Clinical Trials in Ukraine
Orange Paper

2015 Annual Summary

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Contents

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Executive Summary

The Ministry of Health of Ukraine (MoH) approved 202 new clinical trials during 2015 (24.9% decrease in comparison with the 2014 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 188 in 2014 to 144 in 2015 (23.4% decrease). The number of bioequivalence studies (BE) remained approximately the same: 12 in 2014 and 13 in 2015. The number of local clinical trials (LCT) decreased from 69 to 45 clinical trials (representing a 34.8% decrease).

The share of multinational multi-center clinical trials was 71.3% of the total number of clinical trials in 2014, while the share of local clinical trials and bioequivalence studies amounted to 22.3% and 6.4%, accordingly.

The number of Phase I MMCT decreased to one new study in 2015, less than in 2014 with 2 studies. The number of the Phase II and Phase III trials decreased from 38 to 27 and from 142 to 111, respectively. Phase IV trials stood the same as 5 studies in 2014 and in 2015.

Among international sponsors/CROs Quintiles Ukraine, which holds 14% of the market share, was on the top of the heap in 2015. PPD (InnoPharm) Ukraine had 13%, followed by PSI Ukraine with 8%, Synergy Group Ukraine, PRA and MB Quest each had 6%, and ICON had 5%, equaling 58%.

The Ukrainian company PJSC “Farmak” held 20% of the market and ranked number one among domestic pharmaceutical applicants in 2015. It is followed by LLC "Biopharm" and LLC “Zdorovya” with 12% market share each, and LLC "Astra Pharm" and LLC “NVF AKSOMED” (6% each).

In 2015, the majority of MMCTs was initiated in seven leading therapeutic areas: the largest number of studies was initiated in Oncology (28) and Psychiatry and Neurology (22); Pulmonology (18); Rheumatology (16); Endocrinology (9); Hematology (6) and Cardiology (4).

During 2015, the State Expert Center of MoH of Ukraine granted 14 positive permissions for MMCT conducted in pediatrics, five less than in 2014. In the majority of cases, Phase III clinical trials were conducted in pediatric groups. Phase III trials in pediatric patients stayed at approximately the same level – 71.4% in 2015 compared with 79% in 2014.

The Center for Drug Evaluation and Research (CDER) of the FDA approved 121 new drugs during 2015; 35 of them were new molecular entities (NME). 36 of 121 new drugs were (or are being) studied in clinical trials conducted in Ukraine.

During 2015, the Committee for Medicinal Products for Human Use (CHMP) of the European Medicine Agency (EMEA) gave positive recommendations on 113 new drug applications. Negative opinion was adopted for 4 drugs. 50 new drugs which received positive opinions were tested in clinical trials in Ukraine. [1]

The State Expert Center conducted 55 inspections (clinical audits) during 2015. Regulatory updates in 2015 included changes in requirements to documents submitted to Local Ethics Committees and timelines for decision making for significant amendments and Ministry of Health registration of clinical trials on the official site.

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

Clinical Trials by Type and Manufacturing Country

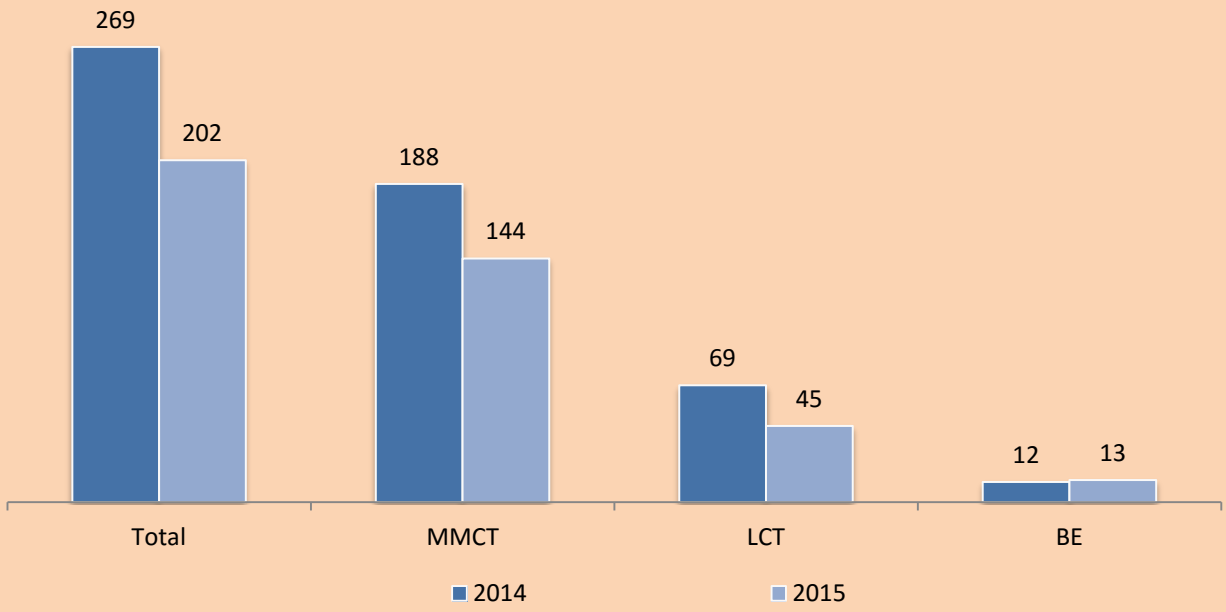
The MoH of Ukraine approved 202 new clinical trials of all types including local and bioequivalence studies during 2015, demonstrating 24.9% decrease in comparison with the last year.

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 188 studies in 2014 to 144 in 2015.

The number of local clinical trials (LCT) has decreased from 81 in 2014 to 58 clinical trials in 2015, 34.8% decrease from last year's figure.

The number of bioequivalence studies (BE) has increased from 12 in 2014 to 13 clinical trials in 2015, an 8.3% increase from last year's figure.

Figure 1. Clinical Trials in Ukraine in 2015

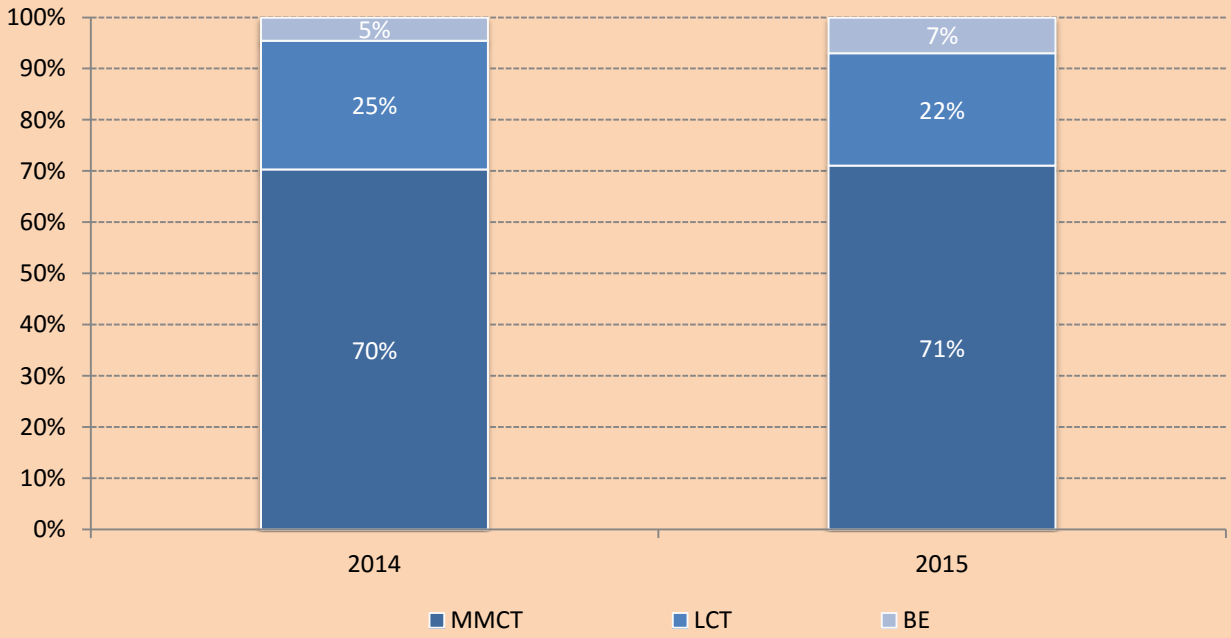


The proportions between different study types (multinational multi-center clinical trials, local studies and bioequivalence trials) changed noticeably since last year (see **Figure 2**).

In comparison with 2014, the share of bioequivalence studies increased from 4.5% to 6.5% of the total number of clinical trials approved in 2015.

The share of the local trials decreased from 25.6% in 2014 to 22.2% in 2015 and the share of multinational multi-center clinical trials increased from 69.9% in 2014 to 71.3% of the total number of trials approved during 2015.

Figure 2. Clinical Trials by Type in 2015

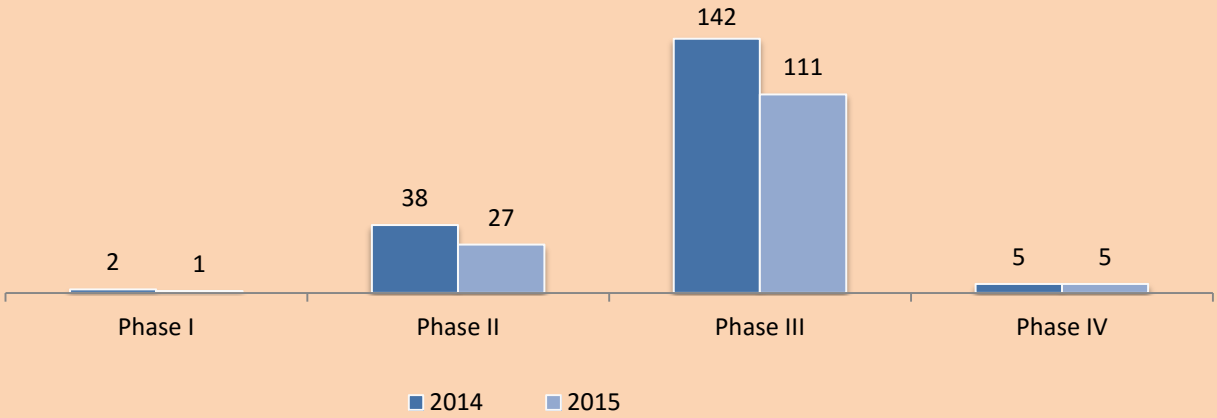


During the clinical trial, the applicant may submit to the Center the significant amendments to the clinical trial protocol (additions or changes of existing information) which are reviewed according to established "Order". During 2015, the Center issued 1065 positive conclusions for MMCT amendments.

MMCT Clinical trials by Phase

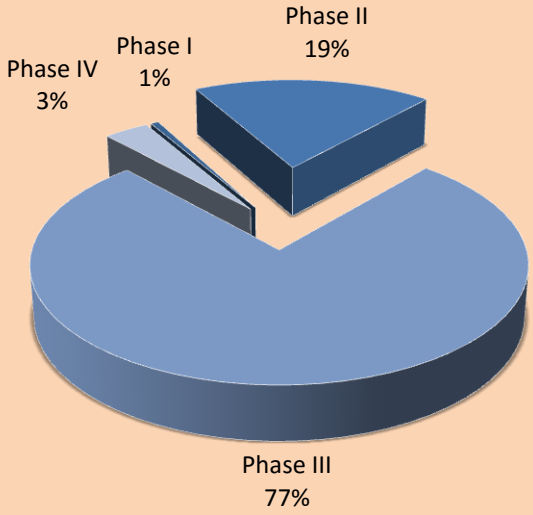
2015 saw only one new Phase I MMCT clinical trial and it one study less than in 2014. Phase IV trials stood at five new studies in 2015, the same figure as in 2014.

Figure 3. Clinical Trials in Ukraine in 2015 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 – in phase III group.

Figure 4. Percentage Breakdown of Ukrainian Clinical Trials by Phase



Rating of International Sponsors

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

Table 1. Applicants of MMCT in Ukraine in 2015

№	Company Name	Market share
1	Quintiles Ukraine	14%
2	PPD (InnoPharm) Ukraine	13%
3	PSI Ukraine	8%
4	Synergy Group Ukraine	6%
5	PRA	6%
6	MB Quest	6%
7	ICON	5%
8	Other 24 applicants	42%

Rating of Ukrainian sponsors

Table 2. Applicants of local clinical trials in Ukraine in 2015

№	Company Name	Market share
1	PJSC “Farmak”	20%

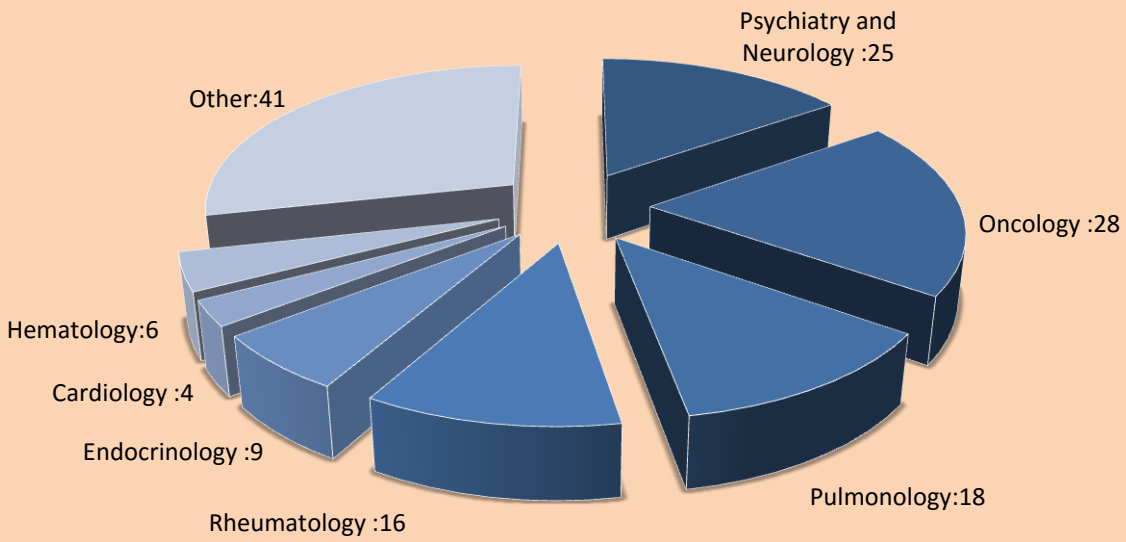
2	LLC "Biopharm"	12%
3	LLC “Zdorovya”	12%
4	LLC "Astra Pharm"	6%
5	LLC “NVF AKSOMED”	6%
6	Other 12 applicants	38%

Therapeutic Areas of MMCT Clinical Trials in 2015

In 2015, the majority of MMCTs was initiated in seven leading therapeutic areas: the largest number of studies was initiated in Oncology (28) and Psychiatry and Neurology (22); Pulmonology (18); Rheumatology (16); Endocrinology (9); Hematology (6) and Cardiology (4).

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

Figure 5. MMCT in Ukraine in 2015 by Therapeutic Area



MMCT Clinical Trials in Pediatrics

During 2015, the State Expert Center of MoH of Ukraine granted 14 positive permissions for MMCT conduct in pediatrics, five less than in 2014. In the majority of cases, Phase III clinical trials were conducted in pediatric groups. Phase III trials in pediatric patients save approximately the same level – 71.4% in 2015 comparing with 79% in 2014. (see **Figure 6**).

Figure 6. Positive conclusions regarding MMCT in Pediatrics (2014-2015 years)

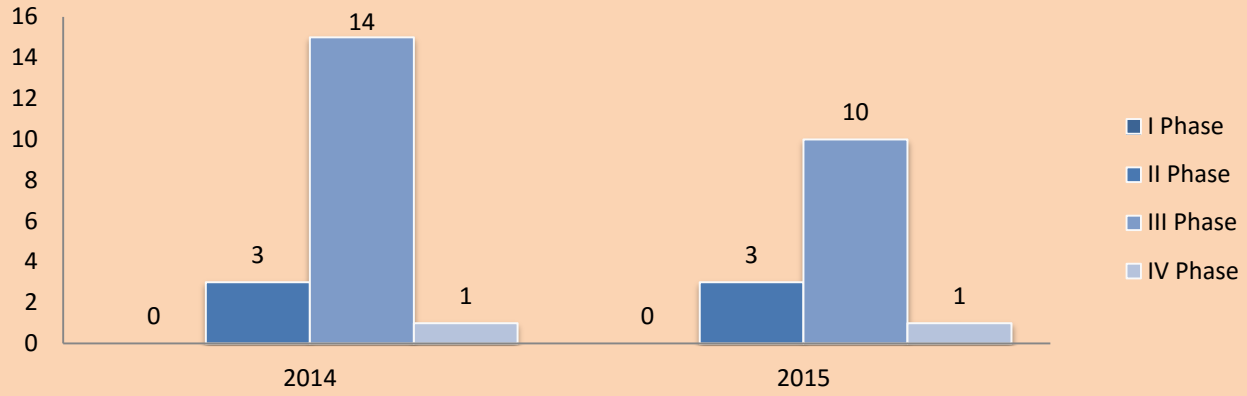


Table 3. Therapeutic Areas of MMCT in Pediatrics (Approved in 2014 and 2015)

Nosology	2014	2015
Psychiatry	4	3
Hematology	3	2
Infectious diseases	3	0
Endocrinology	2	1
Surgery	1	2
Neurology	2	1
Pulmonology	1	1
Oncology	1	2
Urology/Nephrology	1	1

Clinical Trial Results

The Center for Drug Evaluation and Research (CDER) of the FDA approved 121 new drugs during 2015; 35 of them are new molecular entities (NME). 36 of 121 new drugs were (or are being) studied in clinical trials conducted in Ukraine.

Tables 4 and 5 show the drugs which were approved by FDA and EMEA in 2015 that were being tested in clinical trials in Ukraine.

Table 4. New Drugs Approved by FDA in 2015 and Tested in Ukrainian sites

Approval date	Drug (active ingredient)	Company
07/01/2015	RYTARY (CARBIDOPA; LEVODOPA)	IMPAX LABS INC
08/01/2015	SAVAYSA (EDOXABAN TOSYLATE)	DAIICHI SANKYO
30/01/2015	GLYXAMBI (EMPAGLIFLOZIN; LINAGLIPTIN)	BOEHRINGER INGELHEIM

03/02/2015	IBRANCE (PALBOCICLIB)	PFIZER INC
13/02/2015	LENVIMA (LENVATINIB MESYLATE)	EISAI INC
25/02/2015	TOUJEO SOLOSTAR (INSULIN GLARGINE RECOMBINANT)	SANOFI US SERVICES
31/03/2015	PROAIR RESPICLICK (ALBUTEROL SULFATE)	TEVA BRANDED PHARM
18/05/2015	INVEGA TRINZA (PALIPERIDONE PALMITATE)	JANSSEN PHARMS
26/05/2015	HUMALOG KWIKPEN (INSULIN LISPRO RECOMBINANT)	ELI LILLY AND CO
21/05/2015	STIOLTO RESPIMAT (OLODATEROL HYDROCHLORIDE; TIOTROPIUM BROMIDE)	BOEHRINGER INGELHEIM
10/07/2015	REXULTI (BREXPIPRAZOLE)	OTSUKA PHARM CO LTD
13/07/2015	IRESSA (GEFITINIB)	ASTRAZENECA PHARMS
24/08/2015	PROMACTA (ELTROMBOPAG OLAMINE)	NOVARTIS PHARMS CORP
26/08/2015	SYNJARDY (EMPAGLIFLOZIN; METFORMIN HYDROCHLORIDE)	BOEHRINGER INGELHEIM
04/09/2015	DURLAZA (ASPIRIN)	NEW HAVEN PHARMA INC
15/09/2015	SPIRIVA RESPIMAT (TIOTROPIUM BROMIDE)	BOEHRINGER INGELHEIM
17/09/2015	VRAYLAR (CARIPRAZINE)	FOREST LABS LLC
25/09/2015	RYZODEG 70/30 (INSULIN DEGLUDEC; INSULIN ASPART)	NOVO NORDISK INC
25/09/2015	TRESIBA (INSULIN DEGLUDEC)	NOVO NORDISK INC
05/10/2015	ARISTADA (ARIPIPRAZOLE LAUROXIL)	ALKERMES INC
21/10/2015	VELTASSA (PATIROMER SORBITEX CALCIUM)	RELYPSA INC
29/10/2015	SEEBRI (GLYCOPYRROLATE)	NOVARTIS PHARMS CORP
10/29/2015	UTIBRON (GLYCOPYRROLATE; INDACATEROL MALEATE)	NOVARTIS PHARMS CORP
13/11/2015	TAGRISSO (OSIMERTINIB MESYLATE)	ASTRAZENECA PHARMS
20/11/2015	NINLARO (IXAZOMIB CITRATE)	MILLENNIUM PHARMS
11/12/2015	ALECENSA (ALECTINIB)	HOFFMAN-LA ROCHE
16/12/2015	BASAGLAR (INSULIN GLARGINE)	ELI LILLY AND CO
17/12/2015	EMEND (APREPITANT)	MERCK SHARP DOHME
21/12/2015	UPTRAVI (SELEXIPAG)	ACTELION PHARMS LTD
22/12/2015	ZURAMPIC (LESINURAD)	ARDEA BIOSCIENCES INC
		Source: FDA

During 2015, the Committee for Medicinal Products for Human Use (CHMP) of the European Medicine Agency (EMEA) gave positive recommendations on 113 new drug applications.

Negative opinion was adopted for 4 drugs. 50 new drugs which received positive opinions were tested in clinical trials in Ukraine. [1]

Table 5. New Drugs Approved by EMEA in 2015 and Tested in Ukrainian sites

Approval date	Drug	Marketing-authorization applicant
22/01/2015	ORBACTIV	THE MEDICINES COMPANY UK LTD
22/01/2015	SAXENDA	NOVO NORDISK A/S
22/01/2015	SIVEXTRO	CUBIST
26/03/2015	AKYNZEO	HELSINN BIREX PHARMACEUTICALS LTD
26/03/2015	LENVIMA	EISAI EUROPE LTD
26/03/2015	SYNJARDY	BOEHRINGER INGELHEIM GMBH
23/04/2015	LIXIANA	DAIICHI SANKYO EUROPE GMBH
21/05/2015	KEYTRUDA	MERCK SHARP & DOHME LIMITED
21/05/2015	REPATHA	AMGEN EUROPE B.V.
23/07/2015	INTUNIV	SHIRE PHARMACEUTICALS IRELAND LTD
23/07/2015	PRALUENT	SANOFI-AVENTIS GROUPE
24/09/2015	KYPROLIS	AMGEN EUROPE B.V.
24/09/2015	NUCALA	GLAXOSMITHKLINE TRADING SERVICES
24/09/2015	NUMIENT	IMPAX LABORATORIES NETHERLANDS BV
24/09/2015	RAVICTI	HORIZON THERAPEUTICS LIMITED
19/11/2015	EPISALVAN	BIRKEN AG
17/12/2015	IBLIAS	BAYER PHARMA AG
17/12/2015	KOVALTRY	BAYER PHARMA AG
17/12/2015	TAGRISSO	ASTRAZENECA AB
		SOURCE: EMEA

Inspections

FDA inspections

At the Orange Paper 2015 publication date, no information about inspections of the FDA conducted in the Ukrainian investigative sites was available.

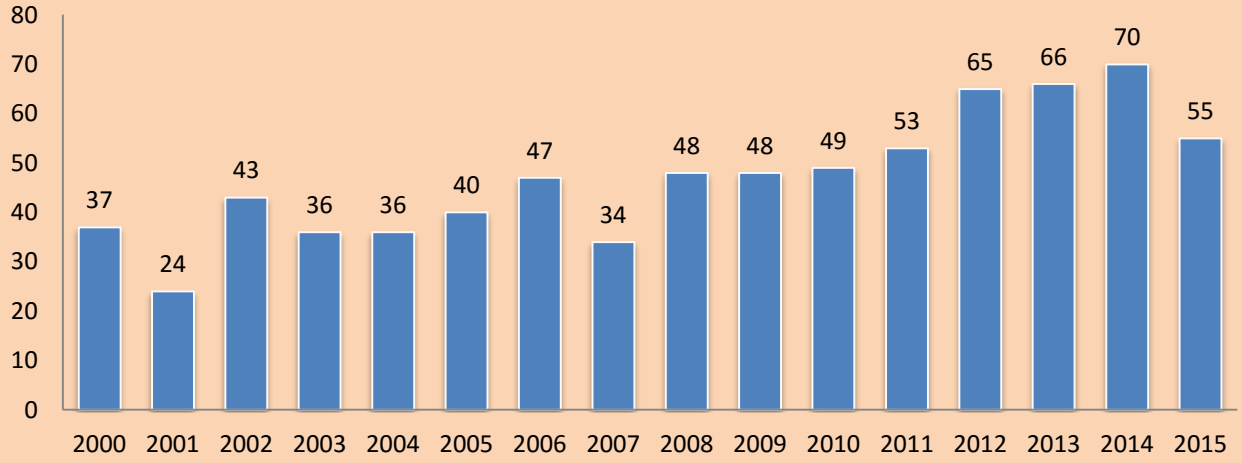
[1] Positive EMEA opinions on new generic, biosimilar and hybrid medicines, are not included

State Expert Center Clinical Audits (Inspections)

One of the main constituents in quality assurance of CT conduct is clinical audits, which are regularly held by the State Expert Center employees. 55 clinical audits were conducted in 2015, 15 audits (21.5%) less than in 2014.

Figure 7. State Expert Center Clinical Audits (Inspections) (2010-2015)

34 audits had non-significant findings and 17 audits found critical observations.
Terminated – clinical trials in 1 site.



Regulatory Update

Regulatory updates in 2015 included changes in requirements to documents submission to Local Ethics Committees and timeline for decision making for significant amendment and Ministry of Health register of clinical trials on the official site. The main changes according to Order #639 of 01.10.2015 are the following:

- Ministry of Health of Ukraine official web-site starts to publish Orders about approval of clinical researches.
- A list of data that should be included into Ministry of Health Order was determined.
- Full Protocol in English and Insurance certificate were added to the list of documents that should be submitted to Local Ethics Committees for study examination.
- Clarification related import of IMP and accompanying study materials was added.
- Terms of LEC examination of substantial amendment was increased from 10 to 15 calendar days.
- Personal data protection statement from Principal Investigator was added into the study application form.

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 current situation in Ukraine is favorable for conducting 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.

The presence of global pharmaceutical companies in the Ukrainian market is gradually increasing, confirming the growing interest in clinical trials in the country.

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 2017 and will cover materials for the 2016.

About Synergy Research Group

Synergy Research Group is a Russian contract research organization successfully operating in Russia 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, Zaporizhzhya, Kharkiv and Odessa (Ukraine) and also in Almaty and Astana (Kazakhstan). The company's headquarters are in Moscow.