Clinical Trials in Ukraine
Orange Paper

Year 2014

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Contents

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Executive Summary

The Ministry of Health of Ukraine (MoH) approved 269 new clinical trials during 2014 (15% increase in comparison with the 2013 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 increased from 177 in 2013 to 188 in 2014 (15% increase). The number of bioequivalence studies (BE) remained the same: 12 in 2013 and 12 in 2014. The number of local clinical trials (LCT) increased from 44 to 69 clinical trials (representing a 57% increase).

The share of multinational multi-center clinical trials was 70% of the total number of clinical trials in 2014, while the share of local clinical trials and bioequivalence studies amounted to 26% and 4%, accordingly.

The number of Phase I MMCT stood at two new studies in 2014, the same figure as in 2013. The number of the Phase II and Phase III trials increased from 33 to 38 and from 135 to 142, respectively. Phase IV trials demonstrated the slight decrease from seven studies in 2013 to five studies in 2014.

Among international sponsors *Quintiles Ukraine* which holds 15% of the market share was on the top of the heap in 2014. It is followed by *PPD (Inno-Pharm) Ukraine, Parexel Ukraine and INC Research Ukraine* with 10% share each, GlaxoSmithKline Pharmaceuticals Ukraine (6%), ICON, AstraZeneca Ukraine (5% each).

Ukrainian company *PJSC "Farmak"* which holds 20% of the market share, ranked number one among domestic pharmaceutical applicants in 2014. It is followed by *LLC "Research Institution Quant M"* with 9% market share, *PJSC SIC "Borshchahivskiy CPP"* (7%), *LLC "Pharma Start"* (6%), *PJSC "Pharmaceutical firm "Darnitsa"* and *PJSC "Kyiv Vitamin Factory"* (5% each).

In 2014, the majority of MMCTs was initiated in seven leading therapeutic areas: the largest number of studies was initiated in Oncology and Pulmonology (30); Psychiatry and Neurology (25); Rheumatology (21); Endocrinology (15); Cardiology (14) and Hematology (8).

During 2014, the State Expert Center of MoH of Ukraine granted 19 positive permissions for MMCT conduct in pediatrics, one less than in 2013. In the majority of cases, Phase III clinical trials were conducted in pediatric groups. Phase III trials in pediatric patients increased from 70% in 2013 to 79% in 2014.

The Center for Drug Evaluation and Research (CDER) of the FDA approved 111 new drugs during 2014; 34 of them are new molecular entities (NME). 15 of 111 new drugs were (or are being) studied in clinical trials conducted in Ukraine.

During 2014, the Committee for Medicinal Products for Human Use (CHMP) of the European Medicine Agency (EMEA) gave positive recommendations on 104 new drug applications[1]. Negative opinion was adopted for six drugs. 34 drugs which received positive opinions were tested in clinical trials in Ukraine.

The State Expert Center conducted 70 inspections (clinical audits) during 2014.

Regulatory updates in 2014 included changes in requirements to insurance documents submission, information to be provided to clinical trial subject in Informed Consent Form, and initial and amendment submission to SEC.

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

Clinical Trials by Type and Manufacturing Country

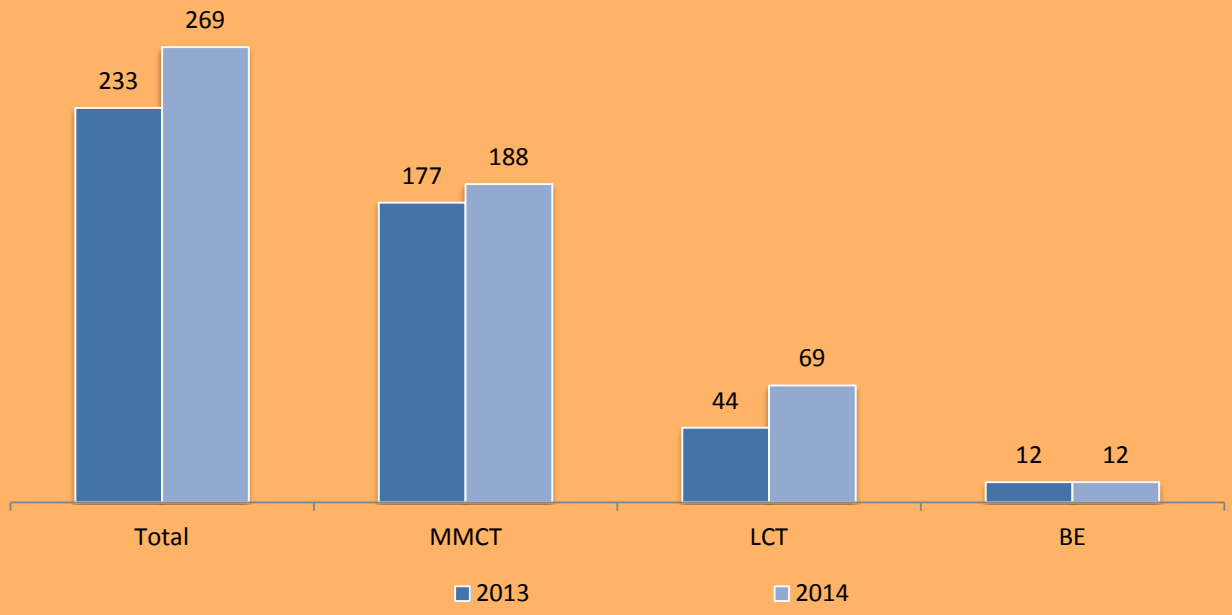
The MoH of Ukraine approved 269 new clinical trials of all types including local and bioequivalence studies during 2014, demonstrating a 15% increase in comparison with 2013.

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 increased from 177 studies in 2013 to 188 in 2014.

The number of local clinical trials (LCT) has increased from 44 in 2013 to 69 clinical trials in 2014, 57% increase from last year's figure.

The number of bioequivalence studies (BE) remained at the same level as in 2013: 12 clinical trials.

Figure 1. Clinical Trials in Ukraine in 2014

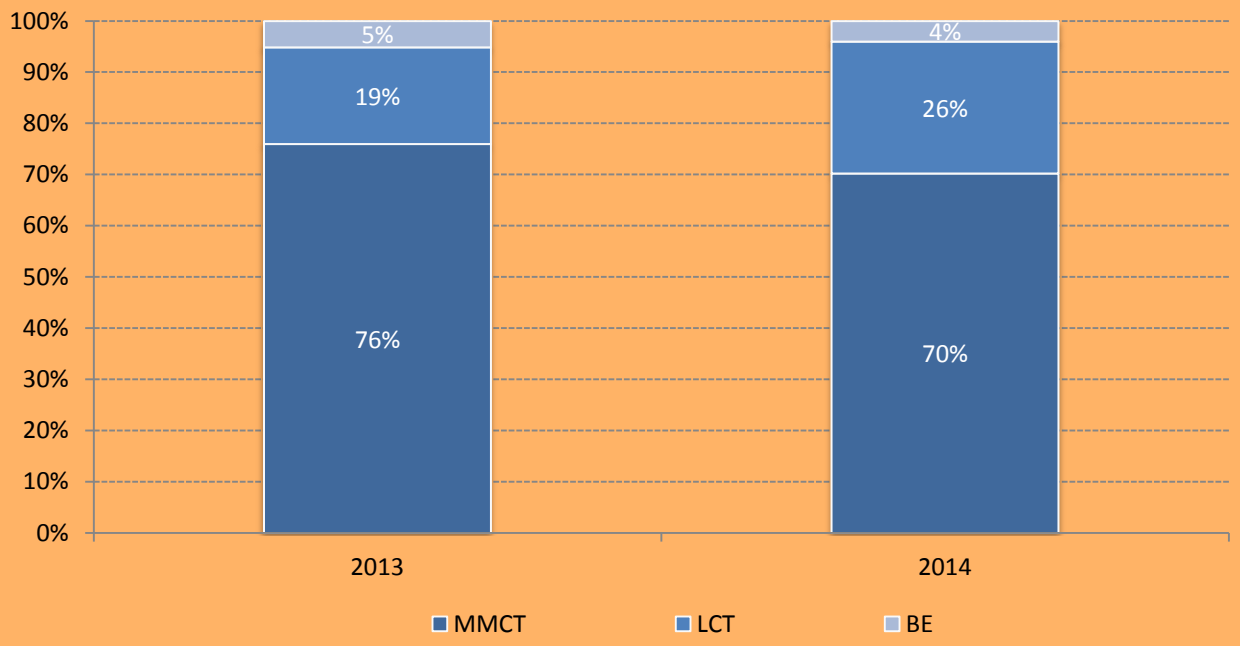


The proportions between different study types (multinational multi-center clinical trials, local studies and bioequivalence trials) changed slightly since last year (see **Figure 2**).

In comparison with 2013, the share of bioequivalence studies decreased from 5% to 4% of the total number of clinical trials approved in 2014.

The share of the local trials increased from 19% to 26% and the share of multinational multi-center clinical trials decreased from 76% to 70% of the total number of trials approved during 2014.

Figure 2. Clinical Trials by Type in 2014

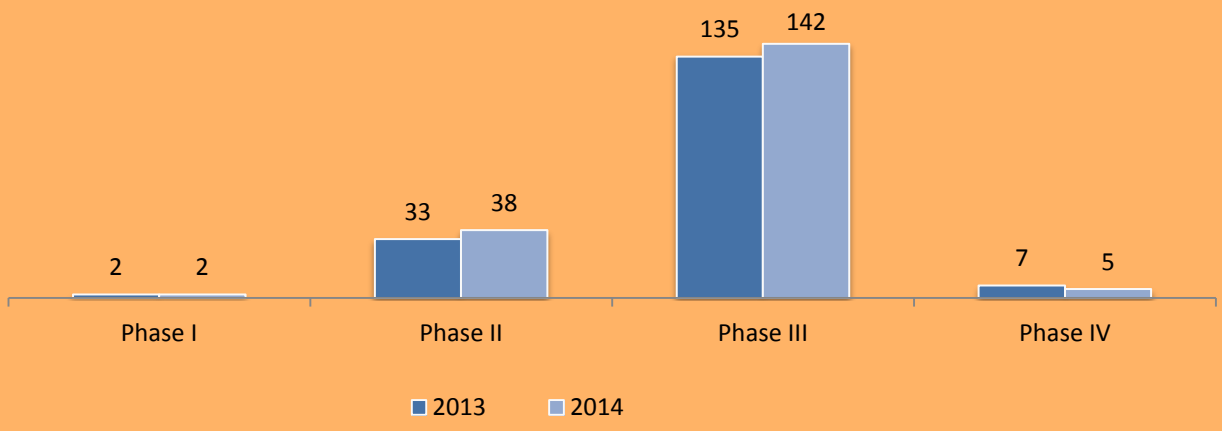


During the clinical trial, the applicant may submit to the Center significant amendments to the clinical trial protocols (additions or changes of existing information) which are reviewed according to established "Order". During 2014, the Center issued 1,242 positive conclusions for MMCT, almost the same figure as in 2013 when 1,245 positive conclusions were issued.

MMCT Clinical trials by Phase

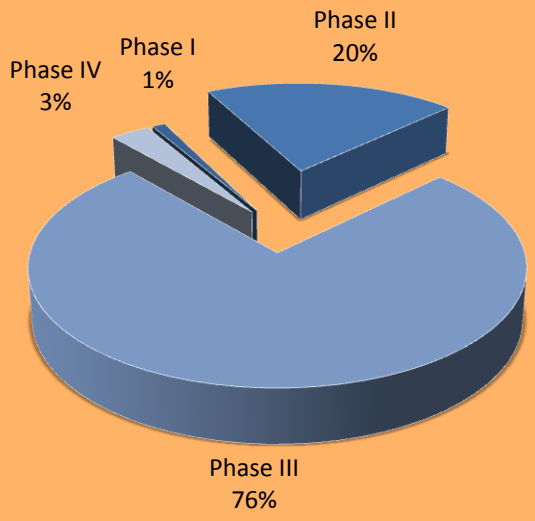
2014 saw 2 new Phase I MMCT clinical trials, the same figure as in 2013. The number of the Phase II trials increased from 33 in 2013 to 38 studies in 2014. The number of Phase III trials increased from 135 to 142 studies. Phase IV trials demonstrated the slight decrease from seven studies in 2013 to five studies in 2014.

Figure 3. Clinical Trials in Ukraine in 2014 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 2014

№	Company Name	Market share
1	Quintiles Ukraine	15%
2	PPD (Inno-Pharm) Ukraine	10%
3	Parexel Ukraine	10%
4	INC Research Ukraine	10%
5	GlaxoSmithKline Pharmaceuticals Ukraine	6%
6	ICON	5%
7	ASTRAZENECA Ukraine	5%
8	Other 32 applicants	39%

Rating of Ukrainian sponsors

Table 2. Applicants of local clinical trials in Ukraine in 2014

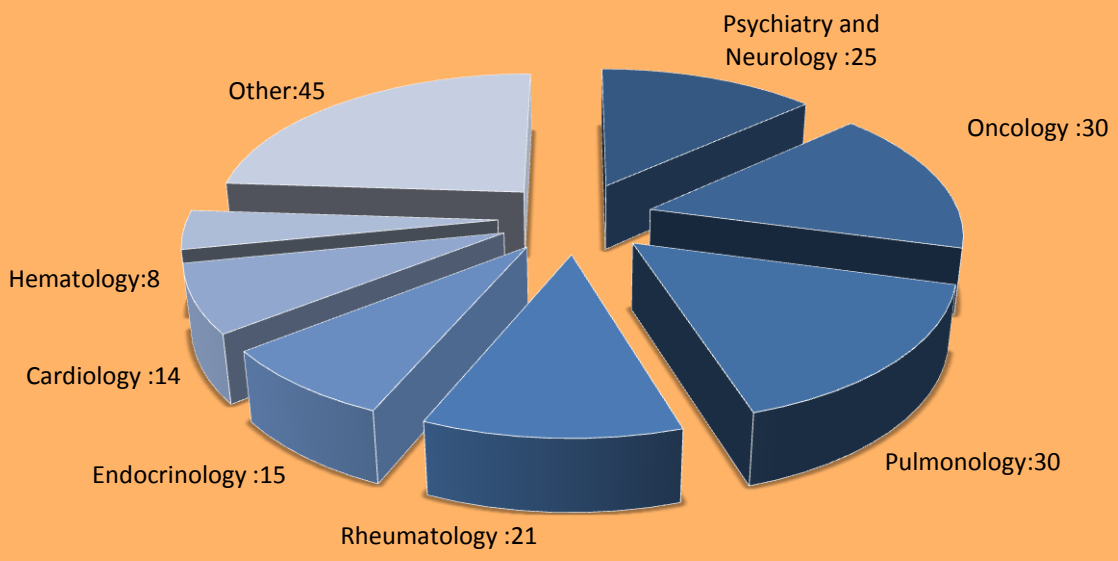
№	Company Name	Market share
1	PJSC "Farmak"	20%
2	LLC "Research Institution Quant M"	9%
3	PJSC SIC "Borshchahivskiy CPP"	7%
4	LLC "Pharma Start"	6%
5	PJSC "Pharmaceutical firm "Darnitsa"	5%
6	PJSC “Kyiv Vitamin Factory”	5%
7	Other 19 applicants	48%

Therapeutic Areas of MMCT Clinical Trials in 2014

In 2014, the majority of MMCTs was initiated in seven leading therapeutic areas: the largest number of studies was initiated in Oncology and Pulmonology (30); Psychiatry and Neurology (25); Rheumatology (21); Endocrinology (15); Cardiology (14); and Hematology (8).

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

Figure 5. MMCT in Ukraine in 2014 by Therapeutic Area

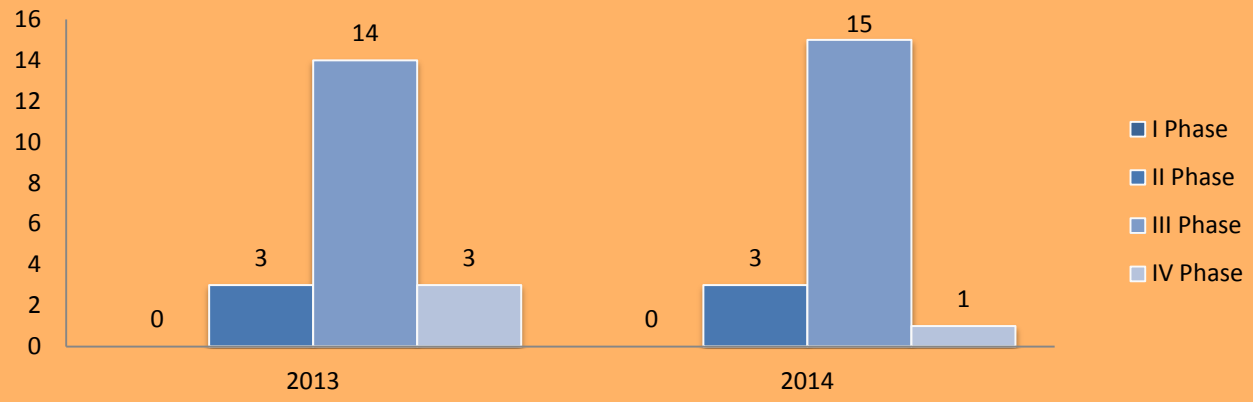


MMCT Clinical Trials in Pediatrics

During 2014, the Center granted 19 positive permissions for MMCT conduct in pediatrics, one permission less than in 2013.

In the majority of cases, Phase III clinical trials were conducted in pediatric groups. In comparison with 2013, the share of Phase III clinical trials increased from 70% to 79% of all clinical trials in pediatric patients during 2014 (see **Figure 6**).

Figure 6. Positive conclusions regarding MMCT in Pediatrics (2013-2014 years)



The main therapeutic areas, where the pediatric clinical trials were initiated in 2014, are: Psychiatry (21%), Hematology and Infectious diseases (16% each) (see **Table 4**).

Table 3. Therapeutic Areas of MMCT in Pediatrics (Approved in 2013 and 2014)

Nosology	2013	2014
Psychiatry	0	4
Hematology	7	3
Infectious diseases	2	3
Endocrinology	3	2
Surgery	1	2
Neurology	1	2
Pulmonology	4	1
Oncology	1	1

Looking at age groups in pediatric studies: 42% of all clinical trials initiated in 2014 involved minors (from 2 to 18 years), 16% – children from 28 days to 18 years, 11% – children from 2 to 11 years, and per 5% (one trial) – from born to 11 years, from 28 days to 4 years, 28 days to 17 years, from 5 to 17 years, from 8 to 15 years and from 10 to 18 years.

Clinical Trial Results

The Center for Drug Evaluation and Research (CDER) of the FDA approved 111 new drugs during 2014; 34 of them are new molecular entities (NME); others are new dosages manufacturers or indications of already marketed drugs. 15 of 111 new drugs were studied in clinical trials involving Ukrainian sites.

The **Table 5** shows the drugs which were approved by FDA in 2014 that were being tested in clinical trials in Ukraine.

Table 4. New Drugs Approved by FDA in 2014 and Tested in Ukrainian sites

Approval date	Drug (active ingredient)	Company
01/08/2014	FARXIGA (DAPAGLIFLOZIN)	ASTRAZENECA AB
02/12/2014	IMBRUVICA (IBRUTINIB)	PHARMACYCLICS INC
03/13/2014	DOCETAXEL (DOCETAXEL)	PFIZER LABS
04/25/2014	ASMANEX HFA (MOMETASONE FUROATE)	MERCK SHARP DOHME
04/30/2014	INCRUSE ELLIPTA (UMECLIDINIUM BROMIDE)	GLAXO GRP ENGLAND
05/05/2014	EPANOVA (OMEGA-3-CARBOXYLIC ACIDS)	ASTRAZENECA PHARMS
05/23/2014	DALVANCE (DALBAVANCIN HYDROCHLORIDE)	DURATA THERAPS INTL
08/08/2014	INVOKAMET (CANAGLIFLOZIN; METFORMIN HYDROCHLORIDE)	JANSSEN PHARMS
08/15/2014	PLEGRIDY (PEGINTERFERON BETA-1A)	BIOGEN IDEC INC
08/20/2014	ARNUITY ELLIPTA (FLUTICASONE FUROATE)	GLAXOSMITHKLINE
09/18/2014	TRULICITY (DULAGLUTIDE)	ELI LILLY AND CO
09/24/2014	SPIRIVA RESPIMAT (TIOTROPIUM BROMIDE)	BOEHRINGER INGELHEIM
10/07/2014	UCERIS (BUDESONIDE)	SALIX PHARMS INC
10/10/2014	AKYNZEO (NETUPITANT; PALONOSETRON HYDROCHLORIDE)	HELSINN HLTHCARE
10/15/2014	OFEV (NINTEDANIB)	BOEHRINGER INGELHEIM
		Source: FDA

During 2014, the Committee for Medical Products for Human Use (CHMP) of the European Medicine Agency (EMEA) approved 104 new drug applications. A negative opinion was adopted for six drugs. 34 drugs which received positive conclusion were (or are) being tested in clinical trials in Ukraine (see **Table 5**).

Table 5. New Drugs Approved by EMEA in 2014 and Tested in Ukrainian Sites

Approval date	Drug	Company

23.01.2014	ADEMPAS	BAYER PHARMA AG
23.01.2014	NOVOTHIRTEEN	NOVO NORDISK A/S
23.01.2014	STELARA	JANSSEN-CILAG INTERNATIONAL N.V.
20.02.2014	ANORO	GLAXO GROUP LTD
20.02.2014	VOKANAMET	JANSSEN-CILAG INTERNATIONAL N.V.
20.03.2014	JARDIANCE	BOEHRINGER INGELHEIM INTERNATIONAL GMBH
20.03.2014	PEGASYS	ROCHE REGISTRATION LIMITED
20.03.2014	TRESIBA	NOVO NORDISK A/S
20.03.2014	VICTOZA	NOVO NORDISK A/S
25.04.2014	MEKINIST	GLAXO GROUP LTD
25.04.2014	GILENYA	NOVARTIS EUROPHARM LTD
25.04.2014	INVEGA	JANSSEN-CILAG INTERNATIONAL N.V.
25.04.2014	NEXAVAR	BAYER PHARMA AG
25.04.2014	PRADAXA	BOEHRINGER INGELHEIM INTERNATIONAL GMBH
25.04.2014	PROLIA	AMGEN EUROPE B.V.
22.05.2014	PLEGRIDY	BIOGEN IDEC LTD
22.05.2014	ARZERRA	GLAXO GROUP LTD
22.05.2014	VFEND	PFIZER LTD
26.06.2014	AVASTIN	ROCHE REGISTRATION LTD
26.06.2014	ELIQUIS	BRISTOL-MYERS SQUIBB / PFIZER EEIG
26.06.2014	ENBREL	PFIZER LTD
24.07.2014	IMBRUVICA	JANSSEN-CILAG INTERNATIONAL NV
24.07.2014	ECALTA	PFIZER LIMITED
24.07.2014	HUMIRA	ABBVIE LTD
24.07.2014	XGEVA	AMGEN EUROPE B.V.
25.09.2014	TRULICITY	ELI LILLY NEDERLAND B.V.
25.09.2014	VARGATEF	BOEHRINGER INGELHEIM INTERNATIONAL GMBH
25.09.2014	PREZISTA	JANSSEN-CILAG INTERNATIONAL N.V.
23.10.2014	LYNPARZA	ASTRAZENECA AB
23.10.2014	XTANDI	ASTELLAS PHARMA EUROPE B.V.
20.11.2014	OFEV	BOEHRINGER INGELHEIM INTERNATIONAL GMBH
18.12.2014	REVLIMID	CELGENE EUROPE LIMITED

18.12.2014	VELCADE	JANSSEN-CILAG INTERNATIONAL N.V.
		Source: EMEA

Inspections

FDA inspections

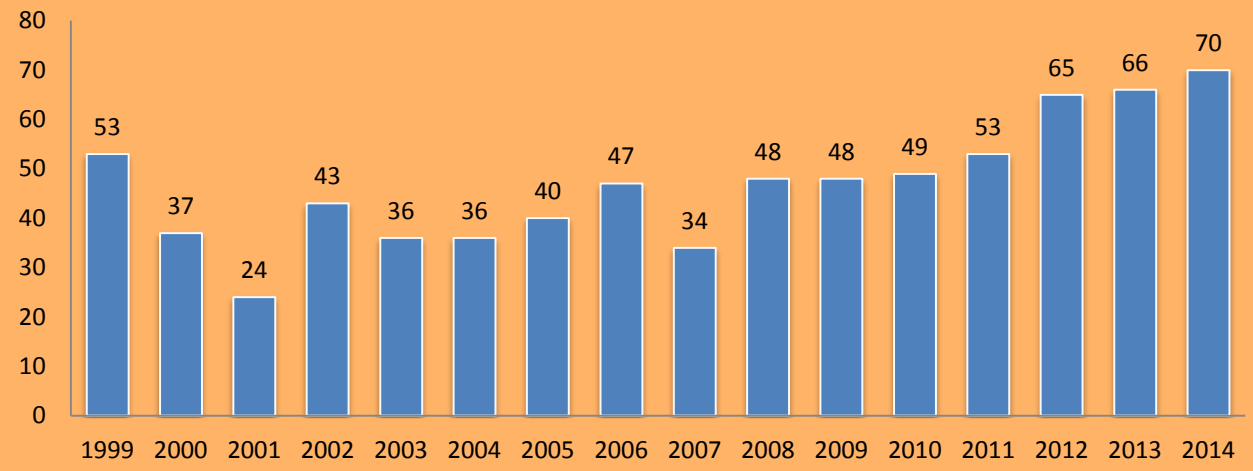
At the Orange Paper 2014 publication date, no information about inspections of the FDA conducted in the Ukrainian investigative sites was available.

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. 70 clinical audits were conducted in 2014, four audits (6%) more than in 2013.

Figure 7. State Expert Center Clinical Audits (Inspections) (1999-2014)

Temporally discontinued – clinical trials in 57 sites
Terminated – clinical trials in nine sites



Regulatory Update

Clinical Trials in Ukraine are conducted in accordance with Order #690 MoH of Ukraine dated 23.09.2009 with changes stated in Order #523 MoH of Ukraine dated 12.07.2012. Order #304 with changes to Order #690 was published on 06.05.2014. The main changes are related to insurance. According to the Order #304, applicant doesn't have to submit an Insurance Certificate and an Insurance Contract to the SEC for getting an SEC conclusion which was required by Order #690. Among other changes is a new appendix «Requirements to informed consent», added by Order #304 describing information which should be provided to patients in Informed Consent Forms.

Order #966 with changes to Order #690 MoH of Ukraine was published on 18.12.2014. The main changes are related to initial and amendment submission to the SEC procedure. Single Window for a Cover Letter and Application submission was established. Initial/Amendment materials are submitted to Expert Department after 3 days due to the documents submission to the Single Window. Order #523 Appendices «Initial/Amendment Cover Letter to SEC» and «Initial/Amendment Application to SEC» were changed.

Summary

The current situation in Ukraine is favorable for clinical trials. Contributing factors to this favorable environment include: country population, a well-developed and structured system of healthcare, highly-qualified stuff 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 February 2016 and will cover data for 2015.

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 Russian and foreign pharmaceutical and biotechnological companies conduct cost-effective clinical trials. Today, Synergy is represented in Moscow, Saint-Petersburg, Novosibirsk, Yekaterinburg, Perm, Krasnodar, and also in Almaty and Astana (Kazakhstan) and Kyiv (Ukraine). The company's headquarters are in Moscow.