Clinical Trials in Ukraine
Orange Paper

Overview and 1st Half Year 2014

48/50, Volynska str., Kyiv, 03151, Ukraine

www.synrg-pharm.com

Contents

48/50, Volynska str., Kyiv, 03151, Ukraine.

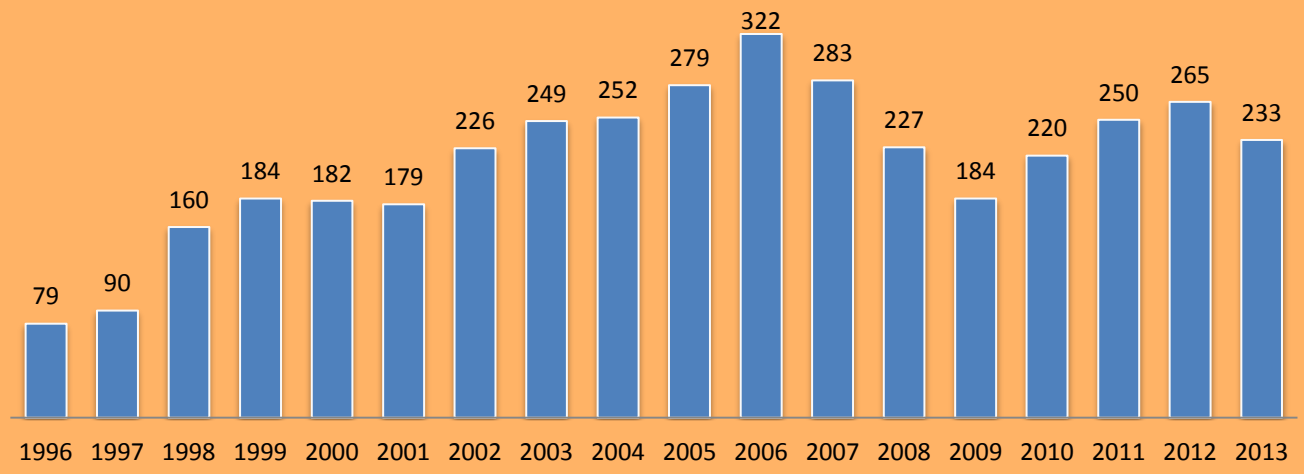
www.synrg-pharm.com

Introduction

The Orange Paper is an analytical report about the clinical trials market in Russia, published quarterly by the contract research organization Synergy Research Group[1]. The first edition of Orange Paper was released in 2006, and at the moment 31 issues have already published. Now, thanks to Synergy Group Ukraine, obtaining information about the market of clinical trials in Ukraine has become possible.

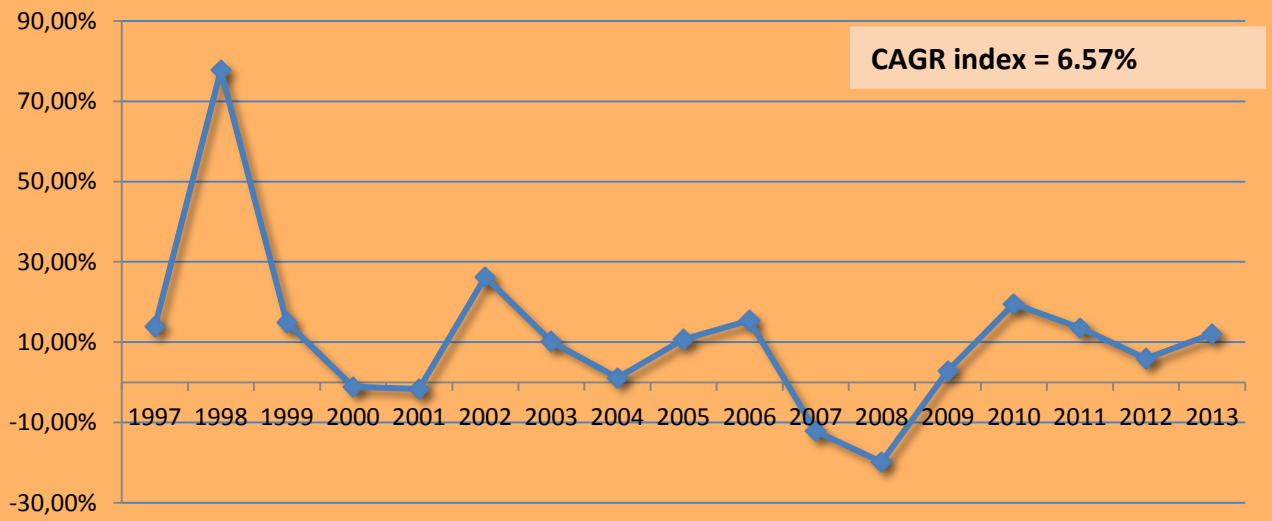
In Ukraine, during the period from 1996 to 2013, applicants had obtained 3,864 positive conclusions[2] about the possibility of conducting clinical trials of drugs, both for domestic and foreign manufacturers, including conduct of multinational multi-center clinical trials (hereinafter – MMCTs) (see. **Figure 1**).

Figure 1. Clinical Trials in Ukraine (1996-2013 year)



According to the CAGR index[3] (Compound annual growth rate), for the period of clinical trial conduct in Ukraine (1996-2013 year), there has been an overall positive trend in the number of approved clinical trials, and the CAGR index is respectively 6.57% (see. **Figure 2**).

Figure 2. CAGR index for Clinical Trials in Ukraine (1996-2013 year)



The potential for successful conduct of clinical trials in Ukraine are based on several factors, such as: demographics, number of investigative sites, appropriate regulation and ethical support,

[1] Orange Paper Russian http://www.synrg-pharm.com/article31.htm
[2] According to the materials of the State Expert Center of MoH of Ukraine http://www.dec.gov.ua/
[3] http://en.wikipedia.org/wiki/Compound_annual_growth_rate

favorable conditions for clinical trials in pediatrics, number of pharmaceutical companies, established quality assurance system.

Demographics

According to data from the State Statistics Service of Ukraine as of the 1st January of 2014, the de-facto population of Ukraine stood at 45,426,200, and resident population was 45,245,900. The majority of the population is 18 to 60 years old, the segment most frequently involved in clinical trials (see. **Table 1**).

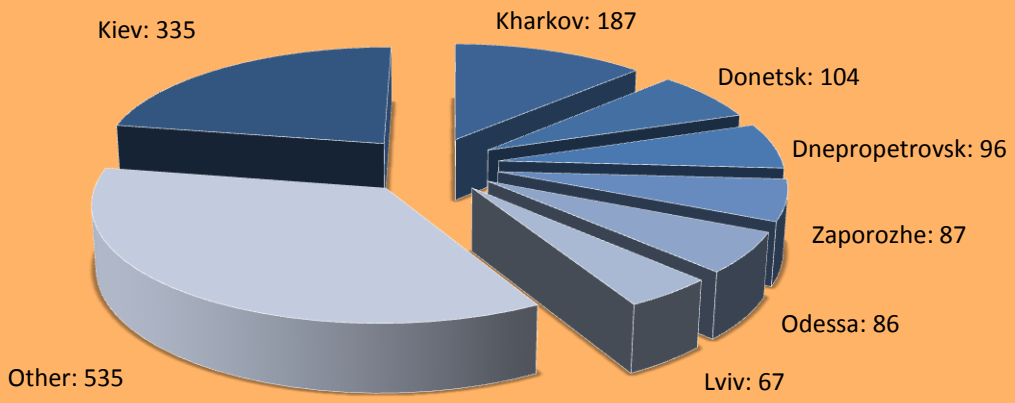
Table 1. Distribution of population by age group (on the 1st January of 2014)

Age	Population
From 0 to 17 years	8 009 900
From 18 to 60 years	27 482 700
More than 60 years	9 753 300

Investigative sites

Investigative sites in Ukraine are characterized by qualified personnel and modern equipment. According todata from the State Expert Center of MoH of Ukraine (hereinafter - the Center), in January 2014 there were 1,476 investigative sites for clinical trial conduct in Ukraine. Most sites are located in major cities such as: Kiev (335), Kharkov (187), Donetsk (104), Dnepropetrovsk (96), Zaporozhe (87), Odessa (86), Lviv (67) (see **Figure 3**). Moreover, in 275 sites the clinical audits of clinical trials were successfully conducted by State Expert Center of MoH of Ukraine.

Figure 3. Number of Investigative Sites in Major Cities



According to clinical trial market expert estimates, only 10-15% of the potential regarding the possibility of conducting trials is used in Ukraine. A centralized health care system and a large number of specialized medical institutions enroll patients with rare diseases.

Regulatory base

The implementation of international guidelines for clinical trials began in Ukraine in 1996, after the adoption of the Law of Ukraine "On Medicines." Articles 7 and 8 of the Law are devoted to the expert review of clinical trial materials, conduct of clinical trials and the rights protection of patients/volunteers.

The next step for Ukrainian regulatory base was conformation to the international requirements and standards of ICH GCP became the guideline (42-7.0: 2005 Medicines. Good Clinical Practice)

approved by the MoH Ukraine on 22.07.2005.To replace this manual, a Guideline for Clinical Trials was approved by the MoH of Ukraine of 16.02.2009 #95 "ST-N of MoH42-7.0:2005 ”Medicines. Good Clinical Practice.“ This guideline is a national translation of CPMP / ICH / 135/95 Note for Guidance on Good Clinical Practice, 2002.

The next step towards the process of harmonization of the Ukrainian regulatory base in the field of clinical trials, according to international requirements and in particular the European legislation, was the Ministry of Health of Ukraine order effective 23.09.2009, #690[1] ”On Approval of the Procedure for Conducting Clinical Trials of Medical Products and Expert Evaluation of Materials Pertinent to Clinical Trials and Model Regulations of the Ethics Committees” (hereinafter – Order). Changes and additions were adopted in the form of orders from the MoH of Ukraine #523[2] dated 12.07.2012 and #304[3] dated 06.05.2014.

On 13t June 2014, the guideline ”Bioequivalence Study”[4] was approved by the order #396 (ST-N MoH 42-7.1:2014) of MoH of Ukraine. This guideline became a regulatory base for conducting Bioequivalence studies.

While conducting clinical trials in Ukraine, it is necessary to fulfill the requirements of CPMP/ICH/135/95, as specified in the Order of the Ministry of Health of Ukraine #690 dated 23.09.2009.

According to the approved "Order":

- The start of a clinical trial becomes possible only after a positive conclusion of the Center approved by the Ministry of Health of Ukraine, as well as a positive opinion of the Ethics Committee at the healthcare settings (hereinafter - HCS), are obtained
- The duration of clinical trial materials review is 60 days, 50 of them are for the expert evaluation by the Center, 10 days are for the decision made by the Ministry of Health
- A detailed list of documents to be submitted along with the application for conducting clinical trials is specified
- The requirements for the Principal Investigator, co-investigators, and HCS where a clinical trial is planned to be conducted are specified
- The timeline for review of amendments to the clinical trial materials is 30 days starting from the date the application for amendment is obtained. The timeline for getting an MoH decision regarding the amendment approval is 5 days
- The requirements regarding the clinical trial information that is to be provided are indicated. The Center should be notified about the start of clinical trial no later than 10 calendar days after the first patient has been enrolled. Timelines for notification about the clinical trial completion is 90 calendar days after completion, or 15 calendar days in the case of premature termination.
- The timeline and format of notification about adverse events and adverse drug reactions, as well as the timelines for notifying the Center about the safety of investigational products (SUSAR, DSUR), are specified
- The rules for conducting clinical audit of clinical trial are defined
- The reasons for termination or temporary discontinuation of clinical trials are defined

During the clinical trial, the applicant may submit to the Center substantial amendments to the clinical trial protocol (additions or changes of existing information), which are reviewed according to established “Order”. Thus, during the period from 2010 to 2013, the Center issued 4,478 positive conclusions (in 2010 – 965 positive conclusions, 2011 – 1,026, 2012 – 1,241, and in 2013 – 1,246).

[1] http://www.moz.gov.ua/ua/portal/dn_20090923_690.html
[2] http://www.moz.gov.ua/ua/portal/dn_20120712_523.htm
[3] http://zakon1.rada.gov.ua/laws/show/z0739-14
[4] http://www.dec.gov.ua/index.php/111-golovna/473-do-uvagi-zayavnikiv-rozrobnikiv-likarskikh-zasobiv-doslidnikiv

Ethical Support of Clinical Trials

Clinical trials in Ukraine may only be conducted with written positive decisions of the Center approved by the MoH, as well as positive decisions of the Ethics Committee at HCS about the possibility of clinical trial conduct.

According to the "Order on Approval of the Procedure for Conducting Clinical Trials of Medical Products and Expert Evaluation of Materials Pertinent to Clinical Trials and Model Regulations of the Ethics Committees" approved by the Ministry of Health of Ukraine dated 23.09.2009 #690:

- The period for revising clinical trial materials with the Ethic Committee at HCS is no longer than 30 calendar days
- Parallel review of clinical trial materials by the Center and the Ethic Committee at HCS is possible
- The rules for submission of the summary of the clinical trial results to the Center/Ethic Committee at HCS are defined (no later than one year after the completion of clinical trial).

It should be noted that a decentralized system of Ethics Committees allows a comprehensive assessment of the quality and ethical aspects of clinical trials by different specialists, which is certainly a positive aspect of clinical trials in Ukraine.

Clinical Trials in Pediatrics

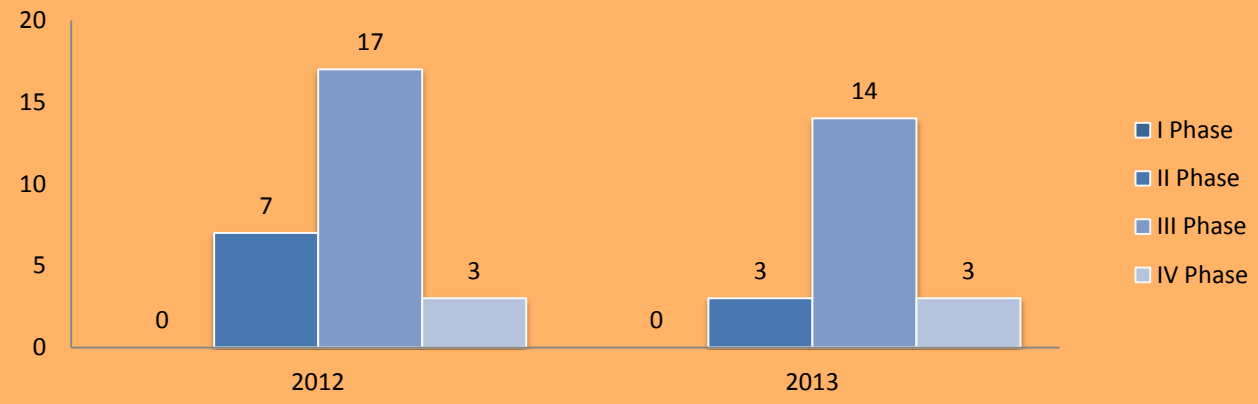
The Ukrainian legislation strictly regulates the conduct of clinical trials involving children. Rules and restrictions about the conduct of clinical trials in pediatrics are described by Ministry of Health of Ukraine #690 from 23.09.2009 "Order on Approval of the Procedure for Conducting Clinical Trials of Medical Products and Expert Evaluation of Materials Pertinent to Clinical Trials and Model Regulations of the Ethics Committees" Section 3 "Clinical Trials with the Participation of Infant and Minor Children." Conducting clinical trials in pediatrics is also regulated by the "Family Code" (2002, with amendments), the "Civil Code" (2004) and "Fundamentals of Legislation on Health Care" (1993, with amendments), and the law of Ukraine "On Medicines."

Features of this type of trials are: necessity to obtain the consent of both parents; prohibition of clinical trials of medicinal products with participation of infant or minor children deprived of parental care, adopted children or orphans.

During the period of 2012-2013 years, the Center granted 47 positive permissions for MMCT conduct in pediatrics.

In majority of cases, a phase III clnical trials were conducted in pediatric groups. They stood at 66% of all clinical trials in pediatric patients (see **Figure 4**).

Figure 4. Positive conclusions about MMCT in Pediatrics (2012-2013 years)



The main therapeutic areas, where the pediatric clinical trials conducted are: Pulmonology (33%), Psychiatry (23%), Hematology (10%) (see **Figures 5 and 6**).

Figure 5. Clinical Trials in Pediatrics (ongoing Clinical Trials, as of the 31st of December 2013)

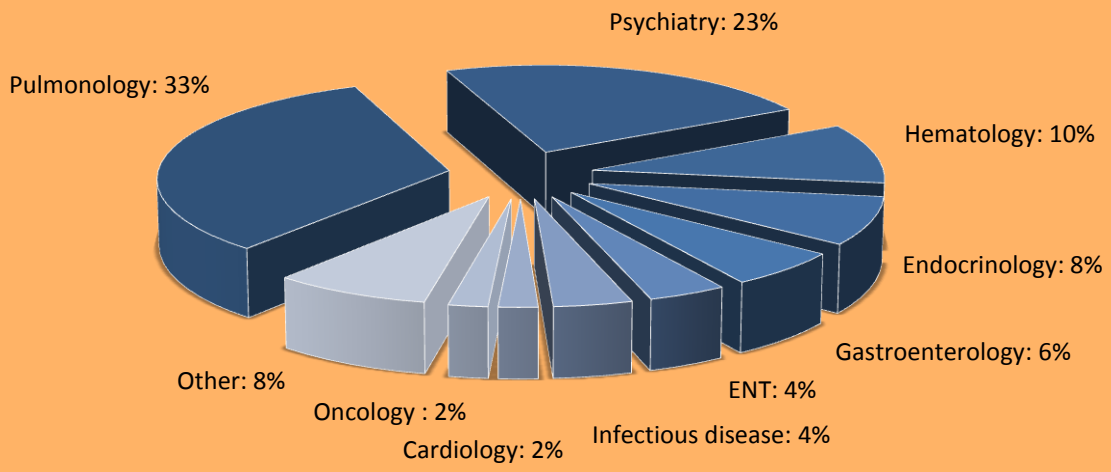
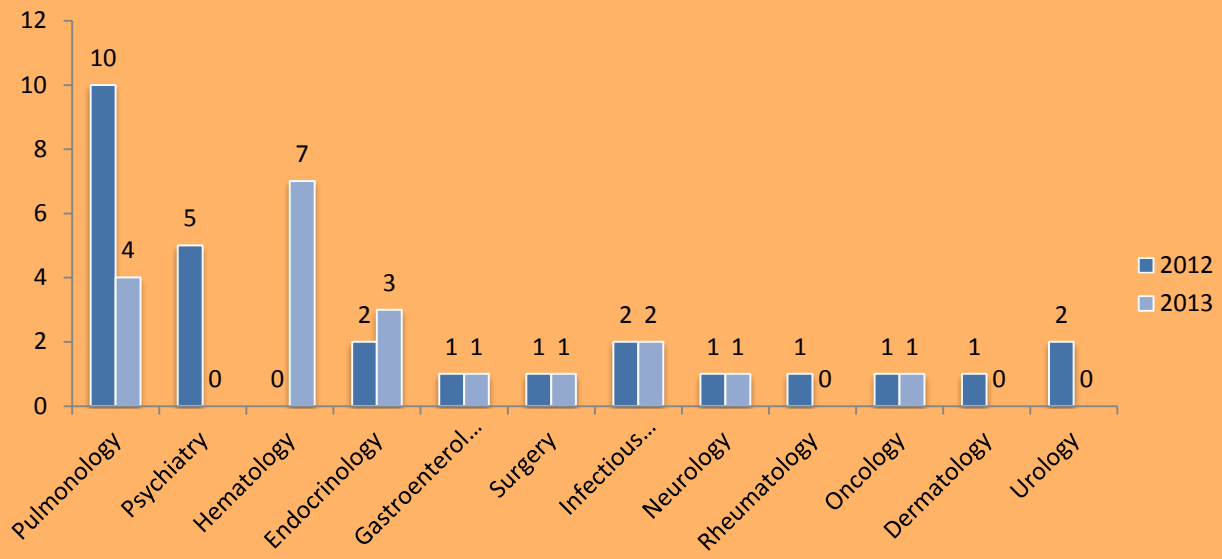


Figure 6. Therapeutic Areas of MMCT in Pediatrics (Approved 2012 to 2013)



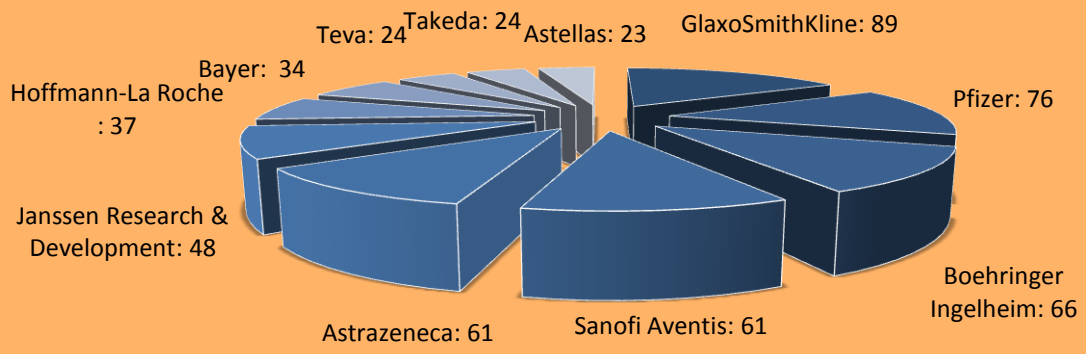
According to the age groups, 63% of all clinical trials involved minors (from 14 to 18 years), 23% – children from 2 to 12 years, 10% – children from 12 to 14 years, and 4% – children up to 24 month.

Clinical Trial Sponsors in Ukraine

Clinical trial sponsors in Ukraine are comprised of both international and local companies manufacturing medicinal products. Most of the foreign pharmaceutical companies have been in the Ukrainian market for more than 15 years and have representative offices in the country which conduct clinical trials on their own initiative.

According toclinicaltrials.gov site statistics, from 1996 to 2014 leading sponsors of clinical trials in Ukraine are: GlaxoSmithKline (89 trials), Pfizer (76), Boehringer Ingelheim (66), Sanofi Aventis (61), Astrazeneca (61), Janssen Research & Development (48), Hoffmann-La Roche (37), Bayer (34), Teva (24), Takeda (24), Astellas (23) (see **Figure 7**).

Figure 7. Sponsors of Clinical Trials in Ukraine, According to Data from clinicaltrials.gov (1996-2014)



Clinical Audits of Clinical Trials by the State Expert Center

One of the main components in quality assurance of clinical trial conduct is clinical audits, which are regularly conducted by State Expert Center employees starting from 1999.

According to the established Order, a clinical audit of clinical trials is a "procedure of an official check by the Center of documents, facilities, equipment and instruments, records, quality assurance system and other resources related to a clinical trial and which may be available in a health care setting, laboratories, premises of the sponsor or the contract research organizations and other sites".
Definition of clinical audit specified in the Order corresponds to the definition of inspection in GCP.

Preliminary plans of clinical audits are posted on the official website of the Center and updated every quarter[1]. The planned date and location of clinical audits are indicated in the plan.

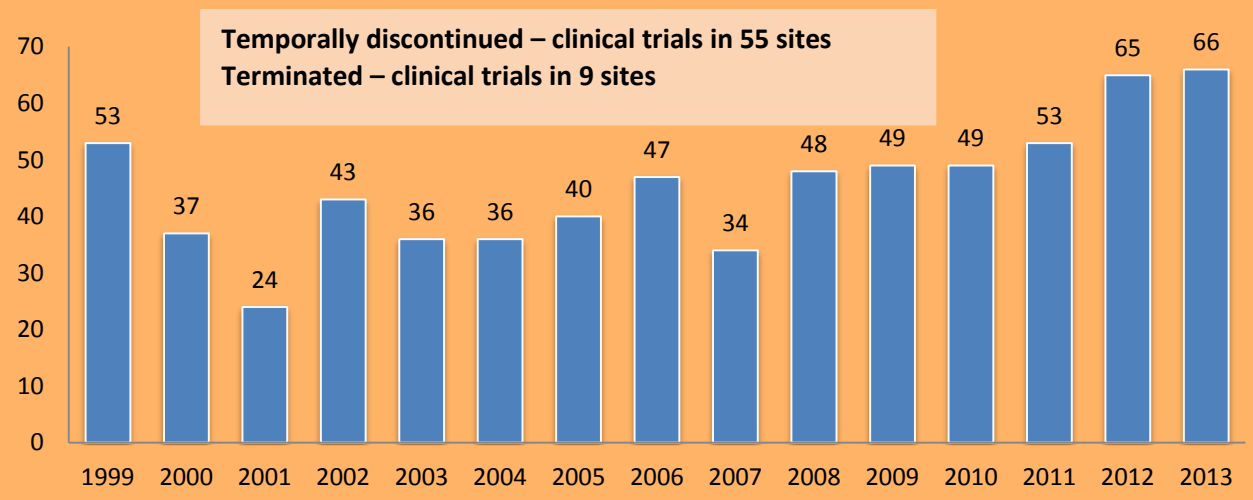
Clinical audits of clinical trials shall be conducted not earlier than 14 calendar days after sending the preliminary notification, and agreeing with the principal investigator and/or sponsor the start date and duration of the inspection, the objectives, list of documents and premises to be inspected.

As the result of a clinical trial inspection, an appropriate act is drawn up, where the findings (if any) and timelines for their resolution are specified. The Center forwards the act with the inspection results to the clinical trial sponsor and principal investigator.

As shown in **Figure 8**, the number of inspections of clinical trials conducted by the Center employees is increasing. In 2013, 66 inspections were conducted.

[1] http://www.dec.gov.ua/index.php/ekspertiza-materialiv-doklinichnikh-ta-klinichnikh-viprobuvan/aktualna-informatsiya

Figure 8. State Expert Center Clinical Audits (Inspections) (1999-2013)



FDA Inspections

From 1996 to 2013, 26 FDA inspections were conducted in Ukraine. Among them, 16 inspections were completed with status NAI (No Action Indicated) and 10 - status of VAI (Voluntary Action Indicated).

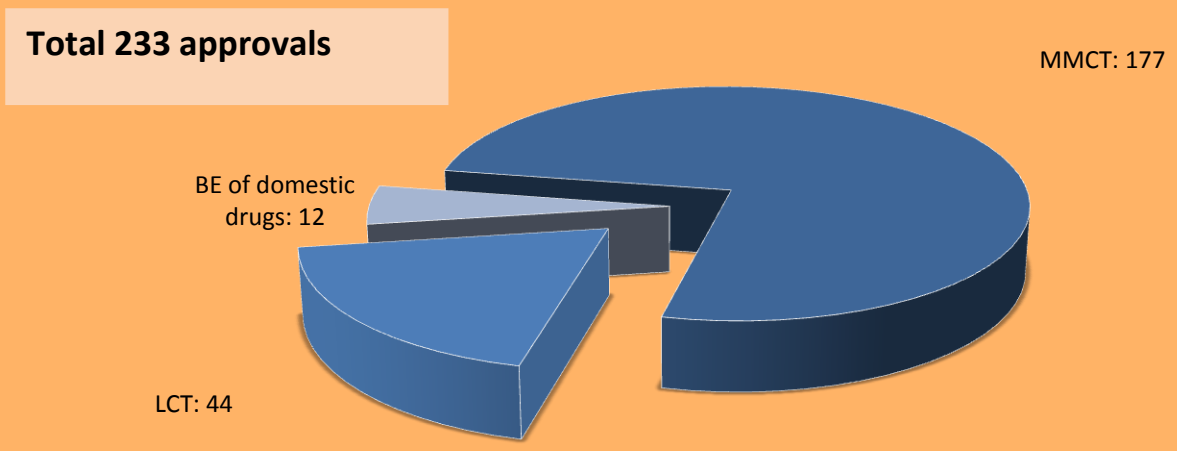
In 2013, the FDA conducted seven inspections in the following cities: Kiev, Dnepropetrovsk (2 sites), Donetsk, Chernihiv, Lviv, and Cherkassy. Inspections were completed with the following results – two VAI conclusions and five NAI, which suggests the high qualifications of investigative sites staff, their good practices and, as a consequence, the high quality of clinical trial conduct.

Year 2013

According to statistics from the State Expert Center of MoH of Ukraine in 2013, there were 233 positive conclusions about clinical trial conduct, and 1246 positive Center conclusions about significant amendments, were issued in 2013.

Distribution by type of clinical trial is indicated in **Figure 9**, where MMCT – multi-center clinical trials, LCT – local clinical trials, BE – bioequivalence.

Figure 9. Clinical Trials in Ukraine in 2013



Clinical Trials by phase in 2013

Of all MMCTs, clinical trials of phase III stood at 135, II phase - 33, I phase – two, IV phase - one clinical trial.

Clinical Trial Sponsors in 2013

Clinical trial applicants are indicated in **Table 2 and Table 3**.

Table 2. Applicants of MMCT in Ukraine (2013)

#	Company name	Market share
1	Quintiles Ukraine	12%
2	PPD (Inno-Pharm) Ukraine	11%
3	PSI Ukraine	4%
4	Janssen Pharmaceutica Ukraine	4%
5	GlaxoSmithKline Pharmaceuticals Ukraine	4%
6	ICON	3%
7	Parexel	3%
8	INC Research Ukraine	3%
9	OOO «PharmaNet Ukraine»	3%
10	Sanofi-Aventis Ukraine	3%
11	Other 38 applicants	50%

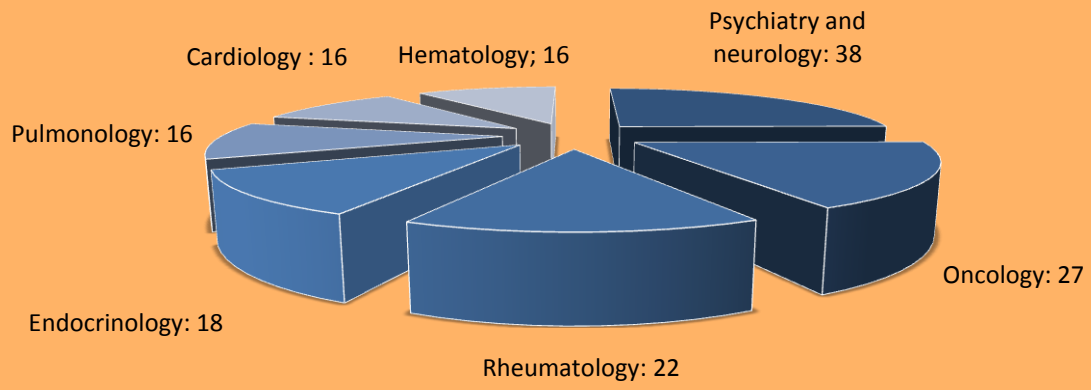
Table 3. Applicants of pre-registration clinical trials in Ukraine in 2013

#	Company name	Market share
1	LLC «PC Zdorovie»	19%
2	LLC «KPE Zdorovie narodu»	12%
3	LLC «ISNA» Ukraine	8%
4	LLC «Olfa» Ukraine	8%
5	PLC «Kievmedpreparat»	8%
6	Other 11 applicants	45%

Therapeutic areas of Clinical Trials started in 2013

In 2013, the majority of MMCTs were initiated in seven therapeutic areas: Psychiatry and Neurology (38), Oncology (27), Rheumatology (22) Endocrinology (18), as well as Pulmonology, Cardiology and Hematology (16 studies, respectively) (see **Figure 10**).

Figure 10. Therapeutic areas of MMCT (Year 2013)



Clinical Trial Results in 2013

The Center for Drug Evaluation and Research (CDER) of the FDA approved 114 new drugs during 2013; 24 of them are new molecular entities (NME); others are new dosages manufacturers or indications of already marketed drugs. 7 of the 114 drugs were studied in clinical trials conducted in Ukraine.

The **Table 4** represents drugs, which were approved by FDA and were being tested in clinical trials in Ukraine in 2013.

Table 4. New Drugs Approved by FDA in 2013 and Tested in Ukrainian sites

Approval date	Drug (active ingredient)	Company
01/25/2013	NESINA (ALOGLIPTIN BENZOATE)	TAKEDA PHARMS USA
03/27/2013	TECFIDERA(DIMETHYL FUMARATE)	BIOGEN IDEC INC
03/29/2013	INVOKANA (CANAGLIFLOZIN)	JANSSEN PHARMS
09/30/2013	BRINTELLIX (VORTIOXETINE HYDROBROMIDE)	TAKEDA PHARMS USA
10/18/2013	OPSUMIT (MACITENTAN)	ACTELION PHARMS LTD
11/08/2013	APTIOM (ESLICARBAZEPINE ACETATE)	SUNOVION PHARMS INC
11/22/2013	OLYSIO (SIMEPREVIR SODIUM)	JANSSEN PRODS
		Source: FDA

During 2013 the Committee for Medical Products for Human Use (CHMP) of the European Medicine Agency (EMEA) approved 101 new drug applications. Negative opinion was adopted for eight drugs. Eight 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 2013 and Tested in Ukrainian Sites

Approval date	Drug	Company
14/01/2013	BOSUTINIB	PFIZER
18/03/2013	AUBAGIO	SANOFI
18/03/2013	TECFIDERA	BIOGEN IDEC
24/06/2013	LEMTRADA	GENZYME (SANOFI COMPANY)
16/09/2013	INVOKANA	JANSSEN RESEARCH & DEVELOPMENT, LLC
21/10/2013	OPSUMIT	ACTELION
21/10/2013	BRINTELLIX	TAKEDA + H. LUNDBECK A/S
16/12/2013	SIRTURO	JANSSEN INFECTIOUS DISEASES BVBA
		Source: EMEA

1st half of 2014

During the first six months of 2014, the number of positive conclusions for clinical trials that were issued by Ukrainian regulatory authorities has increased compared to the same period of last year: 155 opinions, including MMCTs - 108 conclusions (in the first half of 2013 - 123, including MMCTs - 93 conclusions).

Thus, in June 2014 the clinical trial regulatory framework has been improved by adoption of the order #304 as an amendment to the order #690. Major changes are as follows:

- The statement that outlines the necessity to conclude a liability insurance contract of applicant at the time of initial submission was excluded. However, the necessity to conclude it prior to the inclusion of the first patient in the study still remains
- Changes in the section which specifies the requirements for written and oral information provided to the patient (healthy volunteer) or the legal representative/close relative will be contained in a separate addendum to the Order. In addition, the requirements were supplemented with several new provisions

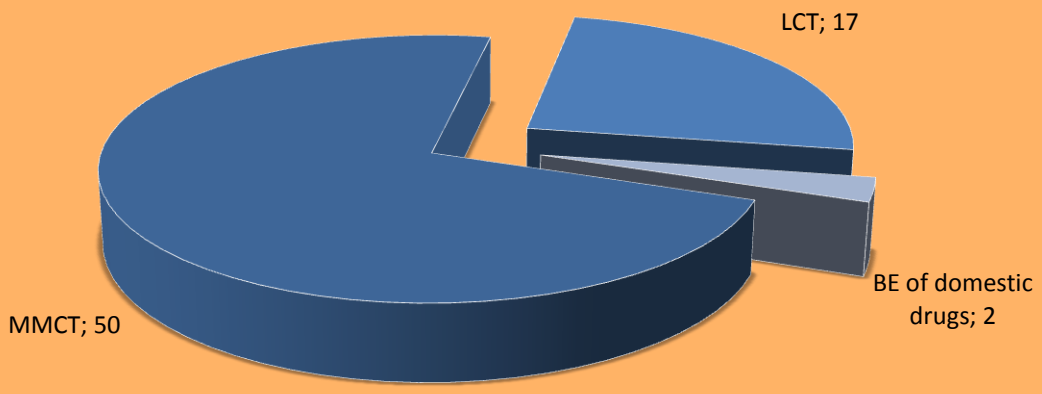
Also, the regulatory base for conducting bioequivalence studies was unified: by the order of MoH of Ukraine #396 of 13.06.2014, the guideline “Bioequivalence study” was approved (ST-N of MoH 42-7.1:2014).

The guideline was prepared according to EU guidelines:

- CPMP/QWP/EWP/1401/98 Rev.1 Guideline on the Investigation of Bioequivalence, 2010 (Guidelines for the bioequivalence study, 2010)
- CPMP/QWP/EWP/1401/98 Rev.1. Appendix IX of Guideline on the Investigation of Bioequivalence: Presentation of Biopharmaceutical and Bioanalytical Data in Module 2.7.1, 2011 (Appendix 4 Submission of biopharmaceutical and bioanalytical data in Module 2.7.1, 2011).

Statistics by phases of clinical trials for the first quarter is represented on the **Figure 11.**

Figure 11. Clinical Trials in Ukraine During 1st Quarter of 2014



Results of Clinical Trials in 1st Half of 2014

The Center for Drug Evaluation and Research (CDER) of the FDA approved 47 new drugs during first six month in 2014; 13 of them are new molecular entities (NME); others are new dosages, manufacturers or indications of already marketed drugs. 2 of the 47 drugs were studied in clinical trials conducted in Ukraine (See **Table 6**).

Table 6. New Drugs Approved by FDA in 1st half of 2014 of and Tested in Ukrainian sites

Approval date	Drug (active ingredient)	Company
01/08/2014	FARXIGA (DAPAGLIFLOZIN)	ASTRAZENECA AB
05/23/2014	DALVANCE (DALBAVANCIN HYDROCHLORIDE)	DURATA THERAPS INTL
		Source: FDA

During the first half of 2014, the Committee for Medicinal Products for Human Use (CHMP) of the European Medicine Agency (EMEA) approved 57 new drug applications. Negative opinion was adopted for five drugs. One of the drugs which received positive opinion was (or is) being tested in clinical trials in Ukraine (see **Table 7**).

Table 7. New Drugs Approved by EMEA in 1st half of 2014 and Tested in Ukrainian sites

Approval date	Drug (active ingredient)	Company
07/03/2014	OLYSIO	JANSSEN R&D IRELAND
		Source: EMEA

Conclusion

The current situation in Ukraine is favorable for clinical trials conduct. 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 March 2015 and will cover materials for the second half of 2014

About Synergy Research Group

Synergy Research Group is a Russian contract research organization successfully operating in Russia and CIS countries 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.