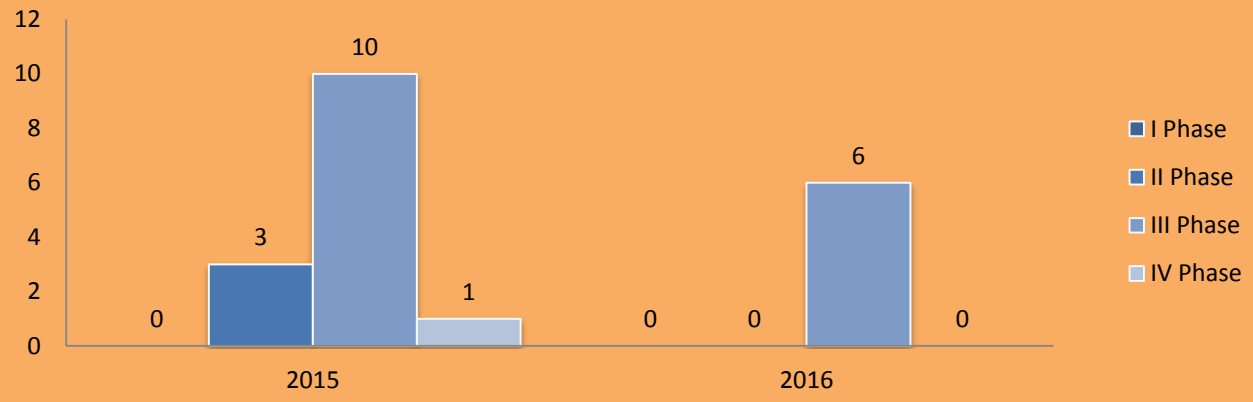


Table 3. Therapeutic Areas of MMCT in Pediatrics (Approved in 2015 and 2016)

Nosology	2015	2016
Psychiatry	3	1
Hematology	2	1
Infectious diseases	0	2
Endocrinology	1	2
Surgery	2	0
Neurology	1	0
Pulmonology	1	0
Oncology	2	0
Urology/Nephrology	1	0

Clinical Trial Results

The Center for Drug Evaluation and Research (CDER) of the FDA approved 105 new drugs during 2016; 15 of them were new molecular entities (NME). 16 of 105 new drugs were (or are being) studied in clinical trials conducted in Ukraine.

Tables 4 shows the drugs which were approved by FDA in 2016 that were (or are being) tested in clinical trials in Ukraine.

Table 4. New Drugs Approved by FDA in 2016 and Tested in Ukrainian Sites

APPROVAL DATE	DRUG (ACTIVE INGREDIENT)	COMPANY
18/02/2016	BRIVARACETAM (BRIVARACETAM)	UCB INC
23/02/2016	XELJANZ XR (TOFACITINIB CITRATE)	PFIZER INC
22/03/2016	TALTZ (IXEKIZUMAB)	ELI LILLY AND CO
23/03/2016	CINQAIR (RESLIZUMAB)	TEVA RESPIRATORY LLC
29/04/2016	NUPLAZID (PIMAVANSERIN TARTRATE)	ACADIA PHARMS INC
29/04/2016	FYCOMPA (PERAMPANEL)	EISAI INC
27/05/2016	ZINBRYTA (DACLIZUMAB)	BIOGEN
27/05/2016	JENTADUETO XR (LINAGLIPTIN; METFORMIN HYDROCHLORIDE)	BOEHRINGER INGELHEIM
27/07/2016	ADLYXIN (LIXISENATIDE)	SANOFI-AVENTIS US
30/08/2016	ERELZI (ETANERCEPT-SZZS)	SANDOZ
16/09/2016	KYLEENA (LEVONORGESTREL)	BAYER HLTHCARE
20/09/2016	INVOKAMET XR (CANAGLIFLOZIN; METFORMIN HYDROCHLORIDE)	JANSSEN PHARMS
23/09/2016	STELARA (USTEKINUMAB)	JANSSEN BIOTECH
21/11/2016	XULTOPHY 100/3.6 (INSULIN DEGLUDEC; LIRAGLUTIDE)	NOVO NORDISK INC
21/11/2016	SOLIQUA 100/33 (INSULIN GLARGINE; LIXISENATIDE)	SANOFI-AVENTIS US
09/12/2016	SYNJARDY XR (EMPAGLIFLOZIN; METFORMIN HYDROCHLORIDE)	BOEHRINGER INGELHEIM
		Source: FDA

During 2016, the Committee for Medicinal Products for Human Use (CHMP) of the European Medicine Agency (EMA) gave positive recommendations on 88 new drug applications[1]. Negative opinion was adopted for 2 drugs. 41 new drugs which received positive opinions were tested in clinical trials in Ukraine.

Tables 5 shows the drugs which were approved by EMA in 2016 that were (or are being) tested in clinical trials in Ukraine.

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

Table 5. New Drugs Approved by EMA in 2016 and Tested in Ukrainian Sites

Approval date	Drug	Company
28/01/2016	COAGADEX	BIO PRODUCTS LABORATORY
28/01/2016	REVLIMID	CELGENE EUROPE LIMITED
28/01/2016	REVOLADE	NOVARTIS EUROPHARM LTD
25/02/2016	TALTZ	ELI LILLY NEDERLAND B.V.
25/02/2016	GIOTRIF	BOEHRINGER INGELHEIM INTERNATIONAL GMBH
25/02/2016	HUMIRA	ABBVIE LTD
01/04/2016	DARZALEX	JANSSEN-CILAG INTERNATIONAL N.V.
01/04/2016	UPTRAVI	ACTELION REGISTRATION LTD
01/04/2016	HALAVEN	EISAI EUROPE LTD
01/04/2016	HUMIRA	ABBVIE LTD
26/05/2016	TYSABRI	BIOGEN IDEC LTD
26/05/2016	SIMPONI	JANSSEN BIOLOGICS B.V.
26/05/2016	HUMIRA	ABBVIE LTD
23/06/2016	CINQAERO	TEVA PHARMACEUTICALS LIMITED
23/06/2016	ILARIS	NOVARTIS EUROPHARM LTD
23/06/2016	KEYTRUDA	MERCK SHARP & DOHME LIMITED
23/06/2016	ROACTEMRA	ROCHE REGISTRATION LIMITED
23/06/2016	RYZODEG	NOVO NORDISK A/S
21/07/2016	KISPLYX	EISAI EUROPE LTD
21/07/2016	IMBRUVICA	JANSSEN-CILAG INTERNATIONAL NV
21/07/2016	XALKORI	PFIZER LIMITED
15/09/2016	NOVORAPID	NOVO NORDISK A/S
15/09/2016	STELARA	JANSSEN-CILAG INTERNATIONAL NV
15/09/2016	GLYXAMBI	BOEHRINGER INGELHEIM INTERNATIONAL GMBH
15/09/2016	IBRANCE	PFIZER LIMITED
13/10/2016	LUCENTIS	NOVARTIS EUROPHARM LTD
13/10/2016	ZEBINIX	BIAL - PORTELA & CA, S.A.

10/11/2016	FIASP	NOVO NORDISK A/S
10/11/2016	SULIQUA	SANOFI-AVENTIS GROUPE
10/11/2016	ARZERRA	NOVARTIS EUROPHARM LTD
10/11/2016	VIMPAT	UCB PHARMA S.A.
10/11/2016	HUMIRA	ABBVIE LTD
15/12/2016	ALECENSA	ROCHE REGISTRATION LIMITED
15/12/2016	LIFMIOR	PFIZER LIMITED
15/12/2016	OLUMIANT	ELI LILLY NEDERLAND B.V.
15/12/2016	ILARIS	NOVARTIS EUROPHARM LTD
15/12/2016	JARDIANCE	BOEHRINGER INGELHEIM INTERNATIONAL GMBH
15/12/2016	JENTADUETO	BOEHRINGER INGELHEIM INTERNATIONAL GMBH
15/12/2016	KEYTRUDA	MERCK SHARP & DOHME LIMITED
15/12/2016	TIVICAY	VIIV HEALTHCARE UK LIMITED
15/12/2016	TRAJENTA	BOEHRINGER INGELHEIM INTERNATIONAL GMBH
		Source: EMA

Inspections

FDA Inspections

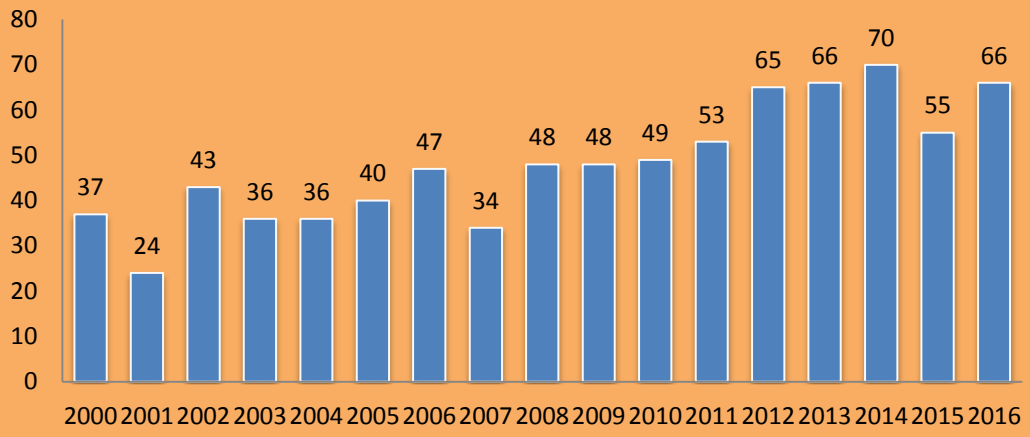
In the period from 2012 to 2016 there were 5 FDA inspections conducted in Ukraine together with representatives of the State Expert Center of Ministry of Health of Ukraine; 2 inspections of EMA and 1 of Japan PMDA (Pharmaceuticals and Medical Devices Agency).

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. 66 clinical audits were conducted in 2016, 11 audits (20%) more than in 2015.

34 audits had non-significant findings and 22 audits found significant observations and 4 audits had critical findings.

Figure 7. State Expert Center Clinical Audits (Inspections) (2000-2016)



Regulatory Update

There were no changes in clinical trials regulation in Ukraine in 2016.

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

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 materials for the 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 representatives who arrange our services in USA, Canada, Lithuania (EU) and Georgia.