Center for Trade Development

CLINICAL TRIALS, PRODUCT REGISTRATION & MARKET ENTRY

Central & Eastern Europe

Pavlina Klimova
Easylink Business Services
Na Berance 57/2, 160 00 Praha 6
Prague, Czech Republic
Phone: (+420) 222-81-22-84
Fax : (+420) 222-81-22-83
e-mail: pklimova@easylink.cz
Website : www.easylink-cee.eu / www.newpa.com
Date: September 2013

TABLE OF CONTENTS

PART A: PROJECT OVERVIEW

The "CLINICAL TRIALS, PRODUCT REGISTRATION & MARKET ENTRY: Central & Eastern Europe" report prepared by EasyLink Business Services, the Commonwealth's Authorized Trade Representative in Central and Eastern Europe maps the regulatory and market environment that biotech and pharmaceutical companies face when conducting clinical trials as well as registering and marketing new products in Central and Eastern Europe.

In the first stage of the project (carried in March 2013) 15 Central and Eastern European markets were evaluated and country overviews were prepared by in-market consultants of EasyLink Business Services (see Part B and C).

After detailed analysis of the initial findings five largest markets in terms of clinical trials annully started (Russia, Poland, the Czech Republic, Hungary, and Ukraine) were selected for in-depth analysis of their regulatory and market environment (see Part D). The second stage was conducted in May and June 2013.

Resources for both parts of the project included desk research of secondary resources and phone interviews with market experts such as regulatory authorities, trade associations, contract research organizations, and medical facilities etc.

Market entry strategy is outlined in Part E.

PART B: CENTRAL & EASTERN EUROPE – REGION OVERVIEW

1. GENERAL OVERVIEW

Out of 15 Central and Eastern European countries subject to this study the **five most populous states** are Russia, Ukraine, Poland, Romania, and the Czech Republic.

When it comes to **GDP per capita**, Slovenia is the number one in the region, followed by the Czech Republic. Ukraine places last; its GDP per capita equals to just about one quarter of the level in the Czech Republic.

Selected country indicators, Central and Eastern Europe

	Area (sq km)	Population (million)	GDP per capita (PPP, USD, 2010)
Belarus	207,600	9.6	13,400
Bulgaria	110,910	7.2	12,800
Croatia	56,542	4.5	17,500
Czech Republic	78,866	10.2	25,600
Estonia	45,226	1.3	19,000
Hungary	93,030	9.9	19,000
Latvia	64,589	2.2	14,500
Lithuania	65,300	3.6	15,900
Poland	312,679	38.5	18,800
Romania	237,500	22.2	11,500
Russia	17,075,200	140.0	15,900
Serbia	77,474	7.4	11,000
Slovakia	48,845	5.5	22,000
Slovenia	20,273	2.0	28,400
Ukraine	603,700	45.7	6,700

Source: Eurostat, CIA - The World Factbook

11 countries are EU members; 4 are not (Belarus, Russia, Serbia, and Ukraine). Croatia joined the EU on July 1, 2013.

In the EU member countries, clinical trials have to be conducted in accordance with the EU Clinical Trials Directive. The directive is criticized for being excessively bureaucratic. Although it aimed to standardize rules across Europe, it was implemented differently in various member states. It particularly causes problems in case of trials run across several EU countries, as the trials have to go through multiple different review processes, which leads to delays.

On July 17, 2012, the Commission adopted a "Proposal for a Regulation of the European Parliament and of the Council on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC". The main aim of the revised proposal is to simplify the rules for conducting clinical trials in Europe, while maintaining the highest standards of patient safety. Once adopted, the proposed Regulation will replace the 2001 Clinical Trials Directive. The objective is to ensure that clinical trials rules are identical throughout the entire EU.

The draft regulation is still to be agreed by the European Parliament and the Council. **The Regulation is expected to come into force by 2016.**

The following types of registration of pharmaceuticals can be used in the European Union:

- **National registration** - if an applicant wishes to register the product in one country only and the product is not already registered in another Member State
- **MRP (mutual recognition procedure)** - if the product already holds a national registration/authorisation in one of the Community member states, the holder of the authorisation may request one or more of the other Member State(s) to recognise this authorisation by submitting an application in accordance with Article 28 of Directive 2001/83/EC. The state where the product already holds an authorisation then becomes a "reference state" and provide an assessment report together with an approved summary of product characteristics, labeling and package leaflet to the "concerned" Member States and to the marketing authorisation holder within 90 days of receipt of the valid application.
- **Decentralized registration** is similar to the MRP procedure, the difference from the MRP procedure is constituted by the fact that the product is not yet registered in any of the Member states. The procedure can be triggered by a Member State which receives an application for a marketing authorisation and finds out that another marketing authorisation for the same medicinal product is being examined in another Member State or an Applicant who submits an application based on the same product in two or more Member States. The state which already started the examination (in case the procedure is triggered by a Member State) or the state designated by the Applicant (in case the procedure is initiated by the Applicant) becomes a reference state. Marketing authorisations in the selected member states are provided within 135 – 300 days depending on the volume of objections the concerned Member States have and when a consensus is reached.
- **Centralised registration** does not take place at national health authorities in individual Member states. The procedure is carried out centrally at the European Medicines Agency based in the UK and the registration is then valid in all EU countries.

Various pharmaceuticals require different types of registration, not all types of registration apply to all products!

2. CLINICAL TRIAL MARKETS: KEY FACTS

Central and Eastern Europe ranks amongst the top regions globally for clinical trials.

The key advantages for conducting clinical trials in this region include:

- Healthcare systems in the CEE countries are centralized with well-developed referral network, which makes recruitment of patients efficient
- Presence of large, untreated patient populations
- Availability of high quality investigational sites
- Cost savings
- Highly qualified investigators
- Solid reputation of clinical research

The leading challenges are as follows:

- English proficiency of clinical investigators varies – it may be relatively high in some CEE countries and low in others
- Regulatory documents must be translated into local languages for submission to local regulatory authorities
- Relevant study materials have to be translated into local languages

In terms of the number of clinical trials annually started the five largest CEE markets are Russia, Poland, the Czech Republic, Hungary, and Ukraine.

Currently, the lowest number of clinical trials take place in Slovenia (the CEE leader in terms of GDP per capita), Belarus and Serbia (7th and 8th most populous amongst countries subject to this study), Croatia, and Lithuania (the largest of the three Baltic states).

Phase II and III clinical trials are the most common in CEE countries because of the large numbers of patient pools associated with these types of clinical trials.

The primary disease areas for study include **oncology, cardiology, rheumatology hypertension, arthritis, and neurology**.

In EU countries the approval process to obtain a clinical trial permit generally takes 50 to 60 days, while in Russia it is around 118 days.

Overview of 15 CEE markets, 2013

Country	Approximate number of clinical trials per year	Majority of trials by phase	Key therapeutic areas for clinical trials	Approval process to obtain a clinical trial permit (number of days)
Belarus	65 (conducted in 2012)	III	Oncology	Not available
Bulgaria	221 (applications per year)	III (66%) II (21%)	Clinical Pharmacological, Oncology	Max. 60 days for ethic commission and max. 60 days for BDA decision
Croatia	113 active trials in 2012; 55 new trials were approved in 2012	III	Oncology, mental and behavioral disorders, and endocrine, nutritional, and metabolic diseases	Central Ethics Committee is to provide an opinion in 30 days, for some studies in 90 days; the timeline for the Ministry of Health ranges from 30 to 60 to 90 days depending on a product
Czech Republic	350 (applications per year – on average); 400 in 2012	II, III (combine for 80%)	Oncology, neurology, rheumatology, and cardiovascular and respiratory diseases	50 (on average), in general 10 days for validation and 60 for evaluation
Estonia	201 (currently ongoing trials), 92 applications submitted in 2012	III (60%) II (35%) IV (5%)	Neurology (30), rheumatology (28), oncology (26), infectious diseases (26)	30 (for Phase II-IV) 60 (for Phase I) 90 (for gene therapy, cell therapy and genetically modified organisms)
Hungary	300-350 (applications per year), 350 in 2012	II (28%), III (63%)	Oncology, autoimmune diseases, neurology, psychiatry	60 (VHP Voluntary Harmonization Procedure: 42 + max 10)
Latvia	241 (running in 2011 and 2010); 69 applications in 2011	III (76%) II (20%) I (2%) IV (2%)	Oncology, neurology, pulmonology, dermatology, endocrinology	30 (Ethics Committee) 60 (State Agency of Medicines of Latvia)
Lithuania	80-120 (applications per year)	III (75%) II (15%)	Cardiology rheumatology endocrinology oncology	60

Country	Approximate number of clinical trials per year	Majority of trials by phase	Key therapeutic areas for clinical trials	Approval process to obtain a clinical trial permit (number of days)
Poland	450 (average number of trials started annually), 592 in 2011, 490 in 2012	III	Oncology, cardiology	60-65
Romania	250 (carried in 2012)	III (73%) II (15%)	Psoriasis, ulcers, diabetes, oncology, cardiology	60 (certain medicines up to 180)
Russia	550-600 (started each year), 916 in 2012	II and III used to account for over 80% of all clinical trials; after changes in legislation, the share declined to almost 70% due to larger volume of bio-equivalence trials	Oncology, cardiology, infections, endocrinology	57 (according to legislation), in reality 118
Serbia	100	II, III	Oncology, cardiology, radiology, neurology	50-60
Slovakia	155 (applications per year)	II (28%) III (58%)	Neurology, gastroenterology, diabetology, rheumatology, ophthalmology	50 (on average)
Slovenia	25 to 30 (permits issued annually)	5 Phase I 4 Phase II 19 Phase III 4 Phase IV trials	Oncology, endocrinology (diabetes), cardiology, pulmology and neurology	60, for human treatment with xenogenic cells, there are no time limitations for decision
Ukraine	250 (on average), 265 (approved in 2012)	III	Oncology, psychiatrics, pulmonology, rheumatology	60 (experts can return clinical study documents with remarks and ask for their reworking, which can significantly prolong the procedure)

Source: Interviews with market experts, EasyLink, 2013

PART C: COUNTRY OVERVIEWS

The section contains brief overviews of the clinical trial and product registration environments in 15 CEE markets.

Detailed analysis of the five largest clinical trials markets in Central and Eastern Europe (Czech Republic, Hungary, Poland, Russia, and Ukraine) follows in Part D and market entry recommendation in Part E.

3. BELARUS

The clinical trials sector in Belarus is not very well developed. According to Mrs. Svetlana Alimpieva from the Center of expertise and trials functioning under the Ministry of health of Belarus, **65 clinical trials were conducted in 2012**, of which 52 studies were finished during the year. 17 studies were initiated by foreign sponsors, out of which **14 were multinational multicentric clinical trials**. The remaining 35 studies were initiated by local sponsors; there were 28 bio-equivalence trials plus 7 studies of completely new medical products that Mrs. Alimpieva referred to as scientific rather than commercial clinical studies.

All processes, procedures and instructions necessary for conducting clinical trials and medicinal products registration are stipulated in the Declaration of the Ministry of health of the Republic of Belarus #216 from December 18, 2008 "On several topics referred to clinical trials of medicinal products and equipment". The other key legislation are:

- "Health act" from June 18, 1993, specifically part 8 and 9 of article 40, with amendments from June 20, 2008
- Statement on state registration (re-registration) of medicinal products and equipment issued in 2008 (can be found in National law register #213, 5/28269)

Most clinical trials conducted in Belarus were **Phase III** studies.

Almost 40% of all studies focus on oncology. At the beginning of 2013, there were 21 oncology studies, 8 cardiology, 7 neurology (disseminated sclerosis), 7 endocrinology, 5 rheumatology, 3 gynecology, 3 transplantology, 2 surgery, plus there were additional studies in some other areas.

In its statement #50 "On several topics referred to clinical trials of medical drugs" from May 7, 2009 the Ministry of health of Belarus officially introduced the "Good clinical practice" codex with attachments on procedures and processes necessary to start clinical trails.

Only state medical institutions accredited by the state are permitted to conduct clinical trials of medicinal products and equipment for human patients. **75 organizations** hold the accreditation for the period from December 2008 to November 2013.

Studies are mostly conducted by Contract Research Organizations; many are affiliates of global companies.

Selected key contract research organizations, Belarus

Organization	Website	Profile
AmberCRO	www.amber-cro.com	CRO operating in Eastern Europe
ClinStar (on March 4, 2013 PRA announced its acquisition of ClinStar)	www.clinstar.com	Operating in Russia, Ukraine, Belarus and in the Baltic States; clinical trial warehouses and distribution centers in Moscow and Kiev provide a full range of services related to storage and distribution of clinical trial materials; over 250 employees
Eastern Clinical Trials	www.easterntrials.com	CRO conducting phase II-IV clinical trials in Russia, Ukraine, Georgia, Belarus and other countries in Eastern Europe; offices in Moscow, Kiev, Tbilisi, Minsk, Bratislava and Budapest
ICON	www.iconplc.com	Global provider of outsourced development services to the pharmaceutical, biotechnology and medical device industries. ICON specializes in the strategic development, management and analysis of programs that support Clinical Development - from compound selection to Phase I-IV clinical studies
MB Quest	www.mbquest.net	Full-service CRO for foreign sponsors conducting Phase I-IV studies in Russia, Ukraine, Georgia, Belarus, and Kazakhstan; operating since 1997; offices in Moscow, St. Petersburg, Novosibirsk, Kiev, Tbilisi, Minsk, and local staff in Kazakhstan
OCT	www.oct-clinicaltrials.com	Operating in Russia, Ukraine, Bulgaria, Belarus, Latvia, Lithuania, Estonia, Poland, and the Czech Republic
Parexel	www.parexel.com	Conducting Phase I-IV studies incorporating a full range of services from clinical study design to bioanalytics to peri-approval and post-marketing services, with emphasis on First in Man and Proof of Concept studies; experience mainly in Cardiovascular, CNS, Infectious Disease, and Oncology; operating in 64 locations throughout 51 countries around the world
Quintiles	www.quintiles.com	Conducting clinical trials in more than 90 countries all over the world
Worldwide Clinical Trials	www.wwctrilas.com	Focus on the area of cardiovascular and central nervous system medicine, Chronic Inflammatory Disease, Metabolic / Endocrinology and Oncology

4. BULGARIA

Bulgarian Drug Agency (BDA) (www.bda.bg) received **230 applications for clinical trials in 2011**, up by 14% compared to 2010. Approximately, 9,500 people participate in clinical trials in Bulgaria annually.

Number of applications for clinical trials received by BDA, 2008-2011

	2008	2009	2010	2011
Number of applications	211	173	201	230
Number of permissions	203	98	143	221
Number of applications withdrawn by the applicant	36	36	5	7
Number of refusals by BDA	22	22	1	4

Multicentric studies accounted for 86% and 79% in 2010 and 2011 respectively.

Phase III studies are the most common; they made up for 66% of studies in 2011. Phase II studies followed with a 21% share in 2011; the share for this category of trials declined from 36% in 2009 to 21% in 2011.

Structure of studies by phase, Bulgaria, 2009-2011

	2009	2010	2011
Phase 1	4	8	12
Phase 1/2	0	0	1
Phase 2	52	54	41
Phase 2/3	0	0	3
Phase 3	80	100	129
Phase 4	10	7	10

The most frequent clinical trials are **clinical pharmacological, oncology/hematology, pneumology, rheumatology, neurology, and hematology**.

Structure of trials by disease, Bulgaria, 2009-2011

	2009	2010	2011
Nonintraventional	13	3	12
Allergology	1	3	
Gastro	10	8	16
Gynecological	1	1	
Dermatology	3	6	5
Endocrine	15	13	14
Infectious disease	1	0	0
Cardiology	16	7	11
Clinical Pharmacological	7	23	28
Neurology	18	24	21
Oncology / Hematology	29	39 / 4	22 / 9
Orthopedic	3	2	2
ENT	2	1	1
Ophthalmological	1	0	5

	2009	2010	2011
Pediatrics	2	4	5
Psychiatry	11	10	12
Pneumology	12	14	27
Rheumatology	13	17	22
Urology	6	3	5
Hematology	4	10	18
Surgery	3	2	4

Clinical trials can begin after the following conditions are fulfilled:

1. The respective ethics committee has given a positive opinion, and
2. The Bulgarian Drug Agency Executive Director has issued a written authorization when one of the tested medicinal products is:
    a) A medicinal product for a gene therapy;
    b) A medicinal product for somatic cell therapy;
    c) A medicinal product containing genetically modified organisms;
    d) A high-technology medicinal product, as specified in the Appendix to Regulation (EC) No. 726/2004 of the European Parliament and of the Council;
    e) A medicinal product containing a biologically active substance(s) of human or animal origin or containing biological components of human or animal origin or such components are used in its manufacturing, or
3. BDA failed to notify the sponsor in writing within the period set by the law that trials may not take place in respect to medicinal products outside those under item 2.

Major pharmaceutical companies such as Roche, Novartis Pharma, and GSK have their own clinical research departments. However, some companies e.g. Pfizer have recently closed their clinical research department in Bulgaria and will probably outsource this activity.

Key contract research organizations, Bulgaria

Organization	Website	Profile
CONVEX	http://convex.bg/	Key CRO in Bulgaria providing a broad range of clinical research services
INC Research	www.incresearch.com	Key CRO in Bulgaria providing a broad range of clinical research services
MLD Trading	www.mldtrading-bg.com	Key CRO in Bulgaria providing a broad range of clinical research services
Premier Research Group	http://premier-research.com/contact/	Key CRO in Bulgaria providing a broad range of clinical research services
Quintiles Bulgaria	http://www.quintiles.com/locations/europe/bulgaria/	Key CRO in Bulgaria providing a broad range of clinical research services

Clinical trials are mainly conducted in large cities in university, multiprofile or specialized hospitals and medical centers! In addition, many smaller hospitals, medical centers and diagnostic consultation centers have also formed ethical committees. At present, there are **about 220 trial sites throughout the country** with a permission to conduct clinical trials.

Key trial sites, Bulgaria, 2012

Trial site	Website
MHAT Plovdiv	http://www.mbal.net/main.php?module=content&cnt_id=1
MHAT Tokuda, Sofia	http://www.tokudabolnica.bg/en
Military Hospital, Sofia	http://www.vma.bg/

Trial site	Website
UMHAT "Alexandrovska", Sofia	http://alexandrovska.com/bg/
UMHAT "Sv. Georgi", Plovdiv	http://www.sv-georgi.com/дк-свети-георги-еоод-пловдив
UMHAT "Sv. Marina", Varna	http://www.svetamarina.com/
UMHAT "Tsaritsa Yoanna-ISUL", Sofia	http://www.isul.eu/english/index.htm
USHAT "Sv. Ekaterina", Sofia	http://www.uhsek.com/
USHAT "Sv. Naum", Sofia	http://www.svnaum.com/en_begin.html

A medical product may only be placed in the market after obtaining a market authorization or certificate of registration issued under the Act of Medicinal Products in Human Medicine. The institution involved in issuing the "Market Authorization" is the Bulgarian Drug Agency (BDA) (www.bda.bg).

In 2011, the breakdown of market authorization acts for medicinal products was as follows:

- Mutual recognition procedure (MRP) – 114
- Decentralized procedure (DP) - 582
- National procedure (NP) - 169

The legislation applicable for medicinal products in the human medicine can be accessed at http://en.bda.bg/images/stories/documents/legal_acts/ZLPHM_en.pdf.

Pharmacies in Bulgaria tend to have their own market entry departments who take care of regulatory and authorization issues. The following consulting companies provide a broad range of services in the pharmaceutical sector including product registration.

Selected consulting companies involved in product registration, Bulgaria

Organization	Website
Biomeda	www.biomeda.net
Chiptrade	http://chimtrade.info/
Medconsult	http://medconsultbg.com
Pharmdedict	http://pharmdedict.com/

5. CROATIA

The regulatory authority for clinical studies in Croatia is the **Agency for Medicinal Products and Medical Devices, HALMED** (www.halmed.hr), which is supervised by the Ministry of Health. The Agency's remit in the field of medicinal products, medical devices and homeopathic products is regulated under the Medicinal Products Act (Official Gazette No. 71/07, 45/09 and 124/11).

Both commercial and non-commercial sponsors of clinical trials are bound by the regulations contained within the EU directives 2001/EC/20 and 2005/EC/28.

Institutions involved in clinical studies are the Ministry of Health, Medicine and Pharmacy Universities, Hospitals, and Clinical Centers. Approximately 50% of the centers are located in Zagreb University Hospital. Other major regional and city hospitals are located in Split, Rijeka, and Osijek.

In 2012, there were **113 active trials** in Croatia; **most of which were Phase III trials**. Only 55 trials were approved last year, which translates into a 25% decline compared to 2011.

The number of patients reached 242 in 2011.

Most clinical trials are commercial studies carried for foreign (multinational) pharmaceutical companies.

Phase I, II, and IV trials, and academic trials and trials on pediatric population are rarely conducted in Croatia.

The highest number of clinical trials have traditionally been in the field of oncology, mental and behavioral disorders, and endocrine, nutritional, and metabolic diseases.

The authorization process starts when a sponsor submits a clinical trial application with all required documentation to the Ministry of Health and the Central Ethics Committee. The approval from the Minister of Health is issued only after a positive approval from the Central Ethics Committee.

In case of assessment of single- and multi-site studies the Central Ethics Committee is obliged to provide an opinion within 30 days. For certain studies (gene therapy, treatment with somatic cells drugs etc.) the opinion has to be given within 90 days. The timeline for the Ministry of Health to render a decision/approval ranges from 30 to 60 to 90 days depending on a medicinal product.

The key advantage for conducting clinical trials in Croatia is that the country provides a natural conduit between EU and non-EU countries, with the added advantage that the Croatian language is easily understood by the non-EU countries that surround Croatia. Therefore, it is not surprising that during the last decade many CROs chose Croatia as their starting point for opening offices in the southern reaches of the CEE region.

Key contract research organizations, Croatia

Organization	Website	Profile
ALTIORA	www.altiora-cro.com	Well-established contract research organization
CLINRES	www.clinres-farmacija.hr	Focus on clinical trials for the pharmaceutical and biotechnology industries
OPTIPHARM	http://optimapharm.hr/en/contact	Providing services in the area of clinical research

Registry of all approved clinical trials is to be established. According to the new Act on Amendments to the Act on drugs the Ministry of Health is mandated to publish all approved trials on its webpage as well as to keep the registry of clinical trials. No details of the scope of the registry have been defined and the registry in not yet functional. The Ministry gave an approval to the School of Medicine at the University of Split to run the national registry of clinical trials (April 1, 2011), based on the registry created as a part of a research project in collaboration with ClinicalTrials.gov (www.regpok.hr).

July 1, 2013 (the date of Croatia joining the EU) is the first date that a Mutual Recognition or Decentralised procedure application can be submitted in Croatia.

Key clinical centers, Croatia

Organization	Website
KBC Zagreb	www.kbc-zagreb.hr
KBC Rijeka	www.kbc-rijeka.hr

The key legislation or regulations pertaining to the conduct of clinical trials in Croatia include:

- Act 71/07 of 9 July 2007 – Act on drugs (Official Gazette No. 71/07)
- Act on Amendments to the Act on drugs (Official Gazette No. 45/09)
- Act on Amendments to the Act on drugs (Official Gazette No. 124/11)
- Act 67/08 of 9 June 2008 – Act on medical devices (Official Gazette No.67/08)
- Act on Amendments to the Act on medical devices (Official Gazette No. 124/11)
- Bylaw 14/2010 of 29 January 2010 about clinical trials on drugs and good clinical practice (Official Gazette No. 14/2010)
- Bylaw 127/10 of 16 November 2010 about amendment of Bylaw about clinical trials on drugs and good clinical practice (Official Gazette No. 127/2010)
- Bylaw (or rule) 121/07 of 26 November 2007 about clinical trials and good clinical practice (Official Gazette No. 121/07) in part applied on medical devices
- Bylaw 125/09 about pharmacovigilance (Official Gazette No.125/09)
- Bylaw about adverse events on medical devices 74/09 of 29 July 2009

6. CZECH REPUBLIC

This country ranks amongst five largest clinical trials markets in Central and Eastern Europe. In-depth analysis of its clinical trials and product registration environment is provided in Part D.

The **Czech Republic** is the third **largest market in Central and Eastern Europe** in terms of clinical trials annually started; it is only surpassed by Russia and Poland.

In the Czech Republic, applications for authorization of clinical studies and clinical trial notifications are assessed by the State Institute for Drug Control (SUKL, www.sukl.cz) and at least one ethics committee (independently of each other). On average, SUKL annually reviews some **350 applications** for clinical studies. A total of 329 and 404 proposals were assessed in 2011 and 2012 respectively. Over the past several years, SUKL has not rejected any application.

Approximately 80% of all clinical trials are commercial studies carried for foreign (multinational) pharmaceutical companies; the remaining 20% of studies are sponsored by academic or professional societies, academic institutions or healthcare facilities from both the Czech Republic and other European countries.

Multinational CROs now conduct about 60 to 70% of clinical studies in the country.

Selected leading contract research organizations, Czech Republic

Organization	Website	Profile
ICON Clinical Research, s.r.o.	www.iconplc.com	Global CRO; also present in the Czech Republic
PPD Czech Republic s.r.o.	www.ppdi.com	Global CRO; also active in the Czech Republic
Prague Clinical Services, s. r. o.	www.pragclin.com	Headquartered in Prague; employing a team of twenty people, also present in the Slovak Republic and Bulgaria
Quintiles Czech Republic s.r.o.	www.quintiles.com	Global CRO; also active in the Czech Republic

Source: Interview with Ms. Stastna, ACRO-CZ

The key therapeutic areas are **oncology, neurology, rheumatology, and cardiovascular and respiratory** diseases.

Between **20,000 and 30,000 patients** annually participate in clinical studies conducted by around **2,000 trial sites** across the country - in most hospitals, especially large teaching, so-called faculty hospitals, and regional hospitals, and in hundreds of outpatient facilities.

Selected key trial sites, Czech Republic

Organization	Website	Profile
Faculty Hospital Brno	www.fnbrno.cz	The largest Medical Center in Moravia
Faculty Hospital Motol	www.fnmotol.cz	The largest medical center in the Czech Republic
Faculty Hospital Plzen	www.fnplzen.cz	University hospital in Western Bohemia
Faculty Hospital Kralovske Vinohrady	www.fnkv.cz	One of the largest hospitals in Prague; a teaching hospital
General University Hospital in Prague	www.vfn.cz	One of the largest healthcare facilities in the Czech Republic; providing healthcare for children and adults in all basic medical fields
Masaryk Memorial Cancer Institute	www.mou.cz	Providing complete diagnostics, treatment, and preventive care in oncology

The Czech Republic is already a favorite location for **Phase II and III studies** (they combine for **80%** of studies). Currently, only slightly above 10 **Phase I** studies are annually applied for in the Czech Republic despite the fact that the Czech Republic is well prepared and equipped to carry them.

The Czech Republic also provides an excellent opportunity for carrying **bridging studies** for U.S. companies producing pharmaceuticals in Russia, and their subsequent registration for the EU market.

Any proprietary medicinal product is subject to marketing authorization (i.e. product registration) prior to its placement in the Czech market. In 2011, 779 applications were submitted; **79%** of applications was for the **mutual recognition procedure (MRP) and decentralized procedure** (DCP) where the Czech Republic is considered a concerned member state. The number of applications for marketing authorization via **national procedure** has been gradually decreasing. **Centralized procedure** is mandatory for biotechnology products, preparations for oncology, diabetes, AIDS and CNS treatment, and orphan medicines. This procedure is carried out centrally at the European Medicines Agency based in the UK and the registration is then valid in all EU countries.

7. ESTONIA

A total of **92 clinical trial applications were submitted in 2012**; 201 trials were ongoing in Estonia as of February 1, 2013. The most popular research areas are **neurology, rheumatology, oncology and infectious diseases**.

Approximately **60% and 35% of trials are Phase III and II** respectively; a few pharmacokinetic and bioequivalence studies are carried out each year.

According to Ülle Toomiste, manager of Clinical Assessment office in State Agency of Medicine in Estonia, the number of participants in ongoing trials is estimated at around **10,000 patients**.

Clinical trials in Estonia are controlled by Medicines Regulatory Authority (State Agency of Medicines of Estonia, www.sam.ee), which is a part of the Ministry of Health.

In order to obtain a clinical trial authorization, notification of a clinical trial in EudraCT format has to be submitted to the State Medicines Agency. It should be done at least 60 days before the planned beginning of the trial. Then, a formal letter of "no objection" is given by the Agency. The time depends on the quality and completeness of the documentation submitted. Together with the previously mentioned notification, a signed declaration by the head of the health care institution study center has to be submitted. According to the European Forum for Good Clinical Practice, in some cases, the import certificate for the study medications can be applied for.

The leading clinical trial sites include Tartu University Hospital (www.kliinikum.ee), West-Tallinn Central Hospital (www.ltkh.ee), East-Tallinn Central Hospital (www.itk.ee), North Estonia Medical Center Foundation (www.regionaalhaigla.ee), and Estonian Genome Center University of Tartu (www.geenivaramu.ee).

The following contract research organizations operate in Estonia. According to Ülle Toomiste, out of all CROs Quintiles submitted the highest number of applications in 2011. Some CROs are cooperating, while others only use their own resources.

Selected leading contract research organizations, Estonia

Organization	Website	Profile
Amber CRO	www.amber-cro.com	Operating in many CEE countries
Dokumeds	www.dokumeds.com	European Clinical Research Organization providing a comprehensive range of services for clinical research and development of pharmaceutical and biotech products
Egeen	www.egeeninc.com	Operating in a number of CEE countries; wholly owned subsidiaries in Estonia and Ukraine and offices in Romania, Poland, and Turkey
ICON	www.iconplc.com	Global provider of outsourced development services to the pharmaceutical, biotechnology and medical device industries

Organization	Website	Profile
Parexel International	www.parexel.com	Also operating in Estonia
Quintiles	www.quintiles.com	The world's largest provider of biopharmaceutical development and commercial outsourcing services; active in approximately 100 countries
Russlan	www.russlanclinical.com	European clinical trial management organization offering a range of clinical research services to clients in the pharmaceutical, biotechnology and medical device industries worldwide

Product registration in Estonia is carried by State Agency of Medicines. Legal provisions require marketing authorization (registration) for all pharmaceutical products in the market. According to Ülle Toomiste, manager of Clinical Assessment office in State Agency of Medicine in Estonia and Dzintars Sarkanbiksis from Amber-Cro decentralized registration is the most popular type of product registration. They both stated that in the EU there are no countries that would be more suitable for the first registration of pharmaceuticals, as the situation in all EU countries is similar due to the EU legislation.

8. HUNGARY

This country ranks amongst five largest clinical trials markets in Central and Eastern Europe. In-depth analysis of its clinical trials and product registration environment is provided in Part D.

Hungary is the **fourth largest market** in the CEE region for conducting clinical trials.

The Directorate of the National Institute for Quality- and Organizational Development in Healthcare and Medicines (GYEMSZI-OGYI) reviews around **300 to 350 applications** for clinical studies annually. Due to the fact that a large portion of the studies are long-term, the number of ongoing studies is much higher (1,886). The same authority also handles product registration.

Between **10,000-17,000 patients** participate in clinical studies in Hungary every year.

Approximately 95% of all clinical trials are commercial trials for pharmaceutical companies; only 5% are sponsored by either academic or professional societies, academic institutions or healthcare facilities mainly from Hungary.

The majority of trials conducted in Hungary have traditionally been **Phase III**, yet the shares of Phase I and Phase II studies have been slowly growing. The primary therapeutic areas include oncology, cardiology (both AMI and hypertension), pulmonology, rheumatology, and neurology.

Overview of ongoing clinical trials, Hungary, February 2013

	Number of trials	Majority of trials by disease
Phase 1	34	Oncology
Phase 2	522	Oncology, pulmonology, dermatology, psychiatry, neurology
Phase 3	1,190	Oncology, pulmonology, dermatology, psychiatry, neurology
Phase 4	140	

There are around **60-70 CROs** in Hungary. About 70% of trials are carried by global CROs.

Selected key local contract research organizations, Hungary

Organization	Website	Profile
BiTrial CRO	www.bitrial.hu	Providing a broad range of services in the CEE region
CPS Cortex Contract Research Organization	www.cortexps.hu	Conducting Phase I-IV clinical trials and non-interventional studies in Hungary and Romania
Hungarotrial Ltd.	www.hungarotrial.hu	Leading independent CRO in CEE; 65 employees; Oncology, Rheumatology, Cardiovascular diseases, PAO, CNS are the key areas; providing a broad range of services; Phase I-IV
M.E. Trial Masters Ltd.	www.trialmasters.eu	Management of Phase II-IV clinical trials in Hungary and Romania

Altogether there are 125 trial sites (the sites tend to be involved in more phases); 14 Phase I sites are accredited by the National Institute of Pharmacy in Hungary, plus there are 86 Phase II, 111 Phase III, and 78 Phase IV trial sites.

Key trial sites, Hungary

Organization	Website
Clinical Centre of the University of Pécs	www.kk.pte.hu
ClinTrial Audit Ltd.	www.clintrial-audit.hu
Drug Research Centre Ltd.	www.drc.hu
Semmelweis University	http://semmelweis-egyetem.hu
University of Debrecen	www.unideb.hu
University of Szeged, Albert Szent-Györgyi Clinical Center, Clinical Research Coordination Center	www.klinikaikutatas.hu

The leading two types of marketing authorization are **decentralized procedure** and **MRP** where Hungary is a concerned member state. In Hungary, the **national registration procedure** also plays an important role; it is used by local producers of branded generics.

The key legislation applicable for human medicines is:

- Act XCV of 2005 on Medicinal Products for Human Use and on the Amendment of Other Regulations Related to Medicinal Products
- Decree 35/2005 (VIII. 26.) of the Minister of Health on the clinical trial and application of correct clinical practices of investigational medicinal products intended for use in humans

Key companies assisting with product registration, Hungary

Company	Website	Profile
Euromedline Kft.	www.euromedline.hu	Founded in 2005; it has handled more than 200 registration procedures
Pharmaroad Ltd.	www.pharmaroad.hu	Providing a full spectrum of registration services
QualipharmaCon Kft.	www.qualipharmacon.hu	Extremely experienced staff (former high level OGYI employees), founded in 2011; very good legal background

9. LATVIA

Clinical trial applications in Latvia are submitted to the State Agency of Medicines of Latvia (SAM, www.zva.gov.lv). The institution received **69 new applications in 2011**, out of which two were not approved. In 2011, 241 clinical trials were in progress. The number of ongoing trials has remained stable over the last 6 years. We estimate the total number of **patients annually participating** in clinical trials in Latvia at around **4,800**; our estimate is based on the figure for the average number of clinical trial participants (20 on average per trial) provided by Olga Tretjuka of SAM.

An application has to be submitted to both the Ethics Committee and to SAM (positive decision is needed from both institutions). The Ethics Committee provides an answer in 30 days, while SAM revises applications for up to 60 days. According to Documeds, the application fee to SAM is EUR 1,450, while the fee an applicant pays to the Ethics Committee varies from EUR 300-1,000.

The most common types of therapeutic areas are **Oncology** (11 out of 67 approved trials in 2011), **Neurology** (8), **Pulmonology** (7), **Dermatology** (7), **Endocrinology** (6), **Psychiatry** (6), **Rheumatology** (5), and **Surgery** (5).

The most common are Phase III trials.

According to Clinical Trial Register, **decentralized procedure** has been the most common method for drug registration in Latvia over the last 5 years. Olga Tretjuka of SAM claims that there are no favorite countries for pharmaceutical registration in the European Union. Pharmaceutical companies and biotech firms select country of research based on patient availability. CROs cooperate only if there is a larger project and then different CROs can be responsible for different countries. For example, in Latvia there are only multinational studies, no mono national trials.

The very key clinical trial site is **Pauls Stradins Clinical University Hospital** (www.stradini.lv) with 29 clinical trials conducted in 2011. Other hospitals worth mentioning are Rigas Austrumu Clinical University Hospital (www.aslimnica.lv), Children Clinical University Hospital (www.bkus.lv), Daugavpils Regional Hospital (www.slimnica.daugapils.lv), Health Center 4 (www.vc4.lv), and Latvian Maritime Medicine Centre (www.ljmc.lv).

''The Pharmaceutical Act'' (from April 1997, amended in November 2012) is the most important source of rules regarding clinical trials in Latvia. The regulations for the conduct of clinical trials constitute another important set of rules. The most important regulation (No. 289) is ''Regulations on Conducting Clinical Trials and Non-interventional studies and Labeling of Investigational Medicinal Products, and Procedure for Conducting Inspections on Compliance with the Requirements of Good Clinical Practice''. The last edition was approved on March 23, 2010 by the Cabinet of Ministers.

In 2011, 38 foreign pharmaceutical companies sponsored clinical research projects in Latvia. Quintiles was the leading CRO in terms of the number of projects involved in 2011, taking part in 11 projects, while there were 9 CROs involved in either one or two projects.

Key contract research organizations, Latvia

Organization	Website	Profile
Amber CRO	www.amber-cro.com	Operating in many CEE countries, considered a local CRO
Crown CRO	www.crowncro.com	Founded in 2005; catering to customers in the pharmaceutical, biotechnology, functional food and device sectors as well as to other contract research organizations
Dokumeds	www.dokumeds.com	DOKUMEDS is a European Clinical Research Organization providing comprehensive range of services for clinical research and development of the pharmaceutical and biotechnology products; considered a local CRO
Ergomed	www.ergomed-cro.com	ERGOMED is a clinical development company providing consultancy and full clinical trial related services; headquarters in Frankfurt and ten regional offices in Guildford, Cambridge, Moscow, Zagreb, Novi Sad, Krakow, Madrid, San Antonio (USA), Geneva and Dubai
ICON	www.iconplc.com	Global provider of outsourced development services to the pharmaceutical, biotechnology and medical device industries
Parexel International	www.parexel.com	Over the past 30 years, PAREXEL has developed significant expertise to assist clients in the worldwide pharmaceutical, biotechnology and medical device industries with the development and launch of their products
Quintiles	www.quintiles.com	The world's largest provider of biopharmaceutical development and commercial outsourcing services with a network of over 27,000 employees conducting business in approximately 100 countries

10. LITHUANIA

The regulatory authority for control of clinical trials is the State Medicines Control Agency at the Ministry of Health of the Republic of Lithuania (SMCA, Valstybine vaistu kontroles tarnyba, www.vvkt.lt). The function of single opinion adoption is given to the Lithuanian Bioethics Committee (LBC, Lietuvos bioetikos komitetas, http://bioetika.sam.lt).

Clinical trial documents can be submitted simultaneously to both institutions, this makes the approval process faster. By law, the maximum term for examination of an application is 60 days, but in practice it could take less, around 6-7 weeks. The other advantage that makes the setup of a clinical trial faster is that permission to conduct a clinical trial received from SMCA allows the import of Investigational Medicinal Products (IMP) and trial-related material from other EU countries, and no separate approval is needed.

The major legislation relating to the conduct of clinical trials are the Act on Pharmacy of Lithuania No. X-709 (June 22, 2006) and the Act on Ethics of Biomedical Research No. VIII-1679 (May 11, 2000).

According to SMCA data, the number of ongoing clinical trials reached 715 in February 2013. On average, **SMCA receives 80 to 120 applications annually**. In 2011, 96 applications were submitted from 42 sponsors.

Out of these 96 applications 89 were granted a permission to proceed with clinical trials (93%), and out of the remaining 7 that did not receive the permission, 4 were not approved and 3 applications were withdrawn by the applicants.

The vast majority of submitted applications (94, in 2011) falls under the category of commercial trials, and only 2 into the category of academic research (2%).

In 2011, 75% of applications submitted were for Phase III (72 applications), and **15% for Phase II** (14 applications). The core areas were **cardiology, rheumatology, endocrinology, and oncology**.

Sponsors of commercial trails are mainly global pharmaceutical companies such as GlaxoSmithKline R&D, F.Hoffmann-La Roche Ltd., Novartis Pharma Services AG, Merck&Co., Inc, Sanofi Aventis Group, Teva Pharmaceutical Industries, Janssen-Cilag International N.V., Bayer HealthCare AG, AstraZeneca AB, Eli Lilly and Company and others.

Clinical trials are conducted in most hospitals, especially major state hospitals, outpatient facilities as well as private medical clinics and medical centers. There were 278 trial centers in Lithuania in 2011.

Lithuania provides a very friendly environment for conducting clinical trials given its quite developed pharmaceutical, medical and health care sectors. Companies such as TEVA, Thermo Fisher Scientific, Valeant, or Valentis have either R&D or production facilities, or both in the country. Lithuania can offer a relatively large pool of highly-qualified specialists, researchers and scientists in pharmacy, biochemistry, microbiology and other biotech fields. Investigators are experienced and motivated, have good understanding of local and EU regulations, and can ensure pool of patients and provide services at reasonable costs.

Selected key contract research organizations, Lithuania

Organization	Website	Profile
Dokumeds Lithuania	www.dokumeds.com	Covering the Baltic States, Ukraine, Russia, Poland, and Romania
JSC Biomapas	www.biomapas.lt	Conducting trials primarily in chronic neurological diseases and psychiatry
JSC Medfiles	www.medfiles.fi/lt	Provides services in the Baltic States and Scandinavian countries

11. POLAND

This country ranks amongst five largest clinical trials markets in Central and Eastern Europe. In-depth analysis of its clinical trials and product registration environment is provided in Part D.

Poland is the **second largest market** for clinical trials in Central and Eastern Europe (after Russia).

The Office for Registration of Medicinal Products, Medical Devices and Biocidal Products (URPL – www.urpl.gov.pl) is in charge of registration and supervision of clinical studies as well as drug registration and monitoring of the pharmaceutical market.

Every year approximately **450 new clinical trials** are registered in Poland, which represents approximately 3% of all new studies registered in the world. Annually **30,000-40,000 patients** participate in clinical trials in Poland.

90-95% of trials are carried by private companies in Poland, as public research institutes/universities very often cannot afford to run clinical trials independently due to tight budgets and rising costs of clinical trials.

About **50%** of trials carried out in Poland are **Phase III**; **Phase II** studies now account for **38%**, and their number has been rising recently.

The leading therapeutic areas include **oncology, cardiology, rheumatology, and immunology**. More than one third of patients participating in clinical trials in Poland are cases of cancer.

The key drivers of the clinical trials market in Poland are the size of the population, effective patient recruitment, and high quality of trials as well as medical staff.

Poland continues to run a relatively small number of clinical trials in comparison to the size of the Polish population. Further development of this market depends mainly on the governmental decisions and regulations. If the legal and formal environment becomes more favorable, **the number of clinical trials could still increase by 20% to 30%.**

According to the PwC data, CROs support 70% of clinical research in Poland in terms of volume and 53% in terms of value.

Key contract research organizations, Poland

Organization	Website	Profile
Accovion Sp. z o.o.	www.accovion.pl	Polish division of a global CRO offering support for clinical research in Poland
Associated Medical Clinical Science Services Sp. z o.o.	www.associated-medical.com.pl	Polish CRO located in Silesia region with a wide portfolio of areas of clinical trials

Organization	Website	Profile
Brillance Sp. z o.o.	www.brillance.pl	Polish CRO operating also in the Czech Republic and Slovakia, providing a full range of clinical trials
Clinmark	www.clinmark.pl	Large Polish CRO operating in the CEE countries; also providing training and consulting services for pharmaceutical companies
Cromsource	www.cromsource.com	Polish division of a global CRO
GP Pharm Medical Sp. z o. o.	www.gppharm.com	Over 10 years of experience; offering a wide scope of clinical trials, with experience in cardiology, dermatology, diabetology, orthopedics, and other areas
INC Research Poland Sp. z o.o.	www.incresearch.com	Global CRO operating 2 offices in Poland (Warsaw and Krakow)
KCR S.A. (Kiecana Clinical Research)	www.kcrcro.com	Leading European CRO (originated in Poland) with offices in USA offering clinical trials for pharmaceutical, biotechnology and medical device companies and in the field of food supplements
Lambda Therapeutic Research Sp. z o.o.	www.lambda-cro.pl www.clinicalresearch.pl	Polish division of an Indian company offering services as CRO for all phases of clinical trials
Medical Network S.A.	www.med-net.pl	One of the biggest and most active CROs in the Polish market providing a wide range of services related to clinical trials
monipol sp. z o.o.	www.monipol.com	Established in 1995; Polish-German CRO operating also in Ukraine; providing services in all phases of clinical research
PRA Poland	www.prainternational.com	Polish division of a large global full-service CRO
PSI Pharma Support Poland Sp. z o.o.	www.psi-cro.com	Polish division of a large global full-service CRO
Quintiles Poland Sp. z o.o	www.quintiles.com/locations/europe/poland	Polish division of a global CRO offering a full range of clinical trial services for all phases

Most clinical trials in Poland concern trials carried out in an outpatient setting (ambulatory). Because of the (large) size of Polish population the country often attracts trials requiring a large number of patients.

Key trials sites/hospitals, Poland

Institution	Website	Profile
Academic Clinical Center in Gdansk	http://usk.onestepcloud.pl/pl_PL	Located in northern Poland, clinical hospital belonging to the Medical University of Gdansk; conducting clinical trials in many fields including urology and oncology
Academic Clinical Hospital in Wroclaw	www.aszk.wroc.pl	Independent clinical research hospital located in south-western part of Poland

Institution	Website	Profile
Central Clinical Hospital of Medical University in Katowice	www.csk.katowice.pl	Clinical hospital conducting clinical trials under auspices of the Medical University in Katowice
Central Clinical Hospital of Medical University in Lodz	www.csk.lodz.pl	Leading clinical and research hospital located in central Poland
Clinical Hospital in Bialystok	http://usk.onestepcloud.pl/pl_PL	Belonging to the Medical University of Bialystok (Eastern Poland); the hospital participates in a wide range of clinical trials
Clinical hospital Przemienienia Pańskiego in Poznan	http://sk1.am.poznan.pl/	Belonging to the Medical University in Poznan, one of the most active clinical trial units; specializing in oncology and cardiology
Gornoslaskie Medical Center in Katowice	www.gcm.pl	The largest Silesian medical center conducting many types of clinical trials
Independent Public Clinical Hospital in Lublin	www.spsk1.lublin.pl	Part of the Medical University of Lublin; carrying clinical trials in a wide range of areas
Independent Public Clinical Hospital in Warsaw	www.spcsk.amwaw.edu.pl	Managed by the Medical University of Warsaw; conducting many clinical trials and research projects especially in the field of civilization (lifestyle) diseases such as heart diseases
Polish Academy of Sciences, Division V: Medical	www.pan.pl	Division of the national institute providing medical research and coordinating work of subordinated units - local clinical hospitals

Chronic and unpredictable registration procedures and excessive bureaucracy are the leading barriers to the development of the Polish clinical trials market. **The average time of trial registration is about 60-65 days**.

12. ROMANIA

Approximately 250 clinical studies were carried out in Romania throughout 2012. The 2012 market value was estimated at approximately EUR 100 million. The key centers for clinical trials are the cities of Bucharest, Iasi, Cluj, Brasov, Targu-Mures.

Approximately 89% of all clinical trials are commercial trials. Their sponsors are mainly pharmaceutical companies, only 11% are sponsored by academic or professional societies, academic institutions or healthcare facilities from both Romania and other European countries.

The vast majority (95%) of all clinical trials conducted in Romania are multicentric and address adults & elderly. Approximately 7% fall under national academic research and are conducted in one or more centers.

Typically, **Phase II and III clinical trials are the most common in Romania** due to the large patient pool. The primary disease areas for study include **psoriasis, lung cancer, oncology in general, cardiology, ulcer, diabetes, arthritis, and vaccines**.

Clinical studies in Romania are conducted mostly in hospitals, particularly large ones (the so called "Judetean", which refers to a county in Romania, as well as teaching and regional hospitals). Some smaller private facilities also carry out such studies.

"Agentia Nationala a Medicamentului si a Dispozitivelor Medicale" (http://www.anm.ro), a part of the Ministry of Health, is the regulatory institution for clinical trials as well as handles product registration.

Clinical studies carried out in Romania are mostly European-wide or at least regional (Romania/Bulgaria or Romania/Greece, etc). They are conducted by local companies hired by larger CROs abroad.

Selected key players, Romania

Organization	Website	Profile
GSK Romania (Brasov)	http://gsk.ro/home.aspx	GSK has recently opened its own research center in Brasov
HofMed	http://hofmed.ro/	The company has been involved in 86 clinical tests in the recruitment of volunteers
Institutul Cantacuzino	www.cantacuzino.ro/ro	Romanian institute for research-development-innovation, focused mainly on bacterial and viral infections
SGS Romania	www.sgsgroup.ro	Specializing in consultancy, dealing with clinical studies among other activities; a certification body for certain standards
SMP Clinical Development SRL	www.smp.ro	Offering clinical research support

The most common product registration procedures are MRP and decentralized registration. Registration via national procedure is rather scarce; it has been used for a few products from China and Arab countries.

The key legislation is:

- EU Directives: 2011/62/UE; 2010/84/UE; UE Regulation 2010 1235/2010.
- National Laws: 236/2009; 266/2008; 264/2007; 95/2006-Drugs; 263/2005; 522/2004; 143/2000; OUG 91/2012; OUG 35/2012.

13. RUSSIA

This country ranks amongst five largest clinical trials markets in Central and Eastern Europe. In-depth analysis of its clinical trials and product registration environment is provided in Part D.

Russia is **the largest clinical trials market** in Central and Eastern Europe.

Assessment of clinical studies is handled by the Ministry of health (www.rosminzdrav.ru), specifically the Department of state control of preclinical ad clinical studies (chief specialist Yu.V.Afonchikov). Federal service for control in medical and social development sphere is in charge of the control over the clinical trial process and procedures, issuing permissions for clinical studies as well as accreditation of medical organizations able to conduct the studies and maintaining the list of those organizations.

A total of **915 new clinical trials** including local and bioequivalence studies were approved during 2012, up by 61% compared to the previous year.

Slightly over **67,000 patients** enrolled in Phase I-IV trials launched during 2012; approximately 75% of patients participated in Phase III trials.

Multinational multi-center clinical trials accounted for 65% of clinical trials in 2011, but mere 40% in 2012. On the other hand, the numbers of bioequivalence and local studies have grown dramatically; they made up for 35% and 25% of studies respectively in 2012.

The large number of generic drugs testing can be explained by the changes in legislation – in 2010 a new act (FZ-61 "On Circulation of Medicinal products") started to regulate the market of clinical studies. **Only drugs tested in the Russian Federation can be later registered in the country**. The same legislation also diminishes the possibility of healthy benevolent patients to take part in Phase I clinical trials for foreign drugs. Because of augmented number of bio-equivalence testing studies, their price went up significantly – from 500-600 thousand rubles to 1.5-2.2 million rubles (around USD 2-3 thousand per 1 patient). Now, the cost of a generics study is almost similar to a complex clinical trial of a completely new drug.

In 2012, clinical trials in Russia were sponsored by companies from 38 countries. The highest number of trials (430) was initiated by Russian sponsors, followed by U.S. sponsors with 143 new studies.

Phase III studies traditionally constitute **the largest proportion** of studies; their number increased 21% to 369 studies in 2012. Phase II trials are the number two category.

In 2012, more than two thirds of new studies were initiated in eight leading therapeutic areas. **Oncology, cardiology, endocrinology, pulmonology, rheumatology, and pediatrics** are the main areas where clinical studies are conducted. Until 2012, clinical studies for psychic diseases were also quite frequent, but after changes in the management team in the Ministry of health, more than a half of projects for testing in this field have not passed the ethics control. ACTO-Russia experts mention **infections, AIDS, and hepatitis to be newly growing sectors** in Russia.

The legislation sets the number of days to obtain a permit at 57 days; however, according to ACTO, in reality, this period is much longer, 118 days on average in 2012, which was 12 days less than in 2011. The average period for approval of imports of biological samples to Russia is 21 days. The total time needed to start a clinical study equaled to 139 days on average in 2012 and 164 days in 2011.

Studies are conducted by multinational and local pharmaceutical companies as well as by contract research organizations. The legislation (RZ-61) stipulates that each organization has to have at least 5 years of relevant experience.

Approximately 100 contract research organizations operate in Russia, out of which 25 are global players. The share of clinical trials carried out by global CROs is estimated at 40%. The largest global CRO working in Russia include Parexel, PPD, PRA, PSI, and Quintiles.

Leading contract research organizations, Russia

Organization	Website	Profile
Almedis	www.almedis.ru	Founded in 2006, Almedis provides a full range of services for allocation, management, and execution of clinical trials: medical writing, feasibility assessment, regulatory approval, site monitoring, site management, project management, medical monitoring, data management, statistical analysis, and clinical study report
ClinStar (on March 4, 2013 PRA announced acquisition of ClinStar)	www.clinstar.com	Managing clinical trials in Russia, Ukraine, Belarus and in the Baltic States; ClinStar owns clinical trial warehouses and distribution centers in Moscow, Russia and Kiev, Ukraine, which provide a full range of services related to storage and distribution of clinical trials materials. The company has over 250 employees.
Covance	www.covance.com	Russian division of a global CRO; providing discovery, pre-clinical, clinical development and commercialization services
Eastern Clinical Trials	www.easterntrials.com	Conducting Phase II-IV clinical trials in Russia, Ukraine, Georgia, Belarus and other countries of Eastern Europe; offices in Moscow, Kiev, Tbilisi, Minsk, Bratislava and Budapest

Organization	Website	Profile
ICON	www.iconplc.com	Global provider of outsourced development services to the pharmaceutical, biotechnology and medical device industries. ICON specializes in the strategic development, management and analysis of programs that support Clinical Development - from compound selection to Phase I-IV clinical studies
MB Quest	www.mbquest.net	Full-service CRO for international sponsors conducting Phase I-IV studies in Russia, Ukraine, Georgia, Belarus, and Kazakhstan; active since 1997; offices in Moscow, St. Petersburg, Novosibirsk, Kiev, Tbilisi, Minsk, and local staff in Kazakhstan
Medpace	www.medpace.com	Providing clinical development services for the pharmaceutical and biotechnology industries in over 40 countries
Parexel	www.parexel.com	Conducting Phase I-IV studies incorporating the full range of services from clinical study design to bioanalytics to peri-approval and post-marketing services, with an emphasis on First in Man and Proof of Concept studies. PAREXEL has experience mainly in Cardiovascular, CNS, Infectious Disease, and Oncology. Russian offices are located in Moscow and St. Petersburg.
PRA international	www.prainternational.com	Global CRO with more than 3,000 employees worldwide and more than 30 years of experience in pharmaceutical and biotech industries
PPD	www.ppdi.com	Its Russian offices are located in Smolensk, Moscow, St. Petersburg and Novosibirsk, employing more than 210 people; Phase I-IIIb trial management and monitoring, post-approval services with phases IIIb-IV
PSI Russia	www.psi-cro.com	Global full-service CRO; the largest office and the operational headquarters are in St. Petersburg, Russia (opened in 1995, 450 people), Ukraine, Romania, Bulgaria, Poland, Estonia, Czech Republic, Switzerland and the USA. The parent company, PSI CRO AG, is in Zug, Switzerland.
Quintiles	www.quintiles.com	Expanded to Russia in 1996; with offices in Moscow, St. Petersburg and Novosibirsk

Organization	Website	Profile
Worldwide Clinical Trials	www.wwctrilas.com	The main Russian office in St. Petersburg provides international contract clinical research services, focusing on early and late-stage drug development services for pharmaceutical and biotechnology companies. Primary focus is in the areas of cardiovascular and central nervous system medicine, Chronic Inflammatory Disease, Metabolic / Endocrinology and Oncology.

Source: ACTO

There are over 9,500 hospitals with a total capacity of 1.6 million beds and about 22,800 outpatient clinics capable of screening 3.6 million potential trial subjects per day.

The number of facilities able to carry clinical studies decreased dramatically during the last two years because of changes in norms that allow medical institutions to conduct the studies. There are now more than 860 centers for clinical trials, those in the table were the most utilized for bio-equivalence trials in 2012.

Key trial centers, Russia, 2012

Medical centers	Total number of trials	Trials initiated by foreign sponsors	Trials initiated by local sponsors
Federal state organization "State scientific-research center for preventive medicine" Ministry of social and medical development, Moscow	22	17	5
Municipal medical organization, clinical hospital #2, Yaroslavl	21	8	13
Federal budget science organization "North-West science center for hygiene and public health" Russian consumer protection control, Saint-Petersburg	18	2	16
Municipal medical organization "Lubertsy region' hospital #2", Moscow region, Lubertsy	15	1	14
State budget educational organization for university professional education Sechenov First Moscow state medical University, Ministry of social and medical development, Moscow	11	1	10
Municipal autonomic organization "Reutov central city hospital", Moscow region, Reutov	10	5	5
Organization under Russian academy for medical sciences (RAMN), Scientific center for bio-medical technologies, Moscow	9	3	6
State educational organization for university professional education "Academic I.P.Pavlov' Saint-Petersburg state medical university", Saint-Petersburg	7	0	7

Medical centers	Total number of trials	Trials initiated by foreign sponsors	Trials initiated by local sponsors
Organization under Russian academy for medical sciences "Scientific-research institute for pharmacology of Siberian department of RAMN", Tomsk	6	5	1
Federal state budget organization "Scientific-research institute for flu investigation" Ministry of social and medical development, Saint-Petersburg	6	4	2
Federal state budget medical organization in Yaroslavl region "Yaroslavl regional clinical narcological hospital", Yaroslavl	6	3	3

Mrs. Svetlana Zavidova, executive director of the Association of organizations for clinical trials (ACTO-Russia), explains that Russia's attractiveness for conducting clinical trials stems from quick recruitment of potential patients for studies. In fact, **there are still high numbers of patients without adequate medical support** (not treated at all or taking insufficient volume of medical products) who are very much motivated to participate in clinical testing of drugs.

Russia provides high standard of clinical research. According to FDA, inspections revealed 56.9% of NAI (No Action Indicated) clinical trials and 41.1% VAI (Voluntary Action Needed) that could be compared to states with the same amount of trials conducted: UK (33.8% and 63.6% respectively) and Germany (39.3% and 58.9% respectively).

Medicinal products must be registered in Russia before their launch on the local market. The Department of state regulation of pharmaceutical product circulation at the Ministry of Health of the Russian Federation is in charge of registration of new medicines and circulation of already registered medicines. Foreign and Russian medical products undergo the same registration procedure.

The following pharmaceutical product categories are subject to state registration:

- original pharmaceutical products
- generic pharmaceutical products
- new combinations of earlier registered pharmaceutical products
- pharmaceutical products registered earlier but manufactured in other pharmaceutical forms, new strengths.

The following products are not subject to state registration:

- medicinal products made by pharmacies, individual entrepreneurs licensed to conduct pharmaceutical business, made under drug prescriptions and on requests of medical institutions, veterinary institutions
- medicinal (herbal) plant raw materials
- medicinal products purchased by physical entities outside the territory of the Russian Federation and intended for personal use
- medicinal products intended for export
- radiopharmaceutical medicinal products made in medical institutions directly

The state registration is not allowed for:

- different pharmaceutical products under the same trade name

- one pharmaceutical product made by one and the same manufacturer under different trade names

The registration procedure consists of 4 stages:

- Creation of a Registration dossier including documents necessary for clinical study initiation, and submission of the Registration dossier to the Ministry of Health of the Russian Federation
- Obtaining a permission for the conduct of a clinical study in the Russian Federation
- Drug quality evaluation and evaluation of the expected benefit to possible risk ratio, which is done after the clinical study of a drug
- The third stage may be divided into 2 sub-stages for convenience:
    - 3a. Drug quality control at the FSBI SCEMP's laboratory and approval of a Normative document (specification and analytical procedures)
    - 3b. Evaluation of the expected benefit to possible risk ratio and approval of Instruction for medical use of a drug
- Decision by the Ministry of Health of the Russian Federation on registration of the pharmaceutical product, its entry in the State Register of pharmaceutical products and marketing authorization issuance

14. SERBIA

Regulation of clinical trials in Serbia falls under the responsibility of **ALIMS, State Agency for Drug Control** (Medicines and Medical Devices Agency of Serbia, www.alims.gov.rs), which reports directly to the Ministry of Health.

According to Dr. Zorica Vucinic, department of clinical evaluation of ALIMS, roughly **100 clinical trials are annually conducted** in 30 to 40 clinical centers throughout the country. The key centers are located in Vojvodina, Srbija, Kragujevac, and Nis.

No database of clinical trials is maintained in Serbia.

Phase I-IV studies are all conducted in Serbia, with Phase II and III being the most common (Phase III studies make up for approximately 50% of the studies).

The key areas in terms of diseases are cardiology, radiology, neurology, and oncology.

In regards to the number of days for the approval process, in 2013, ALIMS requires 10 days for validation and 50 to 60 days for evaluation. In the past, the procedure lasted 80 to 90 days or even longer. The average costs for an application used to reach around EUR 1,000; this year (given a new regulation) the costs declined to about EUR 500.

Most clinical trials are commercial trials carried for foreign (multinational) pharmaceutical companies. Studies are conducted by pharmaceutical companies (large multinational companies operate their own departments that carry clinical studies) e.g. Actavis, Stada AG, Hemofarm, Galenika and PharmaSwiss. Smaller pharmaceutical companies use contract research organizations.

Approximately 30 local and multinational clinical research organizations are present in Serbia; their offices are mostly located in Belgrade.

Key contract research organizations, Serbia

Organization	Website	Profile
KLINIS	www.klinis.rs	Organization of various CROs; it aims to develop the clinical studies sector in Serbia
AXIOM INTERNATIONAL	www.axiom-cro.com	Well-established organization
QUINTILES	www.quintiles.com/locations/europe/serbia/	Quintiles Serbia has been operating since 2004
PAREXEL International d.o.o.	www.parexel.com/about/global-presence/europe/serbia	Leading global bio/pharmaceutical services organization
Worldwide Clinical Trials d.o.o.	www.wwctrials.com	Providing clinical research services, focusing on early and late-stage drug development services for pharmaceutical and biotechnology companies

According to the Association of Clinical Research Professionals (ACRP) - its Serbian chapter is seated in Belgrade - since Serbia is not a part of the European Clinical Trials Database (EUDRACT) environment, it offers a unique opportunity for "non-directive driven, but directive minded" approval processes. The entire regulatory process can be accomplished in just two months, with written trial approval and even an import license (IL), provided a proforma invoice for drug supply is submitted the day after the approval is granted.

The key advantages for conducting clinical trials in Serbia are that the country is in the middle of South Eastern Europe (SEE) and its trade area, providing **duty-free access to a regional market of 55 million people**. Furthermore, Serbia is the only country outside of the Confederation of Independent States (CIS) that enjoys a **free trade agreement with Russia**, offering customs-free access to its market of 150 million people.

The main problem comes from the fact that the common EU practice is not entirely applicable in Serbia.

Review processes on local and ethical levels, as well as regulatory input are well defined and documented in standard operating procedures. Bilingual templates are available for main documents required in a trial approval dossier.

Key clinical centers, Serbia

Organization	Website
Faculty of Medicine	http://mfub.edu.rs
Klinički centar Vojvodine	www.kcv.rs/rsCIR
Klinički centar Srbije	www.kcs.ac.rs
Klinički centar Kragujevac	www.kc-kg.rs
Klinički centar Niš	www.kcnis.co.rs

The medicine registration and authorization process is defined by the Act on Medicines and Medical Devices ("RS Official Gazette", No. 30/2010) and its bylaws, and it is in compliance with the appropriate procedures that apply in the European Union.

If a product has already been registered in any EU country, it is not recognized in Serbia and an application has to be filled out again in Serbia.

15. SLOVAKIA

Applications for clinical trials are submitted to the **State Institute for Drug Control** (SIDC, www.sukl.sk). SIDC receives **approximately 150 applications for clinical trials per year**.

Applications reviewed by SIDC, Slovakia, 2010-2012

Year	Number of clinical trial applications	Number of approved clinical trials
2010	151	NA
2011	162	138
2012	155	130

A clinical trial must be also approved by an independent ethics committee. Ethics committees work at medical facilities where trials take place.

About 90% of all clinical trials are commercial trials carried for foreign (multinational) pharmaceutical companies and only 10% of studies are sponsored by academic or professional societies.

All phases of clinical research are carried in Slovakia. The most frequent are **Phase II (28%) and Phase III (58%) studies**. According to Ms. Mernicka from SIDC, the biggest portion of clinical trials are multicentric. The number of patients annually involved in clinical trials is not tracked by SIDC, and no estimate was provided.

The key legislation in Slovakia is:

- Act No.362/2011 Coll. on Medicines and Medical Devices, as amended
- Act No. 576/2004 Coll. on Health care, services related to health care
- Ministry of Health Decree 433/2011 on requirements for clinical trials and good clinical practice
- Act 459/2012 Coll., amending and supplementing Law no. 362/2011 Coll.

In January 2013 the Act No. 459/2012 Coll. on Medicines and Medical Devices was approved. This shall reduce excessive administrative and financial burdens of sponsors and interference of health insurance in clinical trials. It is expected to lead to an increase in the number of clinical trials, as the Slovak Republic is among the most "reliable" countries for clinical trials (quality index of 0.5) in the European Union.

The organization responsible for the initiation, management and financing of a clinical trial - the sponsor - can lead the trial or may be represented by a contract research organization (CRO). Based on SIDC data the share is about the same (50% each) in Slovakia. CROs can also assist the sponsor in the registration process.

Many CROs conducting clinical trials in Slovakia are headquartered outside of Slovakia, in one of the EU countries.

Selected key CROs, Slovakia

Organization	Website	Profile
Axon CRO, s.r.o.	www.axon-cro.com	Providing a wide range of clinical services to manage Phase I-IV clinical trials
Clinitria Ltd.	www.clinitria.eu	Operating in several CEE countries - Czech Republic, Slovakia, Poland, and Hungary
EastHORN Clinical Services in CEE	www.easthorn.com	CRO organization offering clinical trials
L&V research services Ltd.	www.lv-cro.com	Independent Contract Research Organization (CRO) operating in Slovakia, the Czech Republic, and Hungary
Pharmaceutical Research Associates SK, s.r.o.	N/A	Slovak CRO organization
Quintiles Inc.	www.quintiles.com	Global company also present in Slovakia

Clinical studies in the Slovak Republic are conducted mainly in large teaching hospitals as well as private and public clinics; a very few take place in research institutes. There are **approximately 500-1,000 trial sites**.

Selected key trial sites

Organization	Website	Profile
F.D. Roosevelt Faculty Hospital, Banska Bystrica	www.fnspfdr.sk	The biggest hospital in central Slovakia
Faculty Hospital Bratislava	www.fnspba.sk	The largest medical center in Slovakia
National Cancer Institute, Bratislava	www.nou.sk	The biggest oncology center in Slovakia
National Institute of Cardiovascular Diseases, Bratislava	www.nusch.sk	One of the top and best equipped healthcare centers of cardiovascular medicine in Slovakia
UN. L Pasteur Faculty Hospital, Kosice	www.unlp.sk	The biggest hospital in the eastern part of Slovakia

Based on information provided by SIDC the Slovak Republic has never been stated as a reference state for registration of new drugs. Slovakia is a reference state only in case of registration of generic medicines.

16. SLOVENIA

The number of clinical trials conducted in Slovenia is low compared to other CEE countries subject to this study. **JAZMP** (Public Agency for Drugs and Medical Devices, www.jazmp.si) **issues between 25 and 30 permits** for clinical trials annually. In 2012, a total of 1,574 patients were expected to participate in the studies.

In 2012, the breakdown of 32 studies conducted in Slovenia was as follows:

- 5 Phase I
- 4 Phase II
- 19 Phase III
- 4 Phase IV

Most trials were from the oncology field, followed by endocrinology (diabetes), cardiology, pulmology and neurology. 6 studies were academic, the rest commercial.

The procedures pertaining to clinical trials are outlined on JAZMP website and in Regulations for clinical trials (Official Gazette of the Republic of Slovenia, nr 54/06). In order to begin and conduct clinical trials the following applies:

- meeting the conditions of the Drug Act (Official Gazette of RS nos. 31/2006 and 45/2008) and the above mentioned OG
- positive assessment by JAZMP and National Medical Ethics Committee (www.kme-nmec.si)
- monitoring of condition fulfillment through the trial

JAZMP issues a decision on an application for a clinical trial in 60 days upon receiving the complete application. This deadline applies to cases of drugs acquired in biotechnology process, exceptionally it can be prolonged for 30 days. For human treatment with xenogenic cells, there are no time limitations for a decision.

A rather small number of contract research organizations operate in Slovenia.

Selected key CROs, Slovenia

Organization	Website	Profile
ADAX International d.o.o.	http://adax.si/index.html	Founded in 1991, employing 13 CRAs; coordination of Phase I, II, IIIa, IIIb and IV clinical trials and registration of medicines; recently there have been changes in its ownership
Clinres Farmacija	www.clinres-farmacija.hr	Registered in Croatia, the group includes offices in Slovenia; they offer a full range of services supporting the process of clinical trials
East Best Solution	http://eastbs.com	Registered in Serbia, with authorized representatives in Slovenia; offering a wide range of services
Optipharm	http://optimapharm.hr	Registered in Croatia, also providing services in Slovenia

Most trials are conducted at the Institute of Oncology in Ljubljana (www.onko-i.si/eng). The number two most active trial site is the University Medical Center Ljubljana (www.4.kclj.si/ang/index.php), followed by the University Clinic of Pulmonary and Allergic Diseases Golnik (www.klinika-golnik.si/en), which is a tertiary education and research institution specializing in pulmonary and allergic diseases, and University Medical Center in Maribor (www.ukc-mb.si, no English version).

JAZMP is also the product registration authority. In the last couple of years the most common types of registration were **the decentralized procedure, MRP and centralized procedure** (conducted under EMA). National registration was less common.

The key legislation for human medicines are:

- Medical Products Act (Official Gazette of the Republic of Slovenia (OG of RS), Nos. 32/06 and 45/08); unofficial consolidated text (ZZdr-1-NPB1)
- Medical Devices Act (OG of RS, Nr. 98/2008)
- Public Agencies Act (OG of RS, Nr. 52/2002)

Several companies offer assistance with registration of products; CROs listed above (ADAX, Clinres and East Best Solution) and Medisanus (www.medisanus.com/medisan%20E/index.html), which is an independent consultancy company involved in all areas of drug development and regulatory affairs, the company was established in 2002.

17. UKRAINE

This country ranks amongst five largest clinical trials markets in Central and Eastern Europe. In-depth analysis of its clinical trials and product registration environment is provided in Part D.

Ukraine, the second most populous country in Central and Eastern Europe, is the **fifth largest market in the region in terms of clinical trials annually started**.

In 2012, a total of **265 clinical trials were approved**, out of which **81% were multinational multicentric studies**.

Phase II and III studies now combine for **92%** of studies.

Almost 290,000 patients were enrolled in studies taking place in Ukraine during May 2013.

The three leading therapeutic areas for clinical studies carried in Ukraine include oncology, psychiatrics, and neurology; they are followed by pulmonology, rheumatology, and gastroenterology; studies in cardiology and endocrinology are conducted slightly less often. In 2010, Ukraine started to run clinical trials for AIDS (both adults and minors), but the number of studies in this area remains low.

All procedures pertaining to commercial clinical trials are regulated by the **Ministry of Health of Ukraine**, specifically its State Expert Center (SEC), Department of preclinical and clinical trials. Scientific trials are held independently by the National Academy of Science.

Assessment of ethical, moral, and legal aspects of a clinical trial is made by ethics committees at health care settings where a clinical trial is to be conducted. Central committee for ethics in clinical trials (http://ethicscommission.org.ua) does not exist as of 2012 according to amendments declared by the Decree #523.

The number of days for reviewing an application as declared in the legislation and rules is up to 50 days for analysis of documents for clinical trials and up to 10 days for the Ministry of health expert evaluation. The total time limit shall not exceed 60 days; however, experts can return clinical study documents with remarks and ask for their reworking, so the overall timing can be prolonged significantly.

Clinical studies are conducted by global pharmaceutical, biotechnology and medical device companies and contractors. No accreditation is required for a CRO in Ukraine and the Ministry of health does not maintain any lists of CRO and thus cannot make any recommendations as to the competence and reliability of CROs. So, all risks associated with finding a reliable CRO rest upon a sponsor. Many multinational CROs already operate in Ukraine; they prevail in number over Ukrainian organizations.

Selected contract research organizations, Ukraine

Organization	Website	Profile
Averion	www.averionintl.com	Present in Ukraine since 2008; focusing on studies in oncology and cardiovascular diseases; in the CEE region it is present in Poland, Russia, and Ukraine; with operation centers in the Czech Republic, Slovakia and Hungary
Axis Clinicals	www.axisclinicals.com	Headquartered in India; involved in bio-equivalence bio-ability studies and having therapeutic expertise in oncology, CNS, cardiology, respiratory, orthopedic, endocrinology, metabolism, contraception
Chiltern	www.chiltern.com	Global CRO established in 1982; focus on oncology, CNS-TBA, infectious diseases and vaccines, cardiorespiratory, ophthalmology, pediatrics
ClinStar (acquired by PRA on March 4, 2013)	www.clinstar.com	Managing clinical trials in Russia, Ukraine, Belarus and in the Baltic States
Cromos Pharma	http://cromospharma.com	In Ukraine and Russia the company manages Phase I-IV clinical trials in most therapeutics areas
Covance	www.covance.com	Ukrainian division of a global CRO
Farmasoft CT	www.farmasoft-ct.com.ua	Founded in 2007; a local CRO with 17 specialists specializing in Phase II-IV studies - cardiovascular, endocrine and metabolic, CNS, Pain, Inflammation, Urology
ICON	www.iconplc.com	Global provider of outsourced development services to the pharmaceutical, biotechnology and medical device industries; specializing in the strategic development, management and analysis of programs that support Clinical Development - from compound selection to Phase I-IV clinical studies
INC Research	www.incresearch.com	Focus on the following areas: cardiovascular, CNS, endocrinology, immunology, infectious diseases, oncology, pain, pediatrics, psychiatry, respiratory, women's health
MB Quest	www.mbquest.net	Full-service CRO for international sponsors conducting Phase I-IV studies in Russia, Ukraine, Georgia, Belarus, and Kazakhstan; active since 1997; offices in Moscow, St. Petersburg, Novosibirsk, Kiev, Tbilisi, Minsk, and local staff in Kazakhstan
Parexel	www.parexel.com	Phase I-IV studies; present in 51 countries around the world
PRA international	www.prainternational.com	Global CRO with more than 3,000 employees worldwide and over 30 years of experience in pharmaceutical and biotech industries

Organization	Website	Profile
PPD		Global CRO with offices in 42 countries; involved in Phase I-IIIb trial management and monitoring, post-approval services for Phase IIIb-IV
PSI	www.psi-cro.com	Global full-service CRO; also present in Russia, Ukraine, Romania, Bulgaria, Poland, Estonia, and the Czech Republic
Quintiles	www.quintiles.com	Expanded to Ukraine in 1999; office in Kiev

Medical centers (called healing and prophylactics organizations - LPU) had to have an accreditation from the Ministry of health up until 2009. Since then, any LPU can host a clinical trial, if it can prove that it is able to fulfill all requirements and collect all necessary documents. Director of Department of preclinical and clinical trials Mrs. Nikolaeva assumes that there could be around 2,000 LPUs in Ukraine, including separate departments of hospitals on all regional levels.

Registration of medications is regulated by the Ministry of Health of Ukraine and the State Expert Center as well.

There is just one type of medication registration – State registration – in Ukraine. An applicant must submit an application form and a registry document set (registry dossier) according to the Decree #426 "On approval of Procedure of medicines registration materials expertise". Documents can be in Ukrainian, Russian, or English language. In case English is selected, some documents still have to be translated into Ukrainian or Russian.

The legal base for clinical trials in Ukraine form the Act 45 of "Bases of Ukraine health legislation" from 1996, "Act of Ukraine on medicines" from 2009, Decree #690 "About the procedures of clinical studies of medical products and expertise of materials for clinical studies and regulations on ethics committees" amended by Decree #523 from June 12, 2012, and Decree "On approval of the Procedure for conducting additional studies of medicinal products during expert evaluation of registration materials" from April 17, 2007.

The negative aspects for conducting clinical trials in Ukraine as revealed by experts from European Business Association (http://www.eba.com.ua) are the lack of clinical centers as well as the fact that Ukrainian medical specialists are perceived by foreign sponsors as not enough competent. European Business Association estimates investments into clinical trials at around UAH 1 billion (USD 123 million).

Medicinal products do not necessarilly need to be clinically tested in Ukraine before beginning the procedure of their registration. If clinical trials were conducted according to the U.S. or/and European norms and if the experts from the Department of Registration and Re-registration at the Ministry of Health of Ukraine find no need in conducting additional clinical trials, the procedure of products registration can be launched.

There is no agreement between Ukraine and other countries about automatic recognition of results of clinical trials conducted abroad.

PART D: TOP 5 CEE MARKETS IN DETAIL

This section contains in-depth analysis of the regulatory and market environment pertaining to clinical trials as well as registration and marketing of new products in the five largest clinical trials markets in Central and Eastern Europe (listed alphabetically: the Czech Republic, Hungary, Poland, Russia, and Ukraine).

18. TOP 5 MARKETS: HEAD TO HEAD COMPARISON

Russia is the largest market in Central and Eastern Europe in terms of clinical trials annually started; it is followed by Poland, the Czech Republic, Hungary, and Ukraine.

The ratio of the number of clinical trials carried per a population of one million is the highest in the Czech Republic (39) and Hungary (35), while it is the lowest in Russia (7) and Ukraine (6).

Head to head comparison of the 5 largest CEE markets for clinical trials, 2012

	Area (sq km)	Population (million)	GDP per capita (PPP, USD, 2010)	Approximate number of clinical trials per year	# of trials per 1 mil. people (2012)
Czech Republic	78,866	10.2	25,600	350 (applications per year), 400 in 2012	39
Hungary	93,030	9.9	19,000	300-350 (applications per year), 350 in 2012	35
Poland	312,679	38.5	18,800	450 (trials started annually), 592 in 2011, 490 in 2012	13
Russia	17,075,200	140.0	15,900	550-600 (started each year), 916 in 2012	7
Ukraine	603,700	45.7	6,700	250, 265 approved in 2012	6

Source: EasyLink Business Services, 2013

CZECH REPUBLIC

19. CLINICAL TRIALS

19.1 Country attractiveness and challenges

The key benefits for carrying clinical studies in the Czech Republic include, but are not limited to, the following:

- Highly qualified investigators
- Experience – local medical staff have been involved in clinical studies since early 1990's; between 2007 and 2011 approximately 22,000 doctors participated in clinical studies (some doctors were involved in more than one study during that time)
- Availability of high quality investigational sites for all phases of clinical research
- Healthcare system is centralized with well-developed referral network, which makes recruitment of patients efficient
- Cost savings
- Solid reputation of clinical research
- Willingness of patients to participate in the studies

According to Mr. Petr Janda, chairman ACRO-CZ (the professional association of contract research organizations in the Czech Republic that focus on clinical research and the development of pharmaceuticals), labor cost is now the only difference between carrying clinical studies in Western Europe and the Czech Republic, Slovakia and Hungary. The per hour cost for study monitoring in these three CEE countries is about 30 to even 50% lower compared to Western Europe. The price difference can grow even larger for studies carried out in Bulgaria and Romania, but the quality is not comparable at this time, and lower labor costs for study monitoring are offset by extra costs required for additional activities needed to assure the same quality of trials, as the control has to be tighter.

For instance, Prague Clinical Services, a local CRO, would charge at between **EUR 1.8 to 2.5 million (USD 2.4 to 3.3 million)** for a Phase III clinical study assigned as a turn key project (not just study monitoring) for a generic pharmaceutical carried out in 5 to 6 countries in the CEE region on about 400 patients. The figure already includes all the payments for patients; usually CROs do not include payments for patients in the figure, which makes comparing quotes rather confusing. On average the payment for a patient reaches about CZK 40,000 (USD 2,000).

The other aspects such as payments for patients or facilities must be the same in the Czech Republic as in Western Europe in case of multicentric studies. Another advantage that would apply, provided a study was to be carried in the Czech Republic only, would be prices charged for ambulances/sites for carrying the trial, as the cost would be about 30% lower compared to charges in Western Europe.

The ease of enrolling patients for studies used to be a major advantage in the past, but now with the large number of studies carried out in the country, the studies have to fight for patients. Presence of large, untreated patient populations is also no longer a valid advantage of the Czech Republic.

The process of recruiting patients and related prices are the same in the Czech Republic as in Western Europe.

The quality of clinical trials is checked by internal audits where a sponsor guarantees the quality and documents the entire process. In addition, there can be third party inspections by e.g. SUKL (regulatory authority in the Czech Republic), EMEA or FDA.

The approval process is regulated by the EU Directive. If a tested product is not yet registered in the EU, once the study is approved by SUKL, SUKL issues an import license, which approves the product to be imported with no tariffs. The products have to be labeled appropriately as products for clinical trials.

The CEE region has received excellent FDA audit results. It leads the world in the ratio of highly successful audits by the FDA. When analyzing data from 5,531 FDA clinical trials inspections between 1994 (when the FDA first performed inspections in CEE) and the end of 2010: 401 from clinical trials performed in Western Europe, 230 in CEE, 3,858 in the USA, and 376 in other countries, "the average number of deficiencies per inspection ranged between 0.99 for CEE and 1.97 in Western Europe. No deficiencies were noted during 16.6%, 39.0%, and 21.5% of inspections in Western Europe, CEE and USA, respectively." The portion of inspections after which no follow-up action was indicated stood at 36.9% for Western Europe, 55.7% for CEE, and 44.3% for US sites. The CEE region boasted the lowest percentage of inspections that required official or voluntary action[1].

Phone interviews with several market experts suggest that **the Czech Republic does not yet attract too many Phase I studies**, **even though the country is capable and well equipped to carry this type of studies**.

19.2 Market size

19.2.1 Number of trials

According to Dr. Tomas Boran, department of clinical evaluation of SUKL, on average, **SUKL annually reviews some 350 applications for clinical studies**. A total of 329 and 404 proposals were reviewed in 2011 and 2012 respectively. (In 2010 and 2011, 7 and 9% of applications respectively were withdrawn during the assessment process and no application was rejected by SUKL.)

[1] *Source: Why (not) go east? Comparison of findings from FDA Investigational New Drug study site inspections performed in Central and Eastern Europe with results from the USA, Western Europe, and other parts of the world by Paul H Caldron, Svetlana I Gavrilova, and Siegfried Kropf - www.ncbi.nlm.nih.gov/pmc/articles/PMC3340105/*

The actual number of studies carried out every year is, however, slightly higher, since a significant portion of the studies are long-term.

19.2.2 Number of patients

Between **20,000 and 30,000 patients participate** annually in clinical studies. The studies are conducted in most hospitals, especially large teaching/university, so-called faculty hospitals, and regional hospitals and in hundreds of state and private outpatient facilities.

19.3 Structure of studies conducted

19.3.1 By type of study

Approximately **80%** of all clinical trials are **multicentric commercial trials carried for foreign (multinational) pharmaceutical companies**; the remaining 20% of studies are sponsored by academic or professional societies, academic institutions or healthcare facilities from both the Czech Republic and other European countries.

In the European Economic Area (the EU plus Iceland, Liechtenstein and Norway), approximately 61% of clinical trials are sponsored by the pharmaceutical industry and 39% by non-commercial sponsors, mainly academia[2].

Out of all applications submitted in the Czech Republic in 2010 and 2011, 16 and 14 clinical trials respectively were sponsored by non-commercial organizations (academic research), 4 and 7 applications pertained to orphan drugs and 27 and 44 were for pediatric population.

19.3.2 By phase

Phase II and Phase III trials combine for approximately **80%** of the studies.

The vast majority of applications are for Phase III studies: international, multicentric, randomized, blinded, placebo- or active-substance controlled clinical trials conducted by foreign sponsors.

In roughly **10 clinical studies a year people are administered a completely new substance**. In general, such studies usually involve a limited number of participants (about 24), and the patients are usually paid for their participation.

Number of approved clinical trials by phase, Czech Republic, 2010-2011

	2010	2011
Phase I	14	13
Phase II	80	105
Phase III	191	242
Phase IV	19	20
Bioequivalence	25	24

[2] *Source: European Medicines Agency*

Source: SUKL, 2013

19.3.3 By disease

Traditionally, the key areas in terms of diseases have been **oncology, neurology, reumatology, and respiratory and cardiovascular diseases**. These top 5 therapeutic areas generated 53% and 54% of the applications assessed in 2010 and 2011.

Ms. Stastna, a secretary of ACRO-CZ - professional association of contract research organizations in the Czech Republic, has recently noticed a growing demand for studies in the area of psychiatry.

Breakdown of clinical trials by therapeutic area Czech Republic, 2010-2011

	2010	2011
Oncology	62	89
Neurology	30	54
Reumatology	35	26
Healthy volunteers	25	23
Respiratory and Allergology	15	22
Cardiovascular system	32	22
Diabetology	28	21
Infectious	5	16
Gastrointestinal disease	10	16
Psychiatry	14	15
Urogenital disease	9	13
Pain	9	12
Other	6	11
Internal medicine	NA	9
Pediatrics	6	8
Hematology	12	8
Dermatology	8	7
Ophthalmology	5	7
Gynecology	6	5
Metabolism disorders and Endocrinology	5	4
Transplantation	6	4
Otolaryngology	1	4
Examination procedures	0	2
Emergency	0	0

Source: SUKL, 2013

19.4 Regulatory information

19.4.1 Regulatory institution

In the Czech Republic, clinical studies are assessed by the State Institute for Drug Control (SUKL, www.sukl.cz) and at least one ethics committee (independently of each other).

SUKL focuses on the investigational medicinal product and study design together with specialists for the given clinical area, while the ethics committee reviews the ethic aspects of the study, qualification of doctors and facilities of the trial site.

COMPANY NAME	**State Institute for Drug Control**
Address	Šrobárova 48
Address (city)	Praha 10
Address (ZIP)	100 41
Telephone	+420 272 185 111
Web site	www.sukl.cz
PROFILE	Administration body established by the Act no. 79/1997 Coll.; it falls under direct control of the Ministry of Health
Description	Its duties are: • to ensure that all human pharmaceuticals available in the Czech market meet appropriate standards of quality, safety, and efficacy • to ensure that only safe and functional medical devices are used in the Czech Republic, accompanied by reliable and appropriate information • to contribute to rational use and where appropriate to ethical clinical trials of both medicinal products and medical devices • to ensure that regulatory procedures shall not result in unnecessary obstacles to availability of medicinal products and medical devices nor to introduction of new therapeutic procedures
Year of establishment	Tradition going back to 1918
Ownership structure	State organization
Number of employees	313

There are 11 ethics committees for multicentric clinical trials and approximately 140 ethics committees established at healthcare facilities. In compliance with Section 54 of Act No 378/2007 Coll. on Amendment to the Act on Pharmaceuticals and on Amendments to Other Acts, applications for opinions on multicentric clinical trials are also submitted to the Multicentric Ethics Committees.

Multicentric Ethics Committees, Czech Republic, April 2013

Ethic committee	Website
Ethic committee of Faculty Hospital Motol	www.fnmotol.cz/eticka-komise.html
Ethic committee of Faculty Hospital Olomouc	http://public.fnol.cz/www/ek/default.htm
Ethic committee of Faculty Hospital Hradec Kralove	www.fnhk.cz/cze/index.php?dir=36
Ethic committee of IKEM and Thomayer Hospital	www.ikem.cz/www?docid=1003030&hash=# www.ftn.cz/klinicky-vyzkum-a-ek/eticka-komise
Ethic committee of Faculty Hospital Brno	www.fnbrno.cz/Article.asp?nArticleID=625&nLanguageID=1
Ethic committee of Regional Hospital Liberec	www.nemlib.cz/web/index.php?menu=1_37
Ethic committee of Faculty Hospital St. Anne's Brno	www.fnusa.cz/ekomise.php
Ethic committee of General Faculty Hospital	www.vfn.cz/o-nemocnici/management-vfn/eticka-komise-vfn

Ethic committee of Vítkovické nemocnice a.s.	www.nemvitkovice.cz/obsah/etickakomise/kontakty.aspx
Ethic committee of Faculty Hospital Ostrava	www.fno.cz/eticka-komise
Ethic committee of Faculty Hospital Kralovske Vinohrady	www.fnkv.cz/?show=o_nas&menu=1

Source: SUKL, 2013

19.4.2 Procedure

The first step for a U.S. pharmaceutical producer (not established in the EU market and not ready to carry a clinical trial in-house) is to **select a contract research organization** (a local company or a local branch of a global CRO) **that will prepare all the paperwork and submit it for assessment/notification to SUKL and ethics committee(s)** (for detailed information on CROs operating in the Czech Republic see section 19.5.1 Key contract research organizations).

Where an application or notification is submitted by a sponsor residing outside the territory of the Czech Republic or the EU, the sponsor shall be obliged to submit the power of attorney for the person (natural or legal) whose registered office or address of residence is within the territory of the Czech Republic or the EU/EEA (legal representative) together with the application.

Authorization from SUKL is requested only for study drugs that are prepared by biotechnology (GMOs) and/or containing human or animal tissues. Clinical trials with other drugs (registered/non registered) are notified using the EU Clinical Trial Application form.

Regulatory documentation must be submitted in Czech to local regulatory authorities.

In regards to the number of days it takes to obtain a permit, by law SUKL has 10 days for validation and 60 to 90 days for evaluation, the length varies according to the category of medicinal products. Mr. Boran, SUKL: head of department of clinical evaluation, claims it takes on average 50 days.

The period of assessment of bioequivalence studies has been shortening; it now takes slightly under 30 days.

An increasing number of sponsors of clinical trials, especially from the commercial sector, are choosing the **Voluntary Harmonization Procedure** (VHP), which was introduced in 2010 with an aim to streamline the assessment of applications for multinational trials carried throughout the European Union. VHP is managed by the EMA Clinical Trial Facilitation Group (CTFG). In 2010 and 2011, 9 and 30 clinical trial applications respectively were submitted and assessed in the Czech Republic as part of the VHP.

19.5 Key players

In the Czech Republic, clinical studies are carried by:

- Pharmaceutical companies in-house (a few large multinational companies operate their own departments that carry clinical studies; some outsource staff from CROs)
- Contract research organizations – multinational or local
- Freelancers – they submit an application/notification to SUKL and then provide monitoring; no additional assistance is usually requested from a sponsor

Based on information gathered during interviews with market experts we estimate that **contract research organizations carry approximately 80% to 90% of all clinical studies in the Czech Republic.**

19.5.1 Key contract research organizations

According to Mr. Petr Janda, chairman of ACRO-CZ, between **20 to 25 CROs** (not all of them are members of ACRO-CZ) meet the highest standards set by the ethic codex of ACRO for conducting clinical trials in the Czech Republic. The standards include having own standard operating procedures, quality assurance, and carrying a certain number of studies annually.

According to Ms. Stastna, secretary of ACRO-CZ, members of the association carry about three quarters of all clinical trials conducted in the Czech Republic. Many members are multinational companies that run studies in multiple countries.

Overview of selected leading contract research organizations, Czech Republic, 2013

Company	Local vs global	Website	Activities	2011 Turnover (USD million)	Number of employees
Quintiles Czech Republic s.r.o.	Global	www.quintiles.com	Local branch of a global CRO	24.0	128
PPD Czech Republic s.r.o.	Global	www.ppdi.com	Local branch of a global CRO	11.0	79
Icon Clinical Research s.r.o.	Global	www.iconplc.com	Local branch of a global CRO	7.1	78
Prague Clinical Services, s. r. o.	Local	www.pragclin.com	Focus on Phase II and III trials; capable of carrying also Phase I and IV trials	3.6	Team of 20 experts (4 employees plus contractors)
Pharmaceutical Research Associates CZ, s.r.o.	Global	www.prainternational.com	Local office of a global CRO	3.3	26
Covance Clinical and Periapproval Services LTD	Global	www.covance.com	Local branch of a global CRO	2.3	16

Company	Local vs global	Website	Activities	2011 Turnover (USD million)	Number of employees
CEPHA s.r.o.	Local	www.cepha.cz	Focus on Phase I and bioavailability and bioequivalence studies; also capable to carry Phase II to IV studies; providing a broad range of services	2.3	34
Pharmnet s.r.o.	Local	www.pharmnet.cz	Involved in Phase I – Phase IV studies; offering a wide range of services	2.3	24
Premier Research, s.r.o.	Global	www.premier-research.com	Local office of a global CRO	1.9	8
EastHORN Clinical Services in CEE, s.r.o.	Local	www.easthorn.com	Founded in Prague in 2004, EastHORN has become one of the leading CROs in Central and Eastern Europe, with clinical operations in over 15 countries; carrying Phase I to IV studies; offering a wide range of services	1.1	NA
Medpace Česká republika s.r.o.	Global	www.medpace.com	Local office of a global CRO	1.0	12
ECRON - The Czech Expert s.r.o.	Global	www.ecronacunova.com	Local office of a global CRO	0.2	3
Chiltern International, s.r.o.	Global	www.chiltern.com	Local branch of a global CRO	NA	*27
ClinTec International s.r.o.	Global	www.clintec.com	Local branch of a global CRO	NA	NA

**2009 data*
Source: Company websites, business databases, ACRO-CZ

Detailed profiles of the top four CROs (3 global and 1 local) as well as ACRO-CZ follow below.

A Pennsylvania company seeking to identify a suitable CRO to run a clinical trial in the Czech Republic or other CEE countries shall contact the Authorized Trade Representative in Central Europe with specific requirements and expectations on the partner organization (see section 22.3 Route to market starting on page 78 for details).

According to Mr. Janda, the top multinational CROs are Covance, ICON, PPD, Quintiles, PRA, and Medpace. Out of the studies carried strictly by CROs, the above named global CROs conduct about 60 to 70% of studies.

Local CROs run around 30% of studies; they do not specialize in pivotal studies. Their key area of competence are studies for generic therapeutic equivalents.

Global companies are involved in almost all therapeutic areas, while the local players tend to focus on a smaller range of therapeutic areas, but usually they will not decline to assist in other areas as well if asked for collaboration. However, many pharmaceutical companies at this time require prior experience with studies in the sought therapeutic areas before assigning the study to a given CRO.

Amongst ACRO-CZ members, only a limited number of companies can carry Phase I studies at this time; CEPHA (www.cepha.cz) is the leader, others include e.g. Pharmnet, Easthorn and Prague Clinical Services.

The leading pharmaceutical companies tend to have contracts with global CROs, and in case of studies in the Czech Republic, local branches carry the trials. Most local branches of global CROs are only involved in monitoring of trials; they do not write a study protocol or a final report nor they analyze the findings, as they do not have statistical departments. They only monitor the study and collect the results and then submit them to another party for further processing. Many local CROs also carry mainly monitoring. Local CROs are often contracted by other CROs abroad to assist with the studies in the Czech Republic.

The costs for monitoring by a local CRO compared to a local branch of a global CRO are at about 50%.

There is a rather small number of companies in the Czech Republic that can carry all the work and processes associated with a clinical trial – writing a study protocol, have the protocol approved, monitor the study and then write the final report. According to Mr. Janda, his company - Prague Clinical Services - is the leader amongst local companies, they have ventured outside of the Czech Republic and can carry studies in other countries. The capabilities of many local companies are at this time limited to trial monitoring in the Czech Republic only.

Mr. Janda claims that there are only 6 people in the Czech Republic who can write a final report for a clinical trial, and 2 of them work with Prague Clinical Services.

The following organizations constitute the leading players in the area of clinical trials in the Czech Republic; they are listed alphabetically.

COMPANY NAME	**ACRO-CZ, o.s.**
Address	Nám. Hrdinů 6/1034
Address (city)	Praha 4
Address (ZIP)	140 00
Telephone	+420 241 410 196 +420 721 956 537
Web site	www.acro-cz.cz
PROFILE	Professional association of Contract Research Organizations in the Czech Republic that focus on clinical research and the development of pharmaceuticals
Description	The main goal of the association is to represent CROs in negotiations with state authorities and institutions as well as internationally, to actively participate in discussions regarding the creation of legal and ethical norms in the area of clinical research and to create conditions for further education of its members as well as to develop cooperation in the area of clinical evaluation of pharmaceuticals. Its 15 members are involved in: • Phase I studies • Phase II-IV studies • Statistic processing of clinical evaluations
Year of establishment	2005

COMPANY NAME	**Icon Clinical Research s.r.o.**
Address	V parku 2335/20
Address (city)	Praha - Chodov
Address (ZIP)	148 00
Telephone	+420 272 124 068
Web site	www.iconplc.com
PROFILE	Global provider of outsourced development services
Description	Serving the pharmaceutical, biotechnology, and medical device industries
Year of establishment	2007
Ownership structure	Limited liability company: ICON Holdings – 100% share
Number of employees	78
Turnover	2011: CZK 125 million (USD 7.1 million) 2010: CZK 123 million (USD 6.4 million) 2009: CZK 95 million (USD 5.0 million)

COMPANY NAME	**PPD Czech Republic s.r.o.**
Address	Budějovická alej - Antala Staška 2027/79
Address (city)	Praha 4
Address (ZIP)	140 00
Telephone	+420 233 321 233
Web site	www.ppdi.com
PROFILE	Global CRO; also active in the Czech Republic
Description	Contracts for assistance/work done in the Czech Republic are signed with PPD USA, PPD UK or PPD Bulgaria Focus on monitoring of clinical trials
Year of establishment	1995
Ownership structure	Limited liability company: 97.78% share - PPD International Holdings GmbH and 2.22% share - PPD International Holdings, LLC
Number of employees	79
Turnover	2011: CZK 198 million (USD 11 million) 2010: CZK 190 million (USD 9.9 million) 2009: CZK 173 million (USD 9.1 million)

COMPANY NAME	**Prague Clinical Services, s. r. o.**
Address	Zachova 8
Address (city)	Praha 4
Address (ZIP)	140 00
Telephone	+420 241 029 551
Web site	www.pragclin.com
PROFILE	Headquartered in Prague; a team of twenty people, also present in the Slovak Republic and Bulgaria
Description	Providing a complete range of clinical services Focus on Phase II and III trials, but capable of carrying also Phase I and IV trials Access to a Phase I certified trial site in Thomayer hospital Involved in: 1. Quality Assurance & Drug Safety 2. Clinical data management and biostatistics 3. Medical writing 4. Regulatory affairs 5. Clinical research • Project management of local & international studies • Identification of investigational sites including feasibility & assessment of sites • Preparation of trial-related documents • Management of regulatory & ethical approvals • Organization of investigators' meetings/training of investigators • Set up of an administrative database to track patients & investigational sites • In-depth monitoring including source data verification & drug accountability • Management of investigators' contracts and payments • Study close-out activities • Status reports • Final report Its customer base includes major global CROs and specialty pharmaceutical companies Capable of providing service in the Czech Republic, Slovakia, Bulgaria, Romania, Macedonia, Russia, and Ukraine and a number of countries in Western Europe
Year of establishment	2004
Ownership structure	Limited liability company: Nordic Group B.V. 51/61 share and NORDIC Pharma, s.r.o. 10/61 share
Number of employees	4 (collaborating with a number of external experts)
Turnover	2011: CZK 63 million (USD 3.6 million) 2010: CZK 28 million (USD 1.5 million) 2009: CZK 19 million (USD 1.0 million)

COMPANY NAME	**Quintiles Czech Republic s.r.o.**
Address	Radlická 714
Address (city)	Praha 5
Address (ZIP)	158 00
Telephone	+420 725 781 887
Web site	www.quintiles.com
PROFILE	The largest and strongest CRO in the Czech market
Description	• Planning, management and execution of Phase II and III trials and their analysis • Focus on execution and monitoring of clinical trials assigned for the Czech market
Year of establishment	2010; in the market since 1995 - operating as an organizational unit
Ownership structure	Limited liability company: Quintiles GesmbH 3259/3260 share and Quintiles Eastern Holdings GmbH 1/3260 share
Number of employees	128
Turnover	2011: CZK 417 million (USD 24 million)

19.5.2 Key trial sites – hospitals/universities

Mr. Boran, SUKL: head of department of clinical evaluation, estimates the number of trial sites could exceed 2,000 if major trial centers as well as small ambulatory practices of practitioners are counted; small private practices often carry studies in the area of vaccinations and allergy medicines.

Mr. Janda explains that the key sites are all the teaching hospitals that treat a large number of patients with the type of diseases sought for clinical trials. The key advantage is the tremendous experience of the doctors in the teaching hospitals with clinical trials. Large teaching hospitals have entire clinical trial departments where studies are conducted.

Other key groups are regional hospitals as well as private clinics that are very open to carry the trials and their staff are very flexible and signing contracts with them is a very easy process, as the doctors are often the owners.

State out-patient medical centers are also important, but it is much more difficult to have the trials approved there, mainly due to the way they operate; the process is rather slow and more cumbersome.

According to Mr. Janda, General University Hospital in Prague is the most sought location for clinical trials, followed by the Masaryk Oncology Institute and IKEM.

Selected key trial sites, Czech Republic

Organization	Website	Profile
Faculty Hospital Brno	www.fnbrno.cz	The largest medical center in Moravia
Faculty Hospital Motol	www.fnmotol.cz	The largest medical center in the Czech Republic
Faculty Hospital Plzen	www.fnplzen.cz	Teaching hospital in Western Bohemia
Faculty Hospital Kralovske Vinohrady	www.fnkv.cz	One of the largest hospitals in Prague
General University Hospital in Prague	www.vfn.cz	One of the largest healthcare facilities in the Czech Republic
Institute for Clinical and Experimental Medicine	www.ikem.cz	One of the largest specialized clinical and scientific research centers in the Czech Republic; focus on the treatment of cardiovascular diseases, organ transplants, diabetology, and treatment of metabolic disorders
Masaryk Memorial Cancer Institute	www.mou.cz	Providing complete diagnostics, treatment, and preventive care in oncology; it is the only medical center in the country just focusing on oncology.

Source: EasyLink Business Services and hospital websites, 2013

Ms. Michaela Hanakova, clinical trials start-up manager at Masaryk Memorial Cancer Institute, highlights the extensive experience with carrying clinical trials as the key advantage of using their hospital. In fact, the hospital has its own department of clinical evaluations; their doctors have been carrying clinical trials since early 1990s. The hospital also has their own unit equipped for Phase I trials. Most clinical trials taking place in their hospital are monitored by CROs; she mentioned Novartis as one of the very few, if not the only, pharmaceutical company that has monitored the trials in-house, not contracting a CRO.

20. PRODUCT REGISTRATION

Any proprietary medicinal product is subject to marketing authorization prior to its placement in the Czech market.

The procedure includes an assessment of a dossier (the future marketing authorization holder evidences the safety, efficacy, and quality of the product). Also, the indications, contraindications, dosage of the product, general classification for supply, and the package leaflet for the patient and proposed texts on the labeling of the medicinal products are assessed. The Summary of Product Characteristics (SPC) is a part of the marketing authorization; it serves as the key source of information about the medicinal product for doctors and healthcare professionals[3].

Regardless of where clinical trials are conducted, all clinical trials included in applications for marketing authorization for human medicines in the European Economic Area (EEA) must have been carried out in accordance with the requirements set out in Annex 1 of Directive 2001/83/EC:

- clinical trials conducted in the EEA have to comply with European Union (EU) clinical-trial legislation (Directive 2001/20/EC)
- clinical trials conducted outside the EEA have to comply with ethical principles equivalent to those set out in the EEA, including adhering to international good clinical practice and the Declaration of Helsinki[4]

20.1 Registration authority

The Act no. 378/2007 on Pharmaceuticals stipulates that all drugs (i.e. "medicinal products" as defined by the Czech legislation) imported and marketed in the Czech Republic need to be registered with the State Institute for Drug Control.

Veterinary pharmaceuticals have to be registered with the Institute for State Control of Veterinary Biologicals and Medicines (www.uskvbl.cz).

SUKL is the authority distinguishing pharmaceuticals for human use from other medicinal products.

If a product is not classified by SUKL as a pharmaceutical, the authority does not assess further classification of the product and in disputable cases the concerned responsible institutions (the National Institute of Public Health, the Ministry of Health, and, where applicable – SUKL – Medical Devices Branch) should be addressed.

The most frequent categories of products not classified by SUKL as pharmaceuticals, are dietary supplements, cosmetic products and medical devices.

[3] *Source: SUKL, www.sukl.cz*
[4] *Source: European Medicines Agency, www.ema.europa.eu*

As of January 2008, SUKL also sets the maximum exfactory price and makes decisions on reimbursement of pharmaceuticals (only prices of reimbursed pharmaceuticals are regulated by maximum ex-factory price and/or regressive mark-up scheme). The entities that can apply for price or reimbursement are the marketing authorization holders or insurance funds.

20.2 Types of registration

An applicant for a new marketing authorization (i.e. registration) (the future marketing authorization holder) must be established within the territory of the EU/EEA as well as the manufacturer(s) of the medicinal product who are responsible for batch release.

In 2011, 779 applications were submitted to the marketing authorization department at SUKL after successful validation.

The largest portion of applications (79%) for marketing authorization is generated via the mutual recognition procedure (MRP) and decentralized procedure (DCP) where the Czech Republic is considered a concerned member state. The number of applications for marketing authorization via the national procedure has been gradually decreasing.

Number of applications by registration procedure, Czech Republic, 2011

	2011
National	59
MRP/RMS	13
DCP/RMS	88
CMS (MRP or DCP)	619
Total	*779*
Switch from national to MRP/DCP	2

Note: RMS – Reference Member State, CMS – Concerned Member State, MRP – marketing authorization via mutual recognition procedure, DCP - marketing authorization via decentralized procedure
Source: SUKL, 2013

Various pharmaceuticals require different types of registration, not all types of registration apply to all products!

A U.S. producer of pharmaceuticals and biotechnology products seeking to register a medicinal product in the Czech Republic or other CEE countries should consult a registration specialist (see section 20.4 Key players - companies assisting with registration) to determine which registration procedure is the most appropriate.

National registration cannot be used in cases for which mandatory centralized registration within the EU applies.

Centralized procedure is mandatory for biotechnology products, preparations for oncology, diabetes, AIDS and CNS treatment, and orphan medicines.

According to Mr. Janda, national registration is usually chosen in case of older products where it is not clear that it would be approved in all countries. Generics are often registered via MRP, and the process is done concurrently in 5 to 6 countries.

The registered pharmaceuticals fall into the following categories:

- original
- generic
- medications that have been in the market for a long time (over 10 years in the market)
- herbal pharmaceuticals and homeopathics

20.2.1 National procedure[5]

It is a marketing authorization of a medicinal product only in the Czech Republic, and only where the medicinal product is not authorized in any other EU country.

For national marketing authorization procedure, the timeline for the assessment of generic products is 150 days, for other types of national marketing authorization procedures it is 210 days. The applicant is allowed 180 days to amend shortcomings in the dossier. This period of time is not included in the overall duration of the marketing authorization procedure; the overall time required for the marketing authorization procedure is therefore often longer.

20.2.2 MRP (mutual recognition procedure)[6]

It is based on the principle of the mutual recognition by EU Member States of their respective national marketing authorizations. An application for mutual recognition may be addressed to one or more Member States. The applications submitted must be identical and all Member States must be notified of them. As soon as one Member State decides to evaluate the medicinal product (at which point it becomes the "Reference Member State"), it notifies this decision to other Member States (which then become the "Concerned Member States"), to whom applications have also been submitted. Concerned Member States will then suspend their own evaluations, and await the Reference Member State's decision on the product.

This evaluation procedure undertaken by the Reference Member State may take up to 210 days, and ends with the granting of a marketing authorisation in that Member State. It can also occur that a marketing authorisation had already been granted by the Reference Member State. In such a case, it shall update the existing assessment report in 90 days. As soon as the assessment is completed, copies of this report are sent to all Member States, together with the approved summary of product characteristics (SPC), labelling and package leaflet. The Concerned Member States then have 90 days to recognise the decision of the Reference Member State and the SPC, labelling and package leaflet as approved by it. National marketing authorisations shall be granted within 30 days after acknowledgement of the agreement.

[5] *Source: SUKL*
[6] *Source: European Commission*

Should any Member State refuse to recognise the original national authorisation, on the grounds of potential serious risk to public health, the issue will be referred to the coordination group. Within a timeframe of 60 days, Member States shall, within the coordination group, make all efforts to reach a consensus. In case this fails, the procedure is submitted to the appropriate EMEA scientific committee (CHMP or CVMP, as appropriate), for arbitration. The opinion of the EMEA Committee is then forwarded to the Commission, for the start of the decision making process. As in the centralised procedure, this process entails consulting various Commission Directorates General and the Standing Committee on Human Medicinal Products or the Standing Committee on Veterinary Medicinal Products, as appropriate. The Rules of Procedure of these Committees are here :

20.2.3 Decentralized procedure[7]

As the mutual recognition procedure, it is also based on recognition by national authorities of a first assessment performed by one Member State. It differs in that it applies to medicinal products that have not received a marketing authorisation at the time of application.

An identical application for marketing authorisation is submitted simultaneously to the competent authorities of the Reference Member State and of the Concerned Member States. At the end of the procedure, the draft assessment report, SPC, labelling and package leaflet, as proposed by the Reference Member State, are approved. The subsequent steps are identical to the mutual recognition procedure.

20.2.4 Centralized registration[8]

Except for the three types of registrations above which SUKL is involved in, there is also a centralized registration, a procedure which does not take place at national health authorities in individual Member states. The procedure is carried out centrally at the European Medicines Agency based in the United Kingdom and the registration is then valid in all EU countries. Final statement is provided within 210 days since the validation of the application.

The list of centrally registered medicines can be found on the EMEA website (www.ema.europa.eu).

[7] *Source: European Commission*
[8] *Source: SUKL and EMEA*

20.3 Key legislation for human medicines

The activities of SUKL regarding medicines are primarily defined by the Act no. 378/2007 Coll., on drugs, as amended. Other regulations defining the activities of SUKL include the Act no. 167/1998 Coll., on addictive substance, as amended, the Act no. 160/1992 Coll., on healthcare in non-governmental healthcare facilities, as amended, and the Act no. 40/1995 Coll., on regulation of advertising and on amendment of the Act no. 468/1991 Coll., on radio and television broadcasting, as amended.

The activities of SUKL in the area of prices and payment for drugs are defined by the Act no. 48/1997 Coll., on public health insurance and on amendment of certain related laws, as amended, the Act no. 265/1991 Coll., on competences of authorities of the Czech Republic in the area of pricing, as amended, and the Act no. 526/1990 Coll., on pricing, as amended.

The activities of SUKL in the area of human tissues and cells are defined by the Act no. 296/2008 Coll., on safeguarding quality and safety of human tissues and cells intended for human use and on amendment of the related legislation (the act on human tissues and cells).

The activities of SUKL in the area of medical devices are defined by the Act no. 123/200 Coll., on medical devices and on amendment of certain related legislation, as amended.

20.4 Key players - companies assisting with registration

Product registrations are carried by specialized departments of pharmaceutical companies or companies specializing in product registration. Regulatory consulting is provided by multinational companies as well as local entities that are often very small companies not generally listed in business directories. Therefore, in identifying relevant companies the consultant had to depend on references by experts in the pharmaceutical sector. Below are profiles of selected leading companies assisting with registration.

COMPANY NAME	**4 Life Pharma CZ, s.r.o.**
Address	Ve studenem 1743/8a
Address (city)	Praha 4
Address (ZIP)	147 00
Telephone	+420 244 403 003
Web site	www.4lifepharma.eu
PROFILE	Involved in registration of products and regulatory affairs
Description	Services provided: • Marketing of products • Outsourcing of representatives • Registration of pharmaceuticals 4 LIFE PHARMA LTD. - organizational unit - was established by 4 LIFE PHARMA LTD. (address: Webber Street, SE1 ORE, London) in 2007
Year of establishment	2009
Ownership structure	Limited liability company - Ms. Monika Vonkova - 55% share and Mr. Petr Plocek - 45% share
Number of employees	under 5
Turnover	2011: CZK 29 million (USD 1.6 million) 2010: CZK 21 million (USD 1.1 million)

COMPANY NAME	**A-Pharma s.r.o.**
Address	K Ohrade 528/2
Address (city)	Praha 5
Address (ZIP)	155 00
Telephone	+420 251 081 230
Web site	www.a-pharma.cz
PROFILE	Providing services in the field of clinical trials, registration of pharmaceuticals, data management, biostatistics, quality assurance including GCP auditing, translation of medical texts, GCP training and lectures, and drug safety management
Description	Also active in Slovakia, Hungary, Bosnia, Serbia, and Croatia
Year of establishment	1996
Ownership structure	Limited liability company - Mr. Jindrich Lahovsky and Ms. Jana Lahovska - 50% share each
Number of employees	6
Turnover	Not available

COMPANY NAME	**Archie Samuel s.r.o.**
Address	Slunna 16
Address (city)	Brno
Address (ZIP)	617 00
Telephone	+420 534 008 065
Web site	www.asamuel.cz
PROFILE	Consulting company also involved in regulatory affairs
Description	Focus on • registration of pharmaceuticals, medicinal preparations and food supplements • price and reimbursement procedure • pharmacovigilance
Year of establishment	2005
Ownership structure	Limited liability company: Ms. Jana Prosserova - 100% share
Number of employees	Under 5
Turnover	Not available

COMPANY NAME	**IQ-MED a.s.**
Address	Na Farkáně I, 136/17
Address (city)	Praha 5
Address (ZIP)	150 00
Telephone	+420 774 705 667
Web site	www.iq-med.cz
PROFILE	Pharmaceutical agency
Description	Involved in: • International pricing strategy in EU countries • Regulatory services • Clinical trials • Observational studies • Medical-marketing consulting • Education/training and recruitment in the pharmaceutical industry Registration/regulatory services provided: • Registration of human medical products in the Czech Republic (National Registration, MRP, DCP) • Dossier and handbills arrangement (SPC, PIL) • Professional translations and expertise • Post-registration services • Negotiation of the maximum price with the Ministry of Finance and reimbursement negotiations
Year of establishment	2008
Ownership structure	Joint stock company
Number of employees	Under 5, plus a team of independent consultants
Turnover	2011: CZK 10 million (USD 0.6 million) 2010: CZK 10 million (USD 0.5 million) 2009: CZK 4 million (USD 0.2 million)

COMPANY NAME	**Pharma Consulting – Mačalková Věra**
Address	Na Topolce 1346/3
Address (city)	Praha 4
Address (ZIP)	140 00
Telephone	+420 261 215 952
Web site	www.pharmaconsulting.cz
PROFILE	Regulatory affairs consulting

21. MARKET ENTRY STRATEGY

21.1 Market overview

21.1.1 Market size and breakdown

The Czech pharmaceutical market has been stagnating or slightly decreasing over the past several years, and the trend is expected to continue into near future. The OTC segment has been recently growing by 2 to 3% annually[9]. In the past, the market used to grow by 10% per year.

In 2011, 297 million packages of medicinal products worth almost CZK 59 billion (USD 3.3 billion) in ex-factory price were distributed in the Czech Republic.

In terms of the number of packages sold prescription drugs generate approximately 60% of sales of pharmaceuticals and non-prescription drugs about 40%. In sales values, the share held by prescription drugs reaches almost 90%.

According IMS Health, the number of generic pharmaceuticals sold in the Czech market grew by 75% between 2000 and 2010. The pace of introducing new generics in the Czech market has been accelerating since 2005.

Generics account for 44% of the volume of packages sold, but only one quarter of the expenses on pharmaceuticals. In the category of prescription pharmaceuticals alone, generics make up for a third of the value and 55% of volume of sales in the Czech Republic.

The size of the Czech market with food supplements is estimated at approximately USD 550 million.

21.1.2 Local production

The Czech Republic concentrates mainly production of generics; local producers belong to the leading players not only in Europe, but also around the world.

In 2010, CZK 1.05 billion (USD 59 million) was spent on research and development in this sector in the Czech Republic, 88% of the investment was made by the private sector.

Pharmaceutical production in the Czech Republic is mostly controlled by foreign-owned companies.

There are about 100 producers of pharmaceuticals; in 2011, 21 companies (foreign-owned) generated sales of CZK 23.7 billion (USD 1.3 billion), which accounted for 78% of all the revenues of local producers.

[9] *Media interview with Mr Zidek, general director of local subsidiary of Sanofi*

The number of smaller producers is rather high; they focus on production of a narrow range of generics or biopharmaceuticals. There were 48 producers employing over 20 people in 2011.

Key local producers of pharmaceuticals, Czech Republic, 2013

Company	Website	Profile
Farmak, a.s.	www.farmak.cz	Independent Czech producer of active pharmaceutic ingredients, advanced intermediates and chemical specialties
Lonza Biotec, s.r.o.	www.lonza.com/cz/home	Production of biotech products for the pharmaceutical and food industries
TEVA Pharmaceuticals CR, s.r.o.	www.teva.cz	Subsidiary of Teva Pharmaceutical Industries Ltd; one of top 10 players in the Czech pharmaceutical market
Walmark, a.s.	www.walmark.cz	The leading producer of nutritional supplements in CEE, also offering vitamins and OTC drugs
Zentiva, k.s.	www.zentiva.cz	Generic platform for Sanofi; the third largest and fast growing generics producer in Europe

Source: EasyLink, 2013

The local market is well supplied with global brands; many multinational leaders have established local sales offices in the country.

21.2 Distribution of pharmaceuticals

21.2.1 Distribution structure – key distributors

The list of approved distributors of pharmaceuticals presented by SUKL is quite extensive; it includes producers plus distributors of various sizes, including those distributing just a few products. In 2011, the number of distributors increased by 75 entities reaching a total of **382 medicinal product distribution authorization holders**. Out of the approved distributors, 155 entities are those where a pharmacy operator is also a distribution authorization holder.

Distribution of pharmaceuticals in the Czech Republic has undergone major consolidation since early 1990's. At this time four distributors associated in the Association of Large Pharmaceutical Distributors (www.avel.cz) control the distribution of pharmaceuticals in the country; their combined share is estimated at around 90%. The biggest of the four members alone holds a 44% share. In 1993, AVEL was founded by 13 companies, but after numerous acquisitions and mergers there are now 4 companies left.

Wholesale distributors of pharmaceuticals, Czech Republic, 2013

Company	Website	Profile
ALLIANCE Healthcare, s.r.o.	www.alliance-healthcare.cz	Its market share exceeds 20%; 6 distribution centers throughout the country; dealing with over 600 producers of pharmaceuticals
GEHE PHARMA PRAHA, spol. s. r. o.	www.gehe.cz	The fourth largest pharmaceutical wholesale distributor in the Czech Republic; holding a 17% market share; recently acquired by Penta Investments; 3 distribution centers throughout the country
PHARMOS, a.s.	www.pharmos.cz	The second largest wholesale distributor of pharmaceuticals in the Czech Republic with a 22% market share
PHOENIX lékárenský velkoobchod, a. s.	www.phoenix.cz	The largest wholesale distributor of pharmaceuticals in the Czech Republic; running 6 warehouses throughout the country; its market share is estimated at 44%

Source: Association of Large Pharmaceutical Distributors and company websites, 2013

21.2.2 Key customers – pharmacies and hospitals

There were close to 2,500 pharmacies throughout the Czech Republic in 2012. Out of this four were operated by the Ministry of Defense of the Czech Republic, and there were 243 detached pharmaceutical and medical devices dispensing units, 411 approved medical device dispensaries, 150 vendors of selected medicinal products, 43 nuclear medicine departments of healthcare facilities and 382 distributors of medicinal products.

At the beginning of 2013, the number of brick-and-mortar pharmacies throughout the Czech Republic exceeded 2,700, out of which 200 also operate an e-pharmacy. The leading player in online retail of pharmaceuticals is the e-shop Lekarna.cz.

According to Mr. Jan Rohrbacher, executive director of Alliance Healthcare, the Czech pharmaceutical distribution market is not yet fully saturated, and the market is expected to undergo further consolidation; individual players will be forced to build/create retail chains in order to increase their purchasing power. The following three categories of chains now operate in the market:

- Hard chains – all pharmacies in the chain have the same owner
- Virtual chains – operators of pharmacies retain the ownership, but they associate themselves under one brand (similar to the franchise concept)
- Independent pharmacies – pharmacies of individual owners

Dr. Max, a chain of 270 pharmacies, currently dominates the market; it is owned by Penta, a Central European investment group. Last year, the chain incorporated 55 pharmacies of Lloyds that Penta acquired together with Gehe, a wholesale distributor.

The key countries where pharmaceuticals are imported from include:

- USA – many of the top 10 manufacturers of pharmaceuticals supplying the Czech market are U.S. companies

- Switzerland and the United Kingdom
- Generics are frequently imported from producers located in Poland, Hungary, Slovenia, and Israel

Mr. Jan Rohrbacher predicts the demand for generics to continue growing, as **more pharmacies will be approaching manufacturers to produce generic pharmaceuticals under their private brand!**

Leading chains of pharmacies, Czech Republic, 2013

Company	Website	Profile
Dr. Max	www.drmax.cz	290 pharmacies in over 115 towns throughout the Czech Republic; run by Penta
Alphega	www.alphega-lekarna.cz	179 pharmacies; a part of Alliance Healthcare
Benu	www.benu.cz	140 pharmacies throughout the country; a part of Phoenix

Source: EasyLink, 2013

21.3 End user analysis

Over 60,000 variants of drugs are registered in the Czech Republic; however, only about 8,000 variants are actively traded in the Czech Republic.

A patient can be treated with an unregistered product if it complies with the legislation and it can be supplied via individual import regime, as part of a specific treatment program and as part of a clinical trial.

It is illegal to sell prescription drugs on the Internet. **Only registered OTC products can be sold in eshops that however have to be operated by a brick-and-mortar pharmacy.** Internet sales are rather marginal, generating about 5% of OTC sales in the Czech Republic. Food supplements and diet/weight reduction pills are often purchased in hypermarkets and supermarkets, specialized stores, and pharmacies.

Self-treatment is a common and well-established practice in the Czech Republic, as local consumers seem not to be thrifty in this particular group of products. The spectrum of buyers has changed in that less affluent consumers do not spend as much as they used to.

The Czech Republic belongs to the top 3 countries in Europe in the number of pills of OTC drugs consumed; it is only surpassed by Germany, while Slovakia is the last in the top 3.

In case of OTC drugs and food supplements, the key factor for purchasing is one's experience with the particular product, and local customers are quite loyal to their brand.

The doctors play the key role in deciding what prescription drug shall be selected, a significant number of patients also admit an influence by pharmacists. According to the "Key factors and role of a pharmacist during selection of pharmaceuticals" study by GfK, pharmacists work with a selection of alternatives of prescription drugs in between 34 to 64% of cases/patients. The level of influence depends on the type of disease. Czech patients will select an alternative prescription drug if a higher co-payment applies to the prescription drug selected by the doctor or if it is not on stock in the pharmacy when the patient arrives.

22. ANALYSIS, STRATEGY & CONCLUSION

22.1 Obstacles and challenges

Companies operating at various levels of the Czech pharmaceutical market are subject to a strict and complex regulatory environment, which can be a challenge as well as advantage at the same time. When inquired about problems that sponsors of clinical studies in the Czech Republic face Ms. Stastna, secretary of ACRO-CZ, mentioned that it sometimes took slightly longer to have the studies approved as SUKL requirements seem more stringent compared to the practice in other CEE countries and the application review process being slightly slower.

According to Mr. Janda, ACRO-CZ, in the future the position of the Czech Republic as one of the very top CEE locations for clinical trials could be potentially put under pressure if sponsors are forced to look for cheaper alternatives, leading them to target lower cost countries further East in Europe – especially Belarus, Ukraine or even Georgia. At this time, the legislation pertaining to clinical trials in these countries is not sufficient, and the quality of results is not guaranteed. Carrying clinical trials there requires much closer monitoring to assure the same quality, which leads to extra costs in the end. Their key advantage is the availability of untreated naïve population for certain indications such as hypertension and endocrinology diseases, as there remain many patients who have not been treated at all, while it is rather difficult to find such patients in the Czech Republic. Nonetheless, at this time the undisputed quality of clinical research that the Czech Republic provides and guarantees is well worth the higher initial cost.

22.2 Market potential

Due to the availability of highly qualified providers, positive attitude of participants in clinical trials, and strict legislation pertaining to this field the Czech Republic is expected to remain one of the most sought destinations in the CEE region for carrying clinical trials.

No major shift is expected in the near future when it comes to the number of clinical trials annually conducted and the structure of studies.

The Czech Republic is already a favorite location for **Phase II and III studies** (they combine for **80%** of studies).

Currently, only slightly above 10 Phase I studies are annually applied for in the Czech Republic; several experts interviewed during the course of the project feel that **the country is being rather neglected by foreign sponsors when it comes to Phase I studies despite the fact that the Czech Republic is well prepared and equipped to carry them**.

Ms. Michaela Hanakova, a clinical trials start-up manager at Masaryk Memorial Cancer Institute, pointed out they had a new well-equipped facility for Phase I studies. Their hospital is the only facility in the country specializing entirely in oncology and thus the equipment and facilities are superb. They are now heavily involved in Phase III trials, and those trials are often conducted in 5 to 6 centers throughout the country. In oncology treatment, the Czech Republic is covered by complex oncology centers, which makes recruitment for clinical trials very efficient.

According to Mr. Janda, **the Czech Republic provides an excellent opportunity for carrying bridging studies for U.S. companies that have entered the Russian market to locate production of pharmaceuticals** there after being induced by the Russia's government strategy for encouraging growth in the local pharmaceutical industry for the period of up to 2020. The Russian government shall help local producers to cover the costs of R&D required to boost production of innovative pharmaceuticals. It also aims to create new companies that will be able to attract investment, create new jobs, and produce competitive products. The biotech companies that entered the Russian market are now registering their products in Russia and many companies also want to register the products in the EU. The Czech Republic is in fact a suitable location for carrying the bridging studies as well as for product registration for the EU. Some Czech companies are already collaborating with U.S. companies in this area.

22.3 Route to market

Foreign ownership plays a key role in various areas of the pharmaceuticals sector in the Czech Republic, including clinical trials where the leading role is played by foreign sponsors and global CROs. According to the executive director of the Association of Innovative Pharmaceutical Industry (AIFP), Mr. Jakub Dvořáček, innovative pharmaceutical companies annually invest on average CZK 1 billion (USD 57 million) into R&D in the Czech Republic.

A U.S. producer of pharmaceuticals and biotechnology products seeking to carry a clinical trial or register a medicinal product should **first appoint an in-market specialist** (a CRO or a company assisting with product registration).

In case of outsourcing clinical trials to the Czech Republic the alternatives depend on the type of service required and the number of countries the study should be run in. The sponsor can select:

- **Local CRO**, which will result in cost savings, as **costs for monitoring by local CROs are at about 50% of those charged by local branches of global CROs**.
    - Several local CROs are capable of carrying studies in other CEE countries.
    - It has to be kept in mind that although carrying studies in Russia is almost as expensive as in Western Europe, Russia is very often one of the countries where a multinational multicentric study is carried since in order to be able to register a medicinal product in Russia a clinical study has to be carried there. Czech CROs thus strive to partner up with Russian CROs to have the capability of offering Russia as one of the countries.

- A small number of companies in the Czech Republic can provide full service management and carry all the work and processes associated with clinical trials – e.g. writing a study protocol, having the protocol approved, monitoring the study and then processing its findings and writing a final report.
- Local CROs tend to specialize in a smaller range of therapeutic areas, but usually they will not decline to assist in other areas if asked for collaboration.

- **Global CRO** - Most of the leading global CROs are present in the Czech Republic, or have established partnerships with local CROs to provide the service.
  - One shall expect that local branches of multinational CROs will only be involved in activities pertaining to the study in the Czech Republic.
  - Local branches of global CROs tend not to have the capability to provide full service management for the studies.

HUNGARY

23. CLINICAL TRIALS

23.1 Country attractiveness and challenges

The Hungarian pharmaceutical industry has a century-old tradition; the country is internationally acclaimed for attracting and conducting clinical trials. It is one of the government priorities in healthcare to attract more clinical trials; currently, the country's income from clinical trials reaches around 0.2% of GDP. Hungary is suitable for all types of clinical trials.

According to the "Life sciences in Hungary" brochure by the Hungarian Investment and Trade Agency the benefits of conducting clinical trials in Hungary are as follows:

- Highly motivated and loyal investigators – as the salary level of the medical staff is low and hospitals need external income, it is easy to build up cooperation
- Fast and reliable patient recruitment – as the gatekeeper role of the GPs does not work properly, usually the first physician-patient meeting is on the level of the secondary (rarely tertiary) care in out-patient departments or clinics
- EU-compliant legislation
- Untreated patient populations are widely available as the access to certain expensive medicines is restricted via administrative methods (especially in oncology and in the field of biological therapy: patients need special permission to access, some medicines are only available in certain treatment centers)
- Patients trust physicians and Western medicines
- Outstanding data quality – all healthcare providers have to report all their treatments to the National Health Insurance Fund Administration, it is a routine to collect all necessary data
- Highly educated and well-trained investigators – accredited GCP programs available
- Modern hospital and diagnostics equipment to support complex trials
- Centralized health care systems concentrate large numbers of patients
- High density of well-equipped Phase I study centers
- Local study monitors and CROs are skilled and experienced
- Price advantage: monitoring costs at 60–70% of US prices, investigator and hospital fees 70% below US levels
- Higher incidence of certain disorders (pulmonology, CVD and oncology) than in Western Europe

For tested products (pharmaceuticals) a licence - manufacturing authorization - is needed (according to the EU regulations). In case the tested material contains GMO, then a special permission is required; GYEMSZI-OGYI can issue this license. During a trial a certificate of analysis is needed; in case the regulatory authority requests it the sample of the investigated product should be presented within one day.

According to FDA, in CEE countries inspections revealed 56.9% of NAI (No Action Indicated) clinical trials and 41.1% VAI (Voluntary Action Needed) that could be compared to states with the same amount of trials conducted: UK (33.8% and 63.6% respectively) and Germany (39.3% and 58.9% respectively).

The FDA database currently contains 24 inspection reports from Hungary; of which four are for medical devices. Nine cases of the remaining 20 (45%) were NAI clinical trials; from the 11 VAI trials five were related to Hungarian pharmaceutical manufacturers (EGIS PLC or Gedeon Richter PLC).

23.2 Market size

23.2.1 Number of trials

The regulatory authority - GYEMSZI-OGYI (OGYI) - reviews between **300 and 350 proposals** for clinical studies annually. Due to the fact that a large proportion of the studies are long-term studies, the number of on-going studies is much higher (1,886).

320 clinical studies were authorized in Hungary in 2007; after a moderate decline between 2008 and 2010, which was caused by the fiscal crisis, the number increased to 336 in 2011 and was expected to grow to around 340-350 in 2012.

The most recent data available to the consultant pertaining to the percentage of clinical trial applications rejected by the regulatory authority dates back to 2009 when 4.5% of applications were rejected and 4.2% withdrawn by applicants.

23.2.2 Number of patients

Based on information provided by market experts we estimate that **approximately 10,000 to 20,000 patients** are annually involved in clinical trials in Hungary.

23.3 Structure of studies conducted

23.3.1 By type of study

Approximately **95% of all clinical trials are commercial trials sponsored by** pharmaceutical companies; only 5% of studies are sponsored by academic or professional societies, academic institutions or healthcare facilities mainly from Hungary.

Starting in 2012, non-company sponsored studies were to be organized by the Hungarian Clinical Research Network; however, the network is still being developed.

23.3.2 By phase

Slightly over 50% of trials conducted in Hungary have traditionally been Phase III trials. The shares of Phase I and Phase II studies have been slowly growing. In 2007, 3.4% of clinical trials were Phase I; by 2012, the figure grew to 7.6%. The proportion of Phase II trials increased from 28% to 38% during the same time period.

On the other hand, the proportion of Phase IV trials has been decreasing as the regulation is getting stricter every year; in 2012, they accounted for 3.6%.

Number of approved clinical trials by phase, Hungary, 2007 – Nov. 2012

	2007	2008	2009	2010	2011	2012 (Jan. to Nov.)
Phase I	11	11	14	16	14	25
Phase II	91	94	95	78	97	125
Phase III	180	153	160	179	192	158
Bioequivalence	17	27	23	17	13	7
Phase IV	21	28	21	21	20	12
Total	**320**	**313**	**313**	**311**	**336**	**327**

Source: GYEMSZI-OGYI (OGYI), 2013

23.3.3 By disease

The key therapeutic areas of clinical trials performed in Hungary are **oncology, cardiovascular diseases and CNS** (incl. psychiatry). Biotech research and trials are increasing as well.

OGYI does not publish detailed data pertaining to therapeutic areas. Based on global data sources we estimate that 27% of studies are oncology, 18% CVD and 17% CNS.

Breakdown of clinical trials by phase and therapeutic area, Hungary, Feb. 2013

	Number of ongoing clinical trials	Majority of trials by disease
Phase I	34	Oncology
Phase II	522	Oncology, pulmonology, dermatology, psychiatry, neurology, and cardiovascular diseases
Phase III	1,190	Oncology, pulmonology, dermatology, psychiatry, neurology, and cardiovascular diseases
Phase IV	140	

Source: GYEMSZI-OGYI (OGYI), 2013

23.4 Regulatory information

23.4.1 Regulatory institution

The key authority for authorization of clinical trials for pharmaceuticals is the Directorate of the National Institute for Quality- and Organizational Development in Healthcare and Medicines (GYEMSZI-OGYI).

COMPANY NAME	**Directorate of the National Institute for Quality- and Organizational Development in Healthcare and Medicines**
Address	Zrinyi utca 3.
Address (city)	Budapest
Address (ZIP)	1051
Telephone	+36 1 8869 300
Web site	www.ogyi.hu
PROFILE	The entity falls under indirect control of the Ministry of Health.
Description	Its duties are: • to ensure that all human pharmaceuticals available in the Hungarian market meet appropriate standards of quality, safety, and efficacy • pharmacovigilance • inspections (GCP, GMP, GLP, GDP) • responsibility for methodology (Pharmacopoeia, FoNo, guidelines etc.)
Year of establishment	Tradition going back to 1927
Ownership structure	Government authority
Number of employees	190

23.4.2 Procedure

The approval of clinical trials is regulated at the EU level and is harmonized in member states; however, each country has its own specifics. For example, **there is only one single central ethics committee** - this way there is a single submission mechanism for approvals; also, GYEMSZI-OGYI can issue guidelines that are obligatory for all interested parties.

It is recommended to work with a local CRO or a global CRO with experience in carrying clinical trials in Hungary.

All applications should be submitted to GYEMSZI-OGYI.

Day 0: submission of the application

Validation of the dossier within 5 days after submission

Validation letter (with the list of deficiencies if applicable) is sent to the applicant. The deadline for submission of missing documents is specified in the validation letter. GYEMSZI-OGYI usually provides 15 working days for the applicant to submit the requested supplementary documentation (clock-stop). If the applicant does not reply within the given timeframe, the application will be rejected by the GYEMSZI-OGYI. As soon as the supplementary documentation is submitted, the clock will be restarted.

A copy of the documentation will be sent to the CEC for ethical review and opinion.

During the assessment procedure **questions and comments can be raised** (GNA – Grounds for Non Acceptance or RFI – Request for Further Information) by GYEMSZI-OGYI or CEC. GNA-s or RFI will be communicated with the applicant by GYEMSZI-OGYI or CEC. Deadline for correction is provided in the communication (clock-stop). If the requested information or document arrives in due time, the clock will be restarted. If no adequate response is submitted until the deadline, then the application may be refused by GYEMSZI-OGYI. If necessary, the applicant may request an extension of response time or a suspension of the procedure – in these cases the procedure will be suspended (clock-stop).

The assessment of the documentation will be continued as soon as the response documentation is submitted (the clock will be restarted).

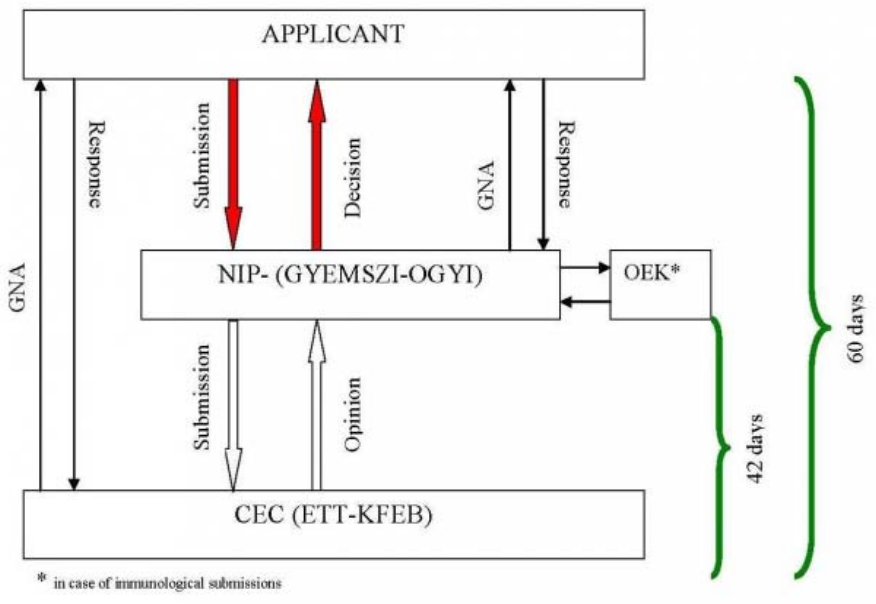
If the documentation is appropriate, questions have been answered properly, and the opinion of CEC is favorable, then GYEMSZI-OGYI provides its approval.

If the documentation is not appropriate or the CEC opinion is not favorable, then GYEMSZI-OGYI rejects the application.

The whole authorisation plus the **approval procedure may last for 60 calendar days** as required by the Medicines Act. However, in case of a deficiency letter, the clock stops. Meeting this deadline the GYEMSZI-OGYI sends the applicant the authorisation/rejection, the first Annex of that is the KFEB opinion.

In case of clinical trials with immunological medicinal products, there is a second co-authority: the National Centre of Epidemiology.

It should be noted that non-interventional trials with IMPs also need authorisation in Hungary. The authority (also acting as ethics committee) is the TUKEB. The procedure may last 45 working days.



Source: GYEMSZI-OGYI (OGYI), 2013

In contrary to e.g. the Czech Republic, **in Hungary the ethical opinion has been centralized**: there **is a single Central Ethics Committee (CEC)** named Committee for Clinical Pharmacology and Ethics of the Medical Research Council (**KFEB**). Its members are appointed by the Minister of Health. This is the only Ethics Committee authorised to approve clinical trial protocols with IMPs. It is a public co-authority: this is a specific Hungarian phenomenon. The opinion of the co-authority (in its field, the ethical approval in the given case) is binding for the decision-making authority. The role of the local (hospital) ethics committees is to safeguard the patients' interest during the trials.

There is **another opportunity to ask for a preliminary opinion of the CEC** (KFEB), and after having the positive opinion to apply to GYEMSZI-OGYI. In this case, when the KFEB (as co-authority) is consulted first – the procedure might take maximum 42 calendar days -, its (positive) opinion has to be added as an amendment to the application to the GYEMSZI-OGYI. The GYEMSZI-OGYI's approval time is going to be decreased with the number of days used by the CEC: in fact, the minimal length of GYEMSZI-OGYI's procedure might be 18 days in this case (in case the CEC used all of its 42 days). The preliminary opinion is valid for 90 days.

The GYEMSZI-OGYI, in agreement with the KFEB, is authorized to issue guidelines ("methodological letters") on clinical trials with investigational medicinal products (e.g. describing when the use of placebo is ethical). Uniquely, KFEB must be subjected to a formal GCP inspection annually performed by GYEMSZI-OGYI.

GYEMSZI-OGYI on its homepage provides the recommended structure for submitting applications. During the procedure **OGYI usually accepts a certificate of analysis of the trial product, but in case of Phase I study they request analytical data of the LOT used in the trial as well**.

Recommended structure of the submission:

- Folder 1: General information – containing cover letter, proof of payment, statement of identity, confirmation of EudraCT number, letter of authorization, application form in xml and pdf format, etc.
- Folder 2: Protocol related – containing final protocol, protocol summary in Hungarian language, signature pages, Scientific Advice, etc.
- Folder 3: Subject related - PIS, ICF, and other patient related documents, etc.
- Folder 4: IMP related - Investigator's Brochure; IMPD, labels in Hungarian language, manufacturing authorizations, certificate of analysis, etc.
- Folder 5: Finance related - insurance, cost division, etc.
- Folder 6: Facilities and Staff related - CVs of principal investigators, site related documents, etc.

The sponsor must possess an indemnity insurance to cover any health issues or other injuries in connection with the trial. The insurance company must be within the European Economic Area.

The fee charged for the entire procedure reaches HUF 580,000 (USD 2,600); it includes the fee for the Central Ethics Committee as well.

The decision of the GYEMSZI-OGYI on authorisation/rejection of a clinical trial application may be challenged in the Court. This applies to the KFEB ethical review as it is annexed to the decision (i.e. formally the GYEMSZI-OGYI decision is challenged).

In case of substantial amendment the approval has to be amended as well. An amendment has to be considered substantial in the following cases:

- It may affect the safety of the trial subjects.
- It may alter the assessment of the scientific documents supporting the trial.
- The sponsor intends to amend the assessment results of the Investigators' Brochure.
- Previous trial results make the amendment of the written patient information necessary.

In this case the procedure takes 22 working days (in case no CEC opinion is needed), in case CEC opinion is needed the CEC has 30 days to decide on the amendment. The fee for the amendment of the approval is HUF 110,000 (USD 500). The amendment of enrolled patients numbers is not a substantial change; in this case the GYEMSZI-OGYI has to be notified.

Clinical trial subjects may receive payment only in bioequivalence, Phase I, non-therapeutic interaction and pharmacokinetic trials, not applicable to children. Otherwise, in Phase II-IV trial payments to subjects are prohibited, the reimbursement of expenses has been confined to loss of income, travel costs and certified costs.

23.5 Key players

23.5.1 Key contract research organizations

Some 60 to 70 contract research organizations operate in Hungary. About 65 to 70% of trials are carried out by multinational CROs; a large number of global CROs (e.g. ICON, Quintiles, Chiltern, PSI or PPD, etc.) already operate in the Hungarian market.

In addition to covering the domestic market some Hungarian CROs offer services in additional countries. Local CROs are often contracted by other CROs abroad to assist with the studies in Hungary. In the past five years there have been radical changes as several local CROs gained the capability to provide the full range of services.

Overview of selected leading contract research organizations, Hungary, 2013

Company	Local vs global	Website	Activities	2011 Turnover (USD million)	Number of employees
Quintiles Magyarország Kft.	Global	www.quintiles.com	Local office of a global CRO	22.4	132
PPD Magyarország Kft.	Global	www.ppdi.com	Local branch of a global CRO	10.6	63
ICON Klinikai Kft.	Global	www.iconplc.com	Local office of a global CRO	9.4	96
Pharmaceutical Research Associates Mo. Kft.	Global	www.prainternational.com	Local office of a global CRO	7.4	69
Hungarotrial Ltd.	Local	www.hungarotrial.hu	It provides services for Phase I through Phase IV clinical trials in Hungary, the Czech Republic, Slovakia, Romania, Serbia, Croatia, Ukraine and Russia	5.1	36
PSI CRO Magyarország Kft.	Global	www.psi-cro.com	Local branch of a global CRO	4.6	32
Bitrial Ltd.	Local	www.bitrial.hu	Expertise in a wide range of therapeutic areas, including oncology, cardiovascular, central nervous system, gynaecology, dermatology, respiratory and allergy / immunology	3.6	21

Company	Local vs global	Website	Activities	2011 Turnover (USD million)	Number of employees
M.E. Trial Masters Ltd.	Local	www.trialmasters.eu	Overall management of Phase II to IV clinical trials in Hungary and Romania	3.5	31
Covance Hungária Kft.	Global	www.covance.com	Local branch of a global CRO	3.4	33
Chiltern International Kft.	Global	www.chiltern.com	Local branch of a global CRO	1.6	3
CPS Cortex Ltd.	Local	www.cortexps.hu/eng	Conducting Phase I-IV clinical trials and non-interventional studies in Hungary and Romania	0.6	7

Source: KIM e-beszámoló

Detailed profiles of the leading local CROs follow below.

A Pennsylvania company seeking to identify a suitable CRO to run a clinical trial in Hungary or other CEE countries shall contact the Authorized Trade Representative in Central Europe with specific requirements and expectations on the partner organization (see section 26.3 Route to market).

The key local CROs include the following companies (turnover and employment data are figures for 2011).

COMPANY NAME	**Bitrial Ltd.**
Address	Fenyes utca 10
Address (city)	Budaors
Address (ZIP)	2040
Telephone	+36 23 444 123
Web site	www.bitrial.hu
PROFILE	Offering a broad range of clinical trial services in the CEE region
Description	• CEE coverage: Bulgaria, Croatia, Hungary, Romania, Serbia, and Ukraine • Expertise in a wide range of therapeutic areas, including oncology, cardiovascular, central nervous system, gynaecology, dermatology, respiratory and allergy / immunology • It offers medical writing as well.
Year of establishment	2005
Ownership structure	dr. Janos Biro (100%)
Number of employees	21
Turnover	HUF 792 million (USD 3.6 million)

COMPANY NAME	**CPS Cortex Ltd.**
Address	Jozsef nador ter 5-6, III. em.
Address (city)	Budapest
Address (ZIP)	1051
Telephone	+36 1 202 47 05
Web site	www.cortexps.hu/eng
PROFILE	Conducting Phase I-IV clinical trials and non-interventional studies in Hungary and Romania
Description	They are able to provide a full range of services.
Year of establishment	2005
Ownership structure	100% - dr. Istvan Boglarka
Number of employees	7
Turnover	HUF 135 million (USD 0.6 million)

COMPANY NAME	**Hungarotrial Ltd.**
Address	Fehervari ut 89-95
Address (city)	Budapest
Address (ZIP)	1119
Telephone	+36 1 203 21 34
Web site	www.hungarotrial.hu
PROFILE	The top CRO in Hungary and one of the CEE region's leading independent CROs It provides services for Phase I through Phase IV clinical trials in Hungary, the Czech Republic, Slovakia, Romania, Serbia, Croatia, Ukraine and Russia
Description	• Three subsidiary companies: HT Research RO S.R.L (Romania), HT Research SK S.R.O. (Slovakia) and HT Research SB D.O.O. (Serbia) • The company offers the full range of services. • Also offering CRA outsourcing
Year of establishment	1999
Ownership structure	Two owners: Lajos Sarosi (95%) and Henriette Sarosi (5%)
Number of employees	36
Turnover	HUF 1,131 billion (USD 5.14 million)

COMPANY NAME	**M.E. Trial Masters Ltd.**
Address	Jozsef A. str. 46.
Address (city)	Budakalasz
Address (ZIP)	2011
Telephone	+36 26 540 620
Web site	www.trialmasters.eu
PROFILE	Overall management of Phase II to IV clinical trials in Hungary and Romania
Description	• The main area of focus are cardiovascular diseases • Has managed combined studies with more than 600 sites and over 10,000 CV patients • Experienced in local trial management
Year of establishment	2000
Ownership structure	Simmers Finance Ltd. (Cyprus) 100%
Number of employees	31
Turnover	HUF 774 million (USD 3.52 million)

23.5.2 Key trial sites – hospitals/universities

Clinical studies are conducted in most hospitals, particularly large university clinics and county hospitals, and in hundreds of outpatient facilities, private as well as state-owned. Altogether there are more than 600 trial sites. Some private providers only specialize in clinical studies.

Selected key trial sites, Hungary

Organization	Website	Profile
Semmelweis University, Budapest	http://semmelweis-egyetem.hu	Trials are carried at different clinics of the university
University of Szeged, Albert Szent-Gyorgyi Clinical Center, Clinical Research Coordination Center, Szeged	www.klinikaikutatas.hu/en	Carrying all phases of clinical studies
University of Debrecen, Department for Clinical Pharmacology, Debrecen	www.deoec.hu/szervezeti_adatlap.aspx?s_id=336&bc=1&web_id=	Phase I-III trials take place in various clinics of the university
Clinical Centre of the University of Pecs, Pecs	www.kk.pte.hu/pages/aloldal.jsf?id=358211	Trials are carried at different clinics of the university
National Institute of Oncology, Budapest	www.oncol.hu	It is the main oncology center in the country – 348 beds, participating in Phase I-III clinical trials
Somogy Megyei Kaposi Mor Oktato Korhaz, Kaposvar	www.kmmk.hu	Almost 7% of trials are performed in this hospital, focus on Phase II-IV trials; access to very good diagnostic imaging background in the Healthcare Centre of the University of Kaposvar (CT, MRI, oncoradiology)

Organization	Website	Profile
Petz Aladar Megyei Oktato Korhaz	www.petz.gyor.hu	This hospital performs almost 7% of trials (phase II-IV)
Drug Research Centre Ltd., Balatonfured	www.drc.hu	Phase I accredited site, conducting Phase I-IV trials; specializing in diabetes, cardiology, and endocrinology
ClinTrial Audit Ltd., Debrecen	www.clintrial-audit.hu	The company carries all phases; a Phase 1 accredited site; also acting as a CRO; currently they are an out-patient provider as well

Altogether 14 Phase I trial sites are accredited by GYEMSZI-OGYI; only Phase I sites have to be accredited.

No accreditation is required for Phase II and Phase III sites; however, they have to meet certain criteria. The principal investigator of a Phase II site is obliged to be specialized in the field of the trial, have a specialization in clinical pharmacology or a valid GCP licence (not older than five years). In case of a Phase III trial a GCP course and license is a must for the principal investigator.

Accredited Phase I trial sites, Hungary, 2013

Center	Principal Investigator	Validity of Accreditation
Debreceni Egyetem Orvos- es Egeszsegtudomanyi Centrum I. szamu Belklinika es Klinikai Farmakologiai Tanszek	Dr. Peter Kovacs	04.29.2013
DRC Gyogyszervizsgalo Kozpont Kft.	Dr. Eva Peterfai	08.31.2013
Pecsi Tudomanyegyetem Orvos-es Egeszsegtudomanyi Centrum I. Belgyogyaszati Klinika, Klinikai Farmakologiai Osztaly	Dr. Tamas Habon	11.31.2013
Orszagos Onkologiai Intezet, Kemoterapia C es Klinikai Farmakologiai Osztaly	Dr. Lajos Geczi	08.31.2013
Fovarosi Onkormanyzat Szent Imre Korhaza, I. Belgyogyaszati Osztaly	Dr. Istvan Kiss	11.01.2013
Semmelweis Egyetem Altalanos Orvostudomanyi Kar, I.sz. Belgyogyaszati Klinika, Klinikai Farmakologiai Reszleg	Dr. Judit Kapocsi	05.31.2015
Budai Irgalmasrendi Korhaz, Klinikai Farmakologiai Reszleg	Dr. Bernadette Rojkovics	10.15.2015
Szegedi Tudomanyegyetem, I.sz. Belgyogyaszati Klinika	Dr. Andrea Tiszai	12.01.2015
Semmelweis Egyetem AOK, II.sz. Gyermekgyogyaszati Klinika	Dr. Gyorgy Fekete	06.15.2014
Kenezy Korhaz Rendelointezet, Klinikai Farmakologiai, Infektologiai es Allergologiai Intezet	Dr. Istvan Varkonyi	06.15.2014
Orszagos Onkologiai Intezet B Belgyogyaszati-Onkologiai es Klinikai Farmakologiai Osztaly	Dr. Istvan Lang	04.15.2015
PRA Magyarorszag Kutatasi es Fejlesztesi Kft.	Dr. Istvan Udvaros	02.15.2014
Dr. Kenessey Albert Korhaz-Rendelointezet	Dr. Anna Altmann	11.15.2014
Pecsi Tudomanyegyetem Klinikai Kozpont Szivgyogyaszati Klinika	Dr. Attila Cziraki	04.20.2015

24. PRODUCT REGISTRATION

24.1 Registration authority

GYEMSZI-OGYI is also the registration authority; it is experienced in handling all types of registrations. According to some experts the actual registration procedure might take longer than stipulated in the legislation.

24.2 Types of registration

The two leading types of marketing authorization/registration applicable for Hungary are decentralized procedure and MRP (mutual recognition procedure) where Hungary is a CMS (concerned member state).

The national registration procedure plays an important role as well. It is often used by Hungarian manufacturers of branded generics. It is suitable for products that will be marketed only in Hungary.

Number of applications by registration procedure, Hungary

		Number of new enquiries	Number of registrations
National registration		173	168
MRP	as RMS	4	10
	as CMS	221	188
Decentralized procedure	as RMS	98	55
	as CMS	692	463
Centralized registration	as rapporteur	2	1
	as co-rapporteur	2	5

Source: GYEMSZI-OGYI, 2009 (this is the most recent data published by the institution)

24.2.1 National registration

National procedure in case of a new application proceeds as follows:

- **Day 0**: the procedure starts with the submission of the application
- **Validation letter** (deficiencies of the documentation) is sent to the applicant – the clock is stopped – the GYEMSZI-OGYI provides 15 days for the applicant to submit the requested supplementary documentation. If the applicant does not reply in time the application will be refused in an official decision.
- As soon as the supplementary documentation is submitted, the clock will be restarted.
- **Day 90**: the comments concerning the documentation from the assessors are sent to the applicant. The applicant has to submit the response documents in 15 days. If the applicant does not reply in time, the application will be refused by the GYEMSZI-OGYI in an official decision.

- If necessary, the applicant may ask for more time: this means that the procedure will be suspended, and the clock will be stopped.
- The assessment of the documentation will be performed as soon as the response documentation is submitted (the clock will be restarted after the possible suspension).
- If the documentation is not appropriate, GYEMSZI-OGYI will refuse the application in a decision.
- **Day 210**: issuing the Marketing Authorization

24.2.2 MRP (mutual recognition procedure)

The mutual recognition procedure is to be used in order to obtain marketing authorizations in several member states if the medicinal product in question has received a marketing authorization in at least one member state at the time of application. Hungary mostly acts as a CMS.

- **DAY -14 – DAY 0:** validation period: it starts when the procedure is entered into the CTS (Communication and Tracking System), and the documentation and the Assessment Report prepared by the RMS has been received by the CMSs
- **DAY 0**: it starts when every CMS has validated the documentation (every deficiency has been supplied)
- **DAY 50**: the CMSs send their comments
- **DAY 60**: the applicant sends the response to the comments
- **DAY 75**: the CMSs send their comments
- **DAY 80**: the applicant sends the response to the comments
- **DAY 85**: the CMSs send their comments
- **DAY 90**: if there is a consensus, the RMS closes the procedure – otherwise the case is referred to the CMDh (Coordination for Mutual Recognition and Decentralized Procedure)
- The applicant submits the Hungarian SmPC, PIL and Labeling, and starts the national phase of the procedure.

24.2.3 Decentralized procedure (DCP)

Hungary may act as:

- the Reference Member State (RMS): the documentation submitted is primarily assessed by GYEMSZI-OGYI
- a Concerned Member State (CMS): the documentation submitted is simultaneously assessed by all competent authorities – on the evidence of the (Preliminary) Assessment Report prepared by the RMS

During the decentralized procedure from all Member States of the EEA **Hungary is chosen by the applicant to act as Reference Member State**, and accordingly the documentation that has been primarily approved by GYEMSZI-OGYI will be - besides continuous consultation - assessed by the other Member States simultaneously.

The procedure in details:

- **Day -14 - Day 0**: validation period – it starts when the procedure appears in the CTS (Communication Tracking System) and the documentation has been submitted to GYEMSZI-OGYI
- **Day 0**: Assessment Step I starts (the validation issues have to be solved by this time)
- **Day 70**: the Preliminary Assessment Report (PrAR) is sent by the Reference Member State (RMS) to all Concerned Member States (CMS)
- **Day 100**: CMSs send their comments to the RMS
- **Day 105**: clock-stop – the procedure is stopped temporarily; the applicant receives the RSI – Request for Supplementary Information document
- Clock-off period: during this period the applicant has to prepare the response document
- **Day 106**: it is decided by the RMS when the applicant's response document is considered to be satisfying
- **Day 120**: the procedure may be closed if there are no more comments from the CMSs' side (a consensus has been reached)
- If there is no consensus reached:
- **Day 120**: Assessment Step II starts, Draft Assessment Report (DAR) is sent by the RMS to all CMSs
- **Day 145**: CMSs send their comments to the RMS
- **Day 150**: the procedure may be closed if there are no more comments from the CMSs' side. In case of a consensus, the Final Assessment Report (FAR) is sent by the RMS to all CMSs
- If there is no consensus reached:
- the remaining questions are sent to the applicant by the RMS, the applicant submits supplementary responses to the RMS
- **Day 180**: the RMS prepares a short report and forwards it to all CMSs
- **Day 205**: CMSs send their final comments
- **Day 210**: the procedure may be closed if there are no more comments from the CMSs' side (a consensus has been reached), otherwise the procedure will be referred to the CMDh (Coordination Group for Mutual Recognition and Decentralized Procedure)
- **30-day-long national phase** starts when the applicant submits Hungarian translations of the final Summary of Product Characteristics, Patient Information Leaflet and Labeling.

The applicant chooses a country from the Member States of the EEA to be the Reference Member State – the competent authority of this country will primarily approve the documentation of the new application. All other Member States, just as Hungarian GYEMSZI-OGYI involved in the procedure will simultaneously assess the documentation besides continuous consultation.

The procedure in details:

- **Day -14- Day 0**: validation period – it starts when the procedure appears in the CTS (Communication Tracking System) and the documentation has been submitted to GYEMSZI-OGYI
- **Day 0**: Assessment Step I starts (the validation issues have to be solved by this time)
- **Day 70**: the Preliminary Assessment Report (PrAR) is sent by the Reference Member State (RMS) to all Concerned Member States (CMS)

- **Day 100**: CMSs send their comments to the RMS
- **Day 105**: clock-stop – the procedure is stopped temporarily; the applicant receives the RSI Request for Supplementary Information document
- Clock-off period: during this period the applicant has to prepare the response document
- **Day106**: it is decided by the RMS when the applicant's response document is considered to be satisfying
- **Day120**: the procedure may be closed if there are no more comments from the CMSs' side - a consensus has been reached.
- If there is no consensus:
- **Day120**: Assessment Step II starts, Draft Assessment Report (DAR) is sent by the RMS to all CMSs
- **Day145**: CMSs send their comments to the RMS
- **Day150**: the procedure may be closed if there are no more comments from the CMSs' side - a consensus has been reached, and the Final Assessment Report (FAR) is sent by the RMS to all CMSs.
- If there is no consensus reached:
- The remaining questions are sent to the applicant by the RMS, the applicant submits supplementary responses to the RMS
- **Day180**: the RMS prepares a short report and forwards it to all CMSs
- **Day205**: CMSs send their final comments
- **Day210**: the procedure may be closed if there are no more comments from the CMSs' side - consensus, otherwise the procedure will be referred to the CMDh (Coordination Group for Mutual Recognition and Decentralized Procedure)
- **30-day-long national phase starts** when the applicant submits Hungarian translations of the final Summary of Product Characteristics, Patient Information Leaflet and Labeling.

24.2.4 Centralised registration

Except for the three types of registrations above which GYEMSZI-OGYI is involved in, there is also a centralized registration, a procedure that does not take place at the national health authorities in individual Member States. The procedure is carried out centrally at the European Medicines Agency based in the UK and the registration is then valid in all EU countries. The list of centrally registered medicines can be found on the EMA website (www.ema.europa.eu).

The final statement is provided within 210 days after the validation of the application.

24.3 Key legislation for human medicines

Clinical trials are regulated by the following legislation:

- 95th Act of 2005 on the medicines for human use and on the modification of other Acts regulating the pharmaceutical market, Articles 3 and 21 (as amended)
- 154th Act of 1997 on health-care, Articles 157 – 164 (as amended)
- 140th Act of 2004 on the general rules of public authority procedures and services (as amended)

- Decree No 235/2009 (20 October 2009) of the Government on the rules governing authorization procedures of biomedical research, clinical trials with investigational medicinal products for human use as well as with medical devices intended for clinical trials
- Decree No 35/2005 (of 26th August 2005) of the Minister of Health on the clinical trial of investigational medicinal products for human use and on the application of good clinical practice (as amended)
- Decree No 23/2002 (of 9th May 2002) of the Minister of Health on biomedical research on human subjects (as amended)
- Decree No 34/2003 (of 7 June 2003) of the Minister of Health, Social and Family Affairs on the Medical Research Council (as amended)
- Decree No 14/1998 (of 11 December 1998) of the Minister of Health on the hospital ethics committees
- Decree No 50/1996 (of 27 December 1996) of the Minister of Welfare on the fees payable for administrative and authoritative procedures of the welfare area
- Oviedo Convention: Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine
- Decree 35/2005 (VIII. 26.) of the Minister of Health on the clinical trial and application of correct clinical practices of investigational medicinal products intended for use in humans. (ICH-GCP)
- COMMISSION DIRECTIVE 2003/94/EC of 8 October 2003 laying down the principles and guidelines of good manufacturing practice in respect of medicinal products for human use and investigational medicinal products for human use – in Hungarian legislation the Decree 44/2005 of the Minister of Health adopts this directive

24.4 Key players - companies assisting with registration

Many companies offer assistance with registration of pharmaceuticals in Hungary; some mainly assist just with translation. The following companies are well-experienced in registration dealings:

COMPANY NAME	**Euromedline Kft.**
Address	Gvadanyi u. 15.11/A fszt. 2
Address (city)	Budapest
Address (ZIP)	H-1144
Telephone	+36 1 220 6710 mob: +36 30 944 7759
Web site	www.euromedline.hu
PROFILE	Involved in registration
Description	Providing comprehensive regulatory services and consultancy for companies in the pharmaceutical industry
Year of establishment	2005
Ownership structure	Private owned: Dr. Ferenc Endrenyi 80% and Ms. Andrea Endrenyi 20%
Number of employees	One permanent employee
Turnover	2012: HUF 9.3 million (USD 41,300)

COMPANY NAME	**QualipharmaCon Kft.**
Address	64-66 Robert Karoly krt.
Address (city)	Budapest
Address (ZIP)	H-1334
Telephone	+36 1 237 0283, mobile: +36 30 211 0337
Web site	www.qualipharmacon.hu
PROFILE	Extremely experienced staff (former high level GYEMSZI-OGYI employees) with in depth knowledge of the regulatory framework
Description	Providing comprehensive regulatory services and consultancy for the pharmaceutical industry
Year of establishment	2011
Ownership structure	Private owned by two people
Number of employees	Two permanent employees and about 20-25 external contractors - experts in various fields
Turnover	2012: HUF 25 million (USD 111,000)

COMPANY NAME	**Pro-Pharma'93 Pharmaceutical Consulting Institute Ltd.**
Address	Magyar Jakobinusok tere 4/B. III.3.
Address (city)	Budapest
Address (ZIP)	H-1122
Telephone	+36 1-231-80-60, +36 1-369-02-80
Web site	www.propharma.hu
PROFILE	Offering services related to registration
Description	Covering all areas of drug development and regulatory affairs including preclinical and clinical projects
Year of establishment	1993
Ownership structure	Private owned
Number of employees	Four permanent employees
Turnover	2011: HUF 48.2 million (USD 214,000)

25. MARKET ENTRY STRATEGY

25.1 Market overview

25.1.1 Market size and breakdown

The healthcare expenditures in Hungary reached HUF 2,013 billion (USD 10 billion) in 2011, and decreased to HUF 2,003 billion (USD 8.9 billion) in 2012; it translated into a 0.5% drop in local currency, but a 10.8% decrease in US dollar terms.

The expenditures on pharmaceuticals declined from HUF 691.61 billion (USD 3.44 billion) in 2011 to HUF 608.22 billion (USD 2.71 billion) in 2012 (down by 12.1% in local currency and 21.2% if calculated in USD). The decline resulted from the restriction of the pharmaceutical budget as a consequence of the convergence program; Hungary as an EU member state was obliged to decrease its government deficit to 3%. The budget for pharmaceutical reimbursements was cut in 2011 and 2012 (by almost 40%); for 2014-2016 the level of drug expenditure of the National Health Insurance Fund Administration is expected to be maintained.

The National Health Insurance Fund (in Hungary, there is a single insurance model, it is like the British system) uses almost all control knobs to manage drug expenditures: from rebates to volume contracts. The 2007 Drug Economic Act established that pharmaceutical companies were required to pay as a contribution to the nation's health care budget an amount equal to 12% of the reimbursement based on the manufacturer price levels to the Tax Authority. A medical representative fee was also reintroduced on February 15, 2009, in the amount of HUF 0.4 million (USD 1,820) per month per representative. Amendments to the legislation with effect from July 1, 2011, elevated the 12% tax to 20% while the medical representative fee was doubled to HUF 0.8 million (USD 3,640) per month per representative.

A real challenge for manufacturers was the implementation of preferred reference pricing (range of 10 percent above the reference price for both active substance reimbursement and therapeutic reimbursement groups) with any failure to keep the price within the preferred range resulting in a 15 percent reduction in the reimbursement amount, this has been combined with a "blind" bid system (manufacturers' price proposals have to be submitted to National Health Insurance Fund Administration without knowing the others' price offers).

Another challenge was/is the introduction of an international reference pricing system - with a 20 percent ceiling above the average of the three lowest prices of a given manufacturer applied in any of the EU countries to retain reimbursement status. The market entry in Hungary is difficult as well: for innovative medicines the market entry is only possible with a volume contract, but both the Ministry of Finance (current name: Ministry for National Economy) and Ministry of Human Resources (responsible for health issues) have to agree. **Hungary is considered to be a country where only a delayed market entry is possible.**

On June 18, 2012, the Hungarian Parliament approved a new measure referred to as the Spanish model. Drug manufacturers are required to pay a 10 percent rebate based on the retail price of the product (excluding reimbursement), with effect from August 1, 2012, in the case of such reimbursed products that have been marketed for a period of at least 6 years with a retail price exceeding HUF 1,000 and that face no current generic competition. Roughly 1,600 drugs are impacted by this measure.

Effective August 1, 2012, the wholesale margin for reimbursed drugs was reduced by regulation; the resulting difference is being allocated to retailers.

25.1.2 Local production

In Hungary 91 companies have a manufacturing license issued by GYEMSZI-OGYI; out of which around 30 are owned by foreign companies. 27% of pharmaceutical expenditures (USD 0.7 billion in 2012) goes to Hungarian manufacturers (their market share when calculated in packages reaches around 40%). 80% of the income of local manufacturers is generated from exports.

The key local manufacturers are Gedeon Richter PLC, EGIS PLS (ATP Servier is the majority shareholder, with 51%), TEVA Magyarorszag PLC (owner of BIOGAL Co.) and Chinoin PLC (Sanofi). Both Richter and Egis focus on biosimilars. Richter's specialty is gynaecology, as 31% of its pharmaceutical sales come from this specialization.

According to the estimate of Szazadveg Economic Research Ltd., the companies manufacturing in Hungary generate 3.7% of the national GDP.

25.2 Distribution of pharmaceuticals

25.2.1 Distribution structure – key distributors

Parties involved in wholesale activities pertaining to medicines for human use in Hungary (including wholesale of active substances and medicinal products) have to have a valid wholesaling authorization for medicines issued by GYEMSZI-OGYI; some companies with a valid manufacturing authorization for medicinal products are wholesale dealers of medicines. Altogether 118 companies hold the wholesale license.

In Hungary the market share of the key three distributors (Hungaropharma, TEVA, and Phoenix) reaches around 90%.

Besides the three largest players four other companies are members of the Hungarian Association of Pharmaceutical Wholesalers (www.php-gynsz.hu) that represents the interests of full-line pharmaceutical wholesale operators; they can be considered a lobby organization. The joint market share of all 7 members reached 98% in 2010.

Key distributors of pharmaceuticals, Hungary, 2013

Company	Website	Profile
Euromedic Trading	www.euromedic-hungary.com	Full-scale hospital wholesaler; supplying institutional and retail pharmacies in hospitals
Hungaropharma Plc.	www.hungaropharma.hu	Owned by Hungarian manufacturers (Gedeon Richter, EGIS and Beres); it is the largest distributor; supplying mainly pharmacies
PHOENIX Pharma Ltd.	www.phoenix.hu	Wholesale of pharmaceuticals, focus on supplying pharmacies
TEVA Hungary PPLC Humantrade	www.teva.hu	It supplies both hospitals and pharmacies

Source: EasyLink Business Services and company websites, 2013

25.2.2 Key customers – pharmacies and hospitals

The hospital sector is centralized; most hospitals (approximately 140) are owned and run by the state, and GYEMSZI is responsible for their operation. Only 9 hospitals are not state-owned; their owners are churches, foundations or private people.

The unpaid debt of the hospital sector is high, reaching around HUF 70-130 billion (USD 300-590 million); the lower figure is the government estimate, the higher is the market estimate.

There are 2,360 public pharmacies and 118 hospital pharmacies (hospitals must have a hospital pharmacy which cannot sell to patients, but most of them have opened their pharmacies to the public as well), plus there are 670 branch pharmacies (it has to be a satellite of a public pharmacy, a public pharmacy can have a maximum 3 branches) and 270 dispensing pharmacies (general practitioners can dispense medicines, with prior authorization, but only in case when there is no public or branch pharmacy in the community). The general sales of some medicines (approximately 500 OTCs; the list is available on GYEMSZI-OGYI website) are possible as well; the number of licensed sites reaches around 500 (most of them are gasoline stations).

As of January 1, 2014 a pharmacist has to own at least a 25% share of the company operating the pharmacy. Pharmacies (the business association operating it) has to be owned by pharmacists; opening a new pharmacy is restricted – different regulations act as the barriers of entry (minimal distance from the closest pharmacy is regulated, number of inhabitants etc.). Only public pharmacies can run an e-pharmacy (currently only 19 pharmacies are running one), but as e-prescription has not been introduced yet only prescription-free products (OTC and some medical devices) are available via e-pharmacy. Home delivery is regulated as well; the delivery of medicines from pharmacies has to be performed by the staff of the pharmacy.

20-25% of pharmacies are in the red, mainly due to the decreased public expenditures, low margins and blind bid system.

Most pharmacies do not maintain any stock of prescription medicines or just a very low quantity.

25.3 End user analysis

According to IMS data co-payment after reimbursed medicines amounted to around HUF 120 billion (USD 533 million) and private expenses to around HUF 107 billion (USD 475 million) in 2011.

71% of patients are content with pharmacy services, although the lack of stockpiling (due to fiscal pressure pharmacies do not stock expensive medicines) makes it quite usual that patients have to return to pharmacies for their medicine. As discussed above general sales of some OTC medicines are possible, but only 11% of the population are using this option.

The generic substitution is preferred both on the GP and pharmacy level, the therapeutic adherence of patients in cases where more generics are available is poor. This is the consequence of the preferred reference pricing program of the National Health Insurance Fund Administration – a pharmacist is obliged to inform the patient about the retail prices of preferred medicines (he/she has to document it as well). Medicines not included in the preferred circle receive lower reimbursement; it means they are more expensive. Due to the generic program the price competition is the main trigger factor of the Hungarian pharmaceutical market, as due to regulated retail prices there is no price competition at the pharmacy level.

The access to some medicines (especially biological drugs) is restricted: they are available only at some healthcare providers, the access is regulated with financial protocols, and patients cannot buy them in pharmacies.

A main issue in Hungary is the compliance of chronic patients; "drug-holiday" is usual, according to estimates non-compliance and non-persistence reaches on average around 50-60% after the first year of treatment.

The market of homeopathic medicines is increasing intensely; especially younger people buy them. According to IMS data and other sources the size of this market can amount to around HUF 2.5 billion (USD 11.1 million).

The size of the vitamins and food supplements market has been estimated at HUF 19-20 billion (USD 84-89 million).

26. ANALYSIS, STRATEGY & CONCLUSION

26.1 Obstacles and challenges

Although Hungary is cost competitive against the U.S., carrying clinical trials in Hungary is more expensive than in several other CEE countries (e.g. Ukraine or Romania). However, higher costs are well compensated by good quality data (the early FPFV and the rapid enrolment (over-enrolment) data).

In Hungary all medical activities performed in the framework of a clinical trial such as examinations and therapies have to be financed from the trial budget. In the financing system all patients participating in a trial have to be considered trial patients; split financing between the sponsor and insurance fund is not possible.

Another price elevating factor is the pricing policy of diagnostic imaging providers; the prices of imaging range between those charged in Germany and Poland. As the providers are mostly owned by private business associations, they bill extreme amounts for diagnostic imaging. A Hungarian CRO, knowing the prevailing prices, can prevent these extra costs.

In some countries a key driver for performing clinical trials might be the future reimbursement. In Hungary – independently of the trial site – the entry rules for the reimbursed medicines market are quite strict. Pricing expertise is a must in Hungary; health technology assessment has to prove the cost effectiveness of a medicine.

A language barrier during communication with other staff participating in a clinical trial is another challenge; this can be solved with hiring a local CRO or CRA outsourcing.

26.2 Market potential

As the Hungarian government supports clinical trials, we can expect an elevation in the number of trials in the following years. The government intentions are present in the reimbursement rules as well. Manufacturers can get a reduction from their payment obligations to the National Health Insurance Fund Administration (i.e. rebate, promoter fee, etc.) in respect to the costs of research and development carried out affecting the healthcare services sector, provided that these expenditures exceed 15% of the social security subsidy paid for the subsidized medicinal products supplied by the marketing authorization holder relative to output prices (import prices).

There is a governmental plan to develop trial sites (via allocation of resources) as part of the framework of the next EU operational program period (2014-2020).

26.3 Route to market

As the first step in case of interest in carrying a clinical trial in Hungary a contract research organization (local or global) already active in Hungary should be appointed; in-depth knowledge of the Hungarian legislative and administrative environment is essential. Although Hungary follows the EU directive in approval of clinical trials, the country like all other EU members has some special expectations and requirements.

In Hungary monitoring costs are at 60–70% of U.S. prices, and investigator and hospital fees 70% below U.S. levels.

Some CROs offer a full range of services: from planning a clinical trial to the registration of the medicine. The number of medical writers is low, most of them are freelancers; this aspect has to be covered in the contract with the CRO. During registration other experienced companies can assist the sponsor.

POLAND

27. CLINICAL TRIALS

27.1 Country attractiveness and challenges

Poland occupies the tenth position in the world in terms of the number of clinical studies; it is the second largest market in Central and Eastern Europe in terms of clinical trials annually started; it is only surpassed by Russia. Both the number of patients involved and number of clinical centers where trials are conducted still show potential for significant growth; Poland still falls behind the Czech Republic and Hungary in terms of the number of trials per 1 million people.

PMR Research estimates that in 2011 the Polish clinical trials market reached PLN 746 million (USD 259 million), up 7% compared to 2010.

Key drivers of the clinical trials market in Poland are the size of the population, effective patient recruitment, high quality of research and quality and experience of the medical staff. Because of the size of Polish population the country often attracts trials requiring large number of patients.

The prevailing number of clinical trials is sponsored by pharmaceutical companies, while the biotechnology sector still belongs to rather emerging areas of the industry in Poland.

Sponsors of many trials going on in Poland require multinational cooperation. Some Polish CROs have branch offices in other CEE countries (especially in the Czech Republic and Slovakia, and also in Germany or Ukraine). Others often work as contractors/subcontractors cooperating with other local CROs, having a wide network of contacts and business relations.

No separate license is required for drugs used during trials. Once the consent from the URPL (governmental registration body) is obtained, the President of URPL issues a special permission for drug import.

Companies that cooperate with CROs in other CEE countries claim that carrying clinical trials in Poland is less expensive than in the Czech Republic; it is comparable to costs in Russia, but it is more expensive compared to Hungary, Ukraine, or Bulgaria. All CROs contacted during the course of this project declined to provide even rough quotes of total costs of carrying a clinical trial in Poland as they vary significantly case by case; they depend on many factors such as the number of patients, therapeutic area, phase, treatment etc.

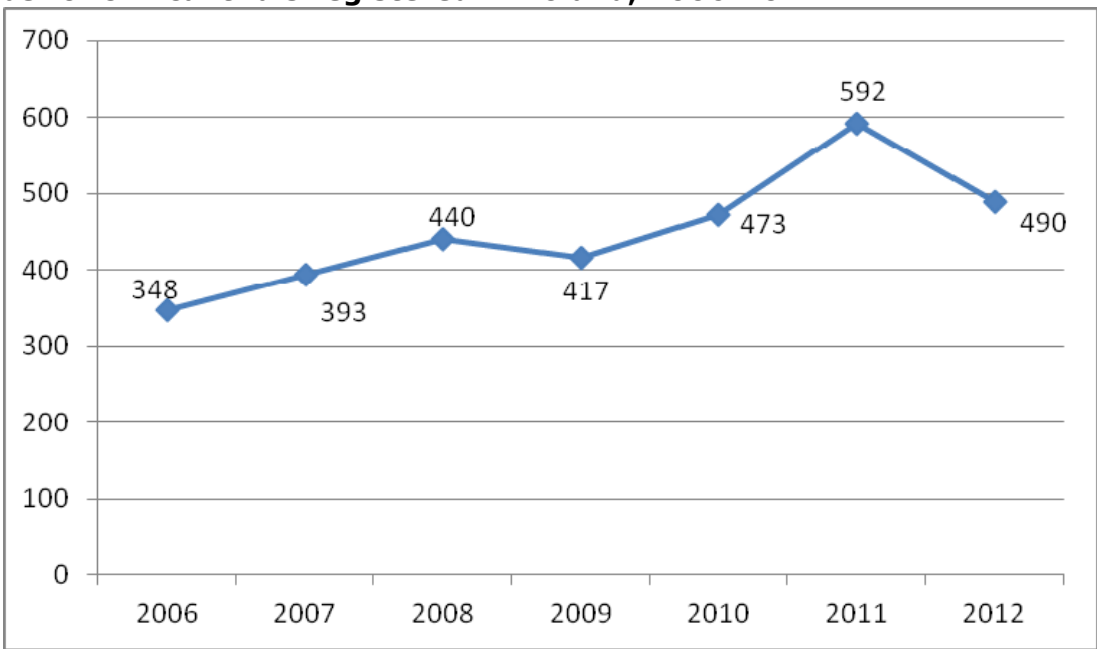
Between January 2009 and September 2012, FDA carried out 42 drug and biotech inspections in Poland. 25 of them (60%) resulted in status NAI "No Action Indicated". Only 1 inspection required obligatory improvement action (FDA's OAI – Official Action Indicated). During the same time period FDA's inspections in Germany achieved only 42% NAI, while in the UK NAI cases reached 41% and in USA 52%. It is also worth noting that none of Polish researchers is included on the FDA's black list.

27.2 Market size

27.2.1 Number of trials

The Polish clinical trials market is relatively saturated, and thus experts do not expect very dynamic increases. In 2012-2013, the growth can reach 3-4% year-on-year. Every year the Polish governmental register records **approximately 450 new clinical trials**, which represents approximately 3% of all new studies registered in the world. According to Pricewaterhouse Coopers the number of clinical trials in Poland has been increasing on average by 1.8% per year since 2003. The most dynamic rise was observed in 2011, when the number of newly registered clinical trials reached almost 600.

Number of clinical trials registered in Poland, 2006-2012



Source: Clinical trials database by WHO, 2013

27.2.2 Number of patients

Every year **30,000-40,000 patients** participate in clinical trials in Poland.

Between 2005-2008, Poland recruited 4.4% of all patients participating in clinical trials in Europe (placing second after Germany with a 6.3% share). The number of patients per one trial reached on average 130-140.

27.3 Structure of studies conducted

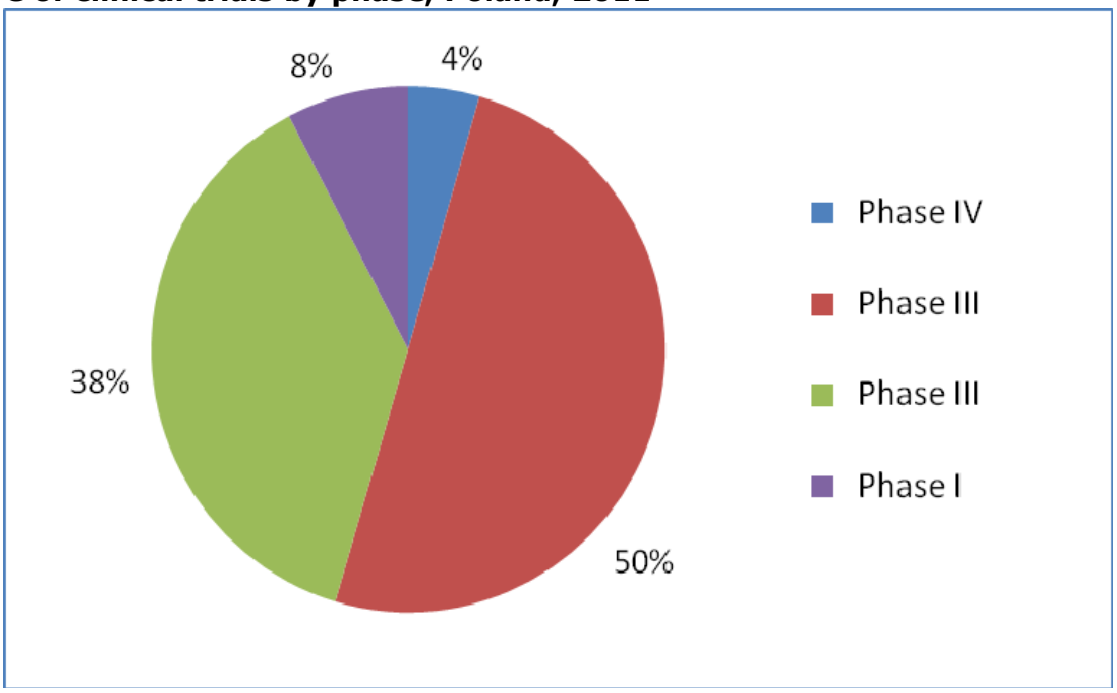
27.3.1 By type of study

90-95% of trials are carried by private companies, as public research institutes/universities very often cannot afford to run clinical trials independently due to tight budgets and rising costs of clinical trials.

27.3.2 By phase

About 50% of trials carried out in Poland are Phase III; Phase II studies now account for 38%. Market experts concur that Phase III trials will undisputedly remain dominant; in the medium term, the share of Phase II trials should increase only moderately.

Share of clinical trials by phase, Poland, 2011



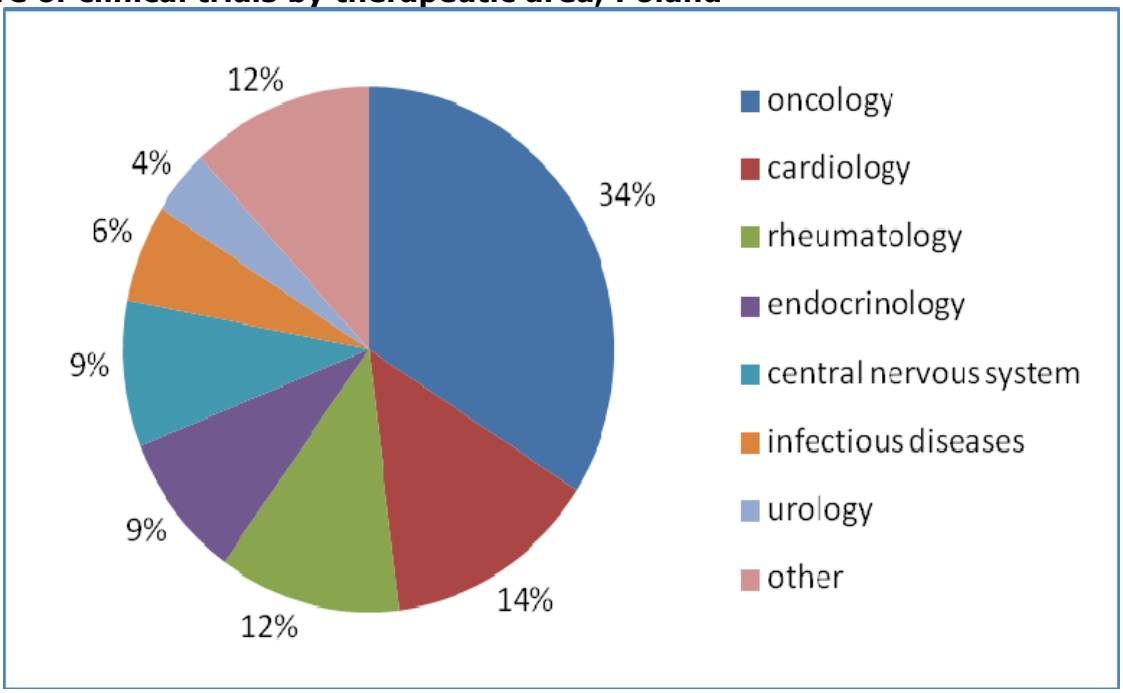
Source: Clinical Research in Poland, Pricewaterhouse Coopers, 2011

Phase IV studies are expected to be increasingly transferred from mature markets (such as Western Europe and USA) to CEE. However, so far the number of trials in this phase records the largest decline. As for the early phases of clinical trials, the Polish market is seen as less developed, despite Poland's large population and efficient recruitment of patients.

27.3.3 By disease

In Poland, most clinical trials are carried out in the field of oncology and cardiology. More than one third of patients participating in clinical trials in Poland are cases of cancer. Other leading therapeutic areas include rheumatology and immunology.

Share of clinical trials by therapeutic area, Poland



Source: Clinical Research in Poland, Pricewaterhouse Coopers, 2011

In the oncology field, Poland is a suitable destination for clinical trials because it is relatively easy to find patient cases with more advanced stages of cancer compared to Western European countries or USA.

27.4 Regulatory information

27.4.1 Regulatory institution

The Office for Registration of Medicinal Products, Medical Devices and Biocidal Products (URPL – www.urpl.gov.pl) is in charge of the registration and supervision of clinical trials. The tasks are executed by the Department of Supervision and Clinical Trials of Medical Products (DNB), which is responsible for the organization and coordination of the permits to conduct a clinical trial. The Department also runs the Central Register of Clinical Trials (CEBK), provides information about clinical trials to EUDAMED database as well as collects and archives final reports on the implementation of clinical trials.

COMPANY NAME	**Office for Registration of Medicinal Products, Medical Devices and Biocidal Products**
Address	Ząbkowska 41
Address (city)	Warszawa
Address (ZIP)	03-736
Telephone	+48 22 492 11 00
Web site	www.urpl.gov.pl
PROFILE	Government administrative authority under the direct supervision of the Ministry of Health
Description	The scope of responsibilities is determined by the Act of 18 March 2011 on the Office for Registration of Medicinal Products, Medical Devices and Biocidal Products. Involved in: • marketing authorization of medicinal and biocidal products • marketing authorization and use of medical devices • monitoring of use of drugs in Poland • registering, monitoring and inspections of clinical trials, including veterinary clinical trials
Ownership structure	State organization

27.4.2 Procedure

Terms of clinical trials of medicinal products are regulated by the Pharmaceutical Act of 6 September 2001 with particular ordinances issued by the Ministry of Health in 2005-2012.

Each clinical trial may be conducted only on the basis of a permit issued by the President of the Office for Registration of Medicinal Products, Medical Devices and Biocidal Products, as well as favorable opinion of the bioethics committee. After analyzing the documents and issuing permit, the President of the Office will register the clinical trial to the Central Register of Clinical Trials.

Each clinical trial shall be carried out in accordance with Good Clinical Practice, which provides the standard that specifies how to plan, conduct, monitor, record, and report the results of clinical trials on humans. Hospitals conduct trials for pharmaceutical companies on the basis of tripartite agreements between the pharmaceutical company (or CRO), the hospital and the researcher responsible for the supervision of the trial. In accordance with Article. 6 § 4 of the Pharmaceutical Act, the import of foreign drugs necessary for the conduct of clinical trials requires to obtain an attestation issued by the President of URPL that imported medicinal products will be used for ongoing trial (no separate license required).

The average period for trial registration reaches 65-75 days, depending on the complexity of project.

In accordance with the rules in the European Union, the process of ethical review and registration of clinical trials in Poland run parallel. However, the initiation of an investigation is possible only after approval of the bioethics committee responsible for coordinating the clinical trial and approval by the Minister of Health, granted on the basis of the consent from the Central Register of Clinical Trials (CEBK) that reviews documentation and protocol relating to the tested drug.

According to the Pharmaceutical Act, the Minister of Health may refrain from issuing an approval, but if his office will not ban the trial – the trial should be able to start after 60 days from the submission of a complete application. Then, the pharmaceutical company obtains from the President of URPL the permission to import drug dedicated exclusively to particular clinical trial.

The doctor managing the trial and its sponsor are required to provide up to date reports to the bioethics committee of side effects reported by patients. The Commission may decide to suspend the trial if the experts agree that the risk is higher than the benefits from continuation of the project. This is an additional protection for the rights of patients participating in the trial. Moreover, the pharmaceutical company provides on a regular basis to all doctors, CEBK and bioethics committees information on adverse reactions that have occurred in other countries participating in the project. These data allow the doctor to decide how to deal with the patient, and provide the committees insight into the current knowledge on the safety of the drug. In case when new relevant data on drugs appear, patients receive updated written information about the trial progress with a request to consider their further participation in it.

The list of documents to be submitted to the Central Register of Clinical Trials (CEBK) include:

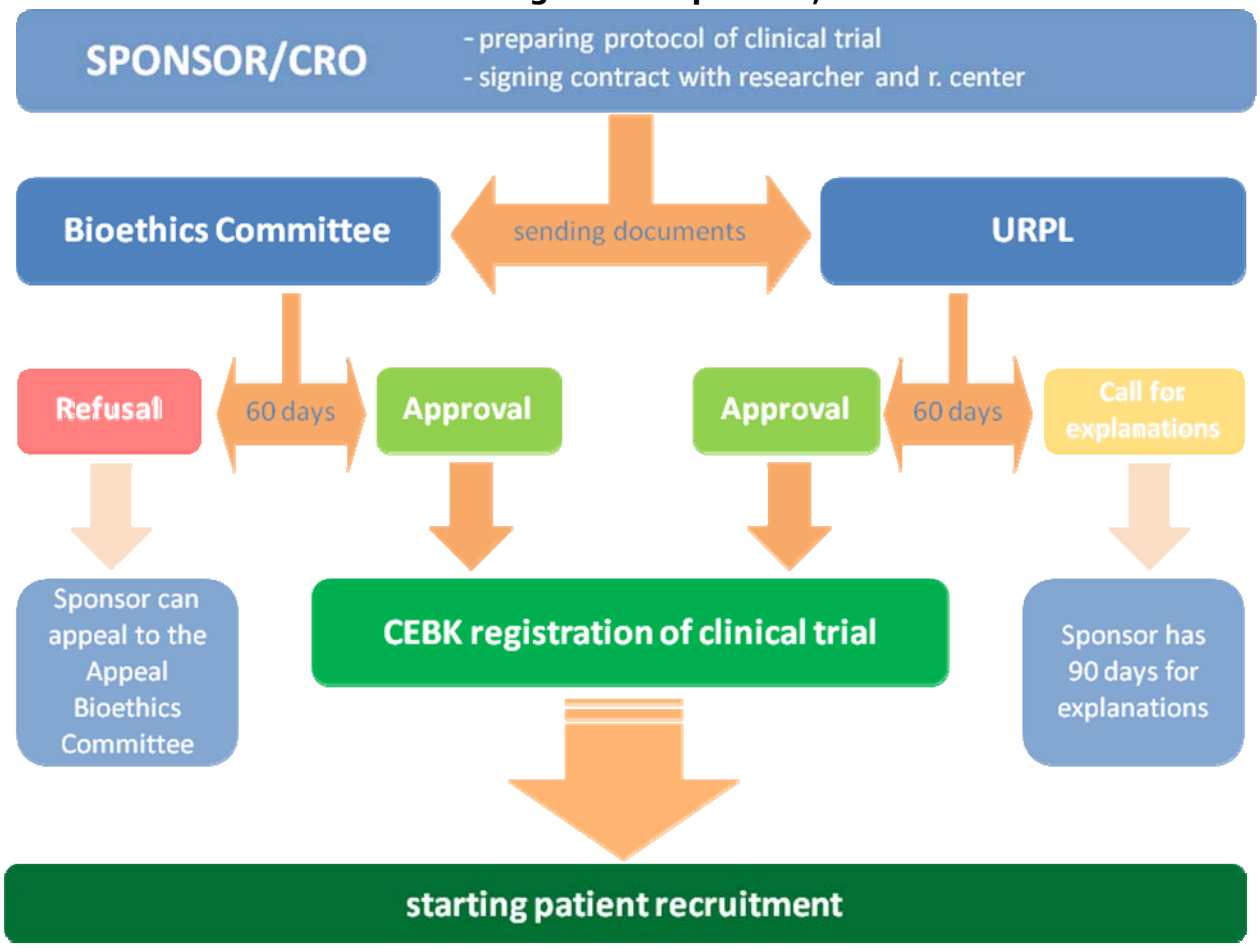
1. Application to the Office of the President to initiate a clinical trial of the medicinal product
2. Cover letter
3. Confirmation document on the reception of EudraCT number
4. Researcher's brochure (in case the trial concerns medicinal products not marketed in the European Union)
5. Summary of Product Characteristics (in case the trial concerns medicinal products authorized in the European Union)
6. Design of the label of an imported medicinal product
7. Clinical observation card – CRF (should be submitted as a hard copy).
8. Description of the scientific and professional experience of the principal researcher (in the form of Curriculum Vitae), signed and dated (principal researchers in case of multi-center trials)
9. Confirmation of payment of application fee
10. Insurance policy
11. Bilateral or trilateral agreement (sponsor-researcher-research center)

The following documents should be submitted to the relevant Bioethics Committee:

1. Application for a positive opinion on the clinical trial
2. Cover letter
3. Clinical Trial Protocol (and summary)
4. Patient information and informed consent
5. Clinical observation card (CRF)

6. CV of the principal researcher
7. Copy of the bilateral/trilateral agreement (with the researcher and research center)
8. Copy of the insurance policy

General scheme of clinical trial registration process, Poland



27.5 Key players

27.5.1 Key contract research organizations

According to the PwC data, CROs support 70% of clinical research in Poland in terms of volume and 53% in terms of value. The number of clinical trials contracted to CROs is rising systematically. However, CROs mainly focus on smaller and medium-size clinical trials. Large clinical trials are often carried internally by specialized departments of pharmaceutical companies.

More and more popular is also becoming the option of so called "in-sourcing" where a CRO outsources their experts to a pharmaceutical company. Such experts work in offices and under direct supervision of the pharmaceutical company on a particular project for the agreed period of time.

As provided by PwC, GSK, AstraZeneca, BMS and Roche seem to be the most active sponsors in the CEE region with regards to the number of research centers they cooperate with.

A Pennsylvania company seeking to identify a suitable CRO to run a clinical trial in Poland or other CEE countries shall contact the Authorized Trade Representative in Central Europe with specific requirements and expectations on the partner organization (see section 30.3 Route to market).

An overview of the leading CROs active in Poland has been provided in chapter 11. POLAND starting on page 30. Profiles of the largest players follow below (employment and revenue figures are not publicly available for all the companies listed).

Below are profiles of top 5 Polish contract research organizations (listed in alphabetical order):

COMPANY NAME	**Brillance Sp. z o.o.**
Address	Królowej Jadwigi 167 B
Address (city)	Krakow
Address (ZIP)	30-212
Telephone	+48 12 623 07 15
Web site	www.brillance.pl
PROFILE	Polish CRO operating also in the Czech Republic and Slovakia
Description	• Focus on Phase II and III trials (not Phase I) • Involved in experts outsourcing to other CROs and pharmaceutical companies and implementation of Good Practices • Providing complex services related to data analysis and management of clinical trials
Year of establishment	2004

COMPANY NAME	**Clinmark Sp. z o.o.**
Address	Czapli 33
Address (city)	Warszawa
Address (ZIP)	02-781
Telephone	+48 22 716 55 30
Web site	www.clinmark.pl
PROFILE	Large Polish CRO operating in other CEE countries; provider of training and consulting services for pharmaceutical companies
Description	• Since its establishment the company has conducted more than 100 clinical trials, both single- and multi-centric • Besides Poland Clinmark provides services in the Czech Republic, Slovakia, Balkan countries, Germany, Hungary, and Georgia. • It offers complex clinical trial management, including Phase I, independent quality audits, data management, statistical analysis, and registration of medicinal products.
Year of establishment	2001

COMPANY NAME	**KCR S.A.**
Address	Postępu 6
Address (city)	Warszawa
Address (ZIP)	02-676
Telephone	+48 22 313 13 13
Web site	www.kcrcro.com
PROFILE	Leading European CRO (started and headquartered in Poland) with offices in USA; offering clinical trials for pharmaceutical, biotechnology and medical device companies and in the field of food supplements
Description	• The company has delivered over 300 clinical trials. • It has 12 branch offices in Europe and USA. • KCR offers full service in the field of clinical trials (all phases), quality assurance and data management.
Year of establishment	1997
Employment	150 CRA's worldwide

COMPANY NAME	**Medical Network S.A.**
Address	Gedymina 28a
Address (city)	Warszawa
Address (ZIP)	04-120
Telephone	+48 22 612 45 73
Web site	www.med-net.pl
PROFILE	One of the biggest and most active CROs in the Polish market; providing a wide range of services related to clinical trials
Description	• The company has performed over 120 clinical trials of all phases, but the focus is mostly on Phase II and III. • It is listed on the Warsaw Stock Exchange. • It cooperates with other CROs from the CEE region.
Year of establishment	2000

COMPANY NAME	**Monipol Sp. z o.o.**
Address	Dluga 31/3
Address (city)	Krakow
Address (ZIP)	31-147
Telephone	+48 12 630 18 50
Web site	www.monipol.com
PROFILE	Polish-German CRO; one of the most experienced Polish CROs
Description	• Carrying all phases of clinical trials (including Phase I trials conducted in their own research center equipped with 24 beds) • Branch offices in Germany and Ukraine.
Year of establishment	1995

In addition to the above profiled Polish companies, a number of multinational CROs have established branch offices in Poland (e.g. Parexel, Quintiles, Covance, PSI, PRA, Accovion, Cromsource, INC Research, Omnicare, and Kendle).

27.5.2 Key trial sites – hospitals/universities

According to Central Statistical Office there are 800 hospitals and 16,000 ambulatory centers in Poland, and every center constitutes a prospective trial site.

One source estimates the number of trial sites in Poland at 1,200. However, in our opinion the figure is underestimated in comparison to figures obtained for other CEE countries; it probably does not include small ambulatory practices of practitioners that often carry studies in the area of vaccinations and allergy medicines.

Selected key trial sites, Poland

Organization	Website	Profile
Academic Clinical Center in Gdansk	http://usk.onestepcloud.pl/pl_PL	Located in northern Poland; a clinical hospital belonging to the Medical University of Gdansk; clinical trials in many fields including urology and oncology
Academic Clinical Hospital in Wroclaw	www.aszk.wroc.pl	Independent clinical research hospital in the south-western part of Poland
Central Clinical Hospital of Medical University in Katowice	www.csk.katowice.pl	Clinical hospital; a part of the Medical University in Katowice
Central Clinical Hospital of Medical University in Lodz	www.csk.lodz.pl	Leading clinical and research hospital in central Poland
Clinical Hospital in Bialystok	http://usk.onestepcloud.pl/pl_PL	Part of the Medical University of Bialystok (eastern Poland); conducting a wide range of clinical trials
Clinical hospital Przemienienia Pańskiego in Poznan	http://sk1.am.poznan.pl/	Part of the Medical University in Poznan; one of the most active clinical trial units, focus on oncology and cardiology
Independent Public Clinical Hospital in Lublin	www.spsk1.lublin.pl	Part of the Medical University of Lublin; clinical trials in a wide range of areas
Independent Public Clinical Hospital in Warsaw	www.spcsk.amwaw.edu.pl/	Managed by the Medical University of Warsaw; clinical trials and research projects especially in the field of civilization (lifestyle) diseases such as heart diseases
Gornoslaskie Medical Center in Katowice	www.gcm.pl	The largest Silesian medical center
Polish Academy of Sciences, Division V: Medical	www.pan.pl	Division of the national institute; providing medical research and coordinating work of subordinated units - local clinical hospitals

28. PRODUCT REGISTRATION

28.1 Registration authority

URPL is also responsible for drug registration and monitoring of the pharmaceutical market.

28.2 Types of registration

In absence of official data on the breakdown of marketing authorizations by type of registration procedure (URPL declined to reveal the figures) we estimate that the mutual recognition and decentralized procedures are the most popular among pharmaceutical companies; however, Poland is not often chosen as the reference country due to administrational indulgence and procedural delays.

28.2.1 National registration

Registration of medicines just in Poland via the national procedure takes 210 days; however, so-called stop-clocks are allowed (the break in the run of the procedure launched from the initiative of URPL in which an applicant is asked to answer some questions or provide additional documentation).

28.2.2 MRP (mutual recognition procedure)

After obtaining the approval of the registration for the medicinal product in Poland, a drug manufacturer may apply for approval of the drug in the market in another EU Member State. This is done through so called mutual recognition procedure (MRP).

To obtain a marketing authorization for a medicinal product in one or more Member States, the applicant shall submit an application in these countries on the basis of the same documentation set as before and applies to one of the countries to become the Reference Member State and to prepare an assessment report on the medicinal product. The procedure starts after 14 days. Within 50 days the interested countries shall send the comments to the applicant and the Reference Country.

In the period of 90 days the procedure shall be completed. The Member States shall notify the applicant and Reference Country about their final opinion. In case of a negative assessment the CMDh secretariat - Coordination Group for Mutual Recognition and Decentralised Procedure (human) at the European Medicines Agency is also informed.

If an agreement has been reached - Country Reference procedure is concluded, if not - contentious points raised by the Member State shall be sent by the National Reference to CMDh in a week. Within five days after the procedure completion, the applicant has to submit high quality translations into foreign languages: summary of product characteristics and package leaflets. The permission for the drug is valid after 30 days from procedure completion.

28.2.3 Decentralized procedure (DCP)

Registration of drugs via DCP (decentralized procedure) is suitable for registration of a drug in parallel in several EU countries. In contrast to the MRP procedure there is no first registration of the drug in one of the EU countries, but one country is designated as a Reference Country and like the MRP procedure it is responsible for the initial evaluation and coordination of the whole process. Drug registration procedure itself lasts 210 days; however, stop-clock is possible – to take a break to answer the questions of individual countries.

28.2.4 Centralised registration

Except for the three types of registrations above that URPL is involved in, there is also a centralised registration, a procedure which does not take place at national health authorities in individual Member states. The procedure is carried out centrally at the European Medicines Agency based in the UK and the registration is then valid in all EU countries. The list of centrally registered medicines can be found on the EMEA website (www.ema.europa.eu).

Final statement is provided within 210 days since the validation of the application.

28.3 Key legislation for human medicines

The **Pharmaceutical Act of 2001 together with its amendments** is the very key act regulating the entire issue of human medicines; among other areas it covers registration and monitoring of medicines and medical products, named patient procedures, and clinical trials (see www.gif.gov.pl/rep/gif/pliki/Pharmaceutical%20Law%20-%20June2009.pdf for details).

28.4 Key players - companies assisting with registration

Many pharmaceutical companies maintain a dedicated department working internally on drug registration. However, the registration process can also be outsourced to a company specializing in services in the field of medical and pharmaceutical consulting. Also, many CROs provide drug registration support.

Experts interviewed during the course of the project mentioned the following companies as the leading providers of pharmaceutical consulting in Poland.

COMPANY NAME	**APC Instytut Sp. z o.o.**
Address	Grójecka 22/24/ lok 4
Address (city)	Warszawa
Address (ZIP)	02-301
Telephone	+48 22 668 68 23
Web site	www.apcinstytut.pl
PROFILE	Providing consulting services for the pharmaceutical sector
Description	Specializing in the following areas: • Regulatory affairs (drug registration in Poland and the EU) • Pharmacovigilance (drug safety) • Outsourcing of contractual sales force • Recruitment, training, sales and marketing management services
Year of establishment	1996

COMPANY NAME	**Comac Sp. z o.o.**
Address	Lakowa 2
Address (city)	Dabrowka
Address (ZIP)	05-252
Telephone	+48 22 799 94 14
Web site	www.comac.biz
PROFILE	Active in the field of medical advisory, particularly in regulatory affairs
Description	The company offers consulting in the area of drug registration procedures, sales and marketing issues, hospital audits, and safety of clinical trials.
Year of establishment	1988

COMPANY NAME	**OINPHARMA Sp. z o.o.**
Address	Słomińskiego 19 lok. 3
Address (city)	Warszawa
Address (ZIP)	00-195
Telephone	+48 22 578 00 00
Web site	www.oinpharma.pl
PROFILE	Consulting and advisory services for pharmaceutical, cosmetics and food manufacturers
Description	Involved in: • medicinal products and cosmetics registration • pharmacovigilance • preparation and verification of internal SOPs • pharmaceutical business development and distribution for both RX and OTC drugs • leaflet readability testing • training seminars for employees of pharmaceutical companies • sales force outsourcing
Year of establishment	2004 (over 40 years of experience as Polfa Information Institute)

COMPANY NAME	**RadFarm Sp. z o.o.**
Address	Królewicza Jakuba 1A
Address (city)	Warszawa
Address (ZIP)	02-956
Telephone	+48 22 550 04 10
Web site	www.radfarm.pl
PROFILE	Medical consulting company
Description	Providing a wide range of services for pharmaceutical companies, including drug registration, marketing, sales force outsourcing and management as well as training
Year of establishment	2000

29. MARKET ENTRY STRATEGY

29.1 Market overview

29.1.1 Market size and breakdown

In 2012, the total value of the Polish pharmaceutical market reached USD 8.8 billion. The segment of prescription medicines (RX) constitutes about 65% and those not requiring prescription (OTC) about 35% of the value of the market.

In 2011, Poles bought 711 million units of RX drugs and 973 million packs of OTC drugs. The average price of an OTC medical product amounted to PLN 8.37 (USD 2.79).

The largest category among RX drugs are blood hypertension products.

In 2011, the OTC and RX sectors recorded an 8% and 6% increase in sales value respectively compared to 2010. The fastest growing category were food supplements with a rise of almost 17% y-o-y.

The best selling OTC drugs by therapeutic category were for cough and other breathing and respiratory problems, where sales value amounted to PLN 1.4 billion (USD 466 million). Other types of common purchased drugs included vitamins, minerals, and food supplements that totaled to PLN 922 million (USD 300 million) and painkillers reaching PLN 861 million (USD 287 million).

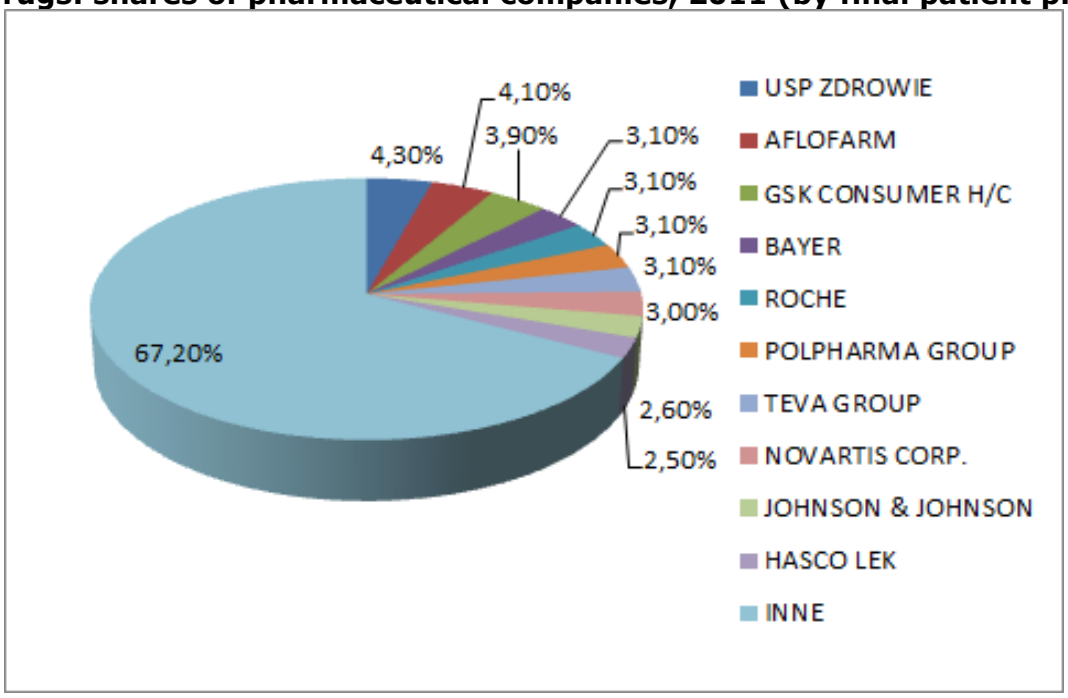
The Polish pharmaceutical market is undergoing regulatory changes in terms of drugs trading by pharmacies and RX drugs refunding by the government. New reimbursement policy that entered into force at the beginning of 2012 introduced fixed margins for RX drugs calculated from the cheapest drug in a particular group; it put many limitations on marketing operations performed by pharmacies as well as increased their obligations towards prescription handling.

The new legislation resulted in a 5-6% market drop in the first half of 2012. The average turnover of a pharmacy amounted to PLN 159,000 (USD 53,000) in September 2012, down by about 9% compared to the same period of 2011. The largest decline (10%) was noted in the RX sector.

In the first quarter of 2013 the market revived; however, in case of RX drugs its dynamics and value remain below the 2011 level. The situation in the OTC sector is much better, as it grew 15% compared to 2011.

The OTC drug sector is supplied by a number of producers. The key players include USP Zdrowie, Aflofarm, and GSK. The difference in shares of other manufacturers remains insignificant.

OTC drugs: shares of pharmaceutical companies, 2011 (by final patient prices)



Source: Polish Association of OTC Drugs Manufacturers

29.1.2 Local production

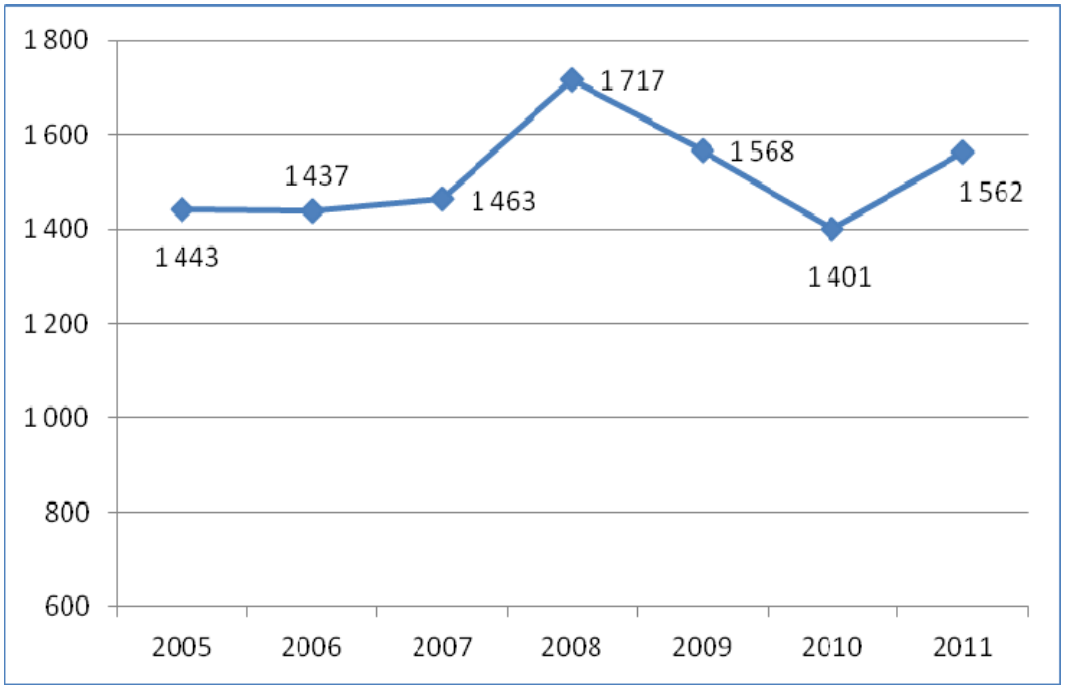
The annual production volume of drugs in Poland ranges from 1.4 to 1.7 thousand tons.

Sanofi-Aventis, Polpharma and GlaxoSmithKlein are the largest manufacturers; they combine for approximately 17% of drug production in Poland. Other companies with production plants in Poland include Sandoz, Roche, Novartis, Servier, Merck & Co, Pfizer, and Teva.

Polish companies such as Polpharma or Adamed mainly focus on the production of generic drugs, which is due to the lack of sufficient resources to finance innovation.

In 2011, the value of imports of drugs into Poland amounted to USD 5 billion, while exports exceeded USD 2 billion.

Production of pharmaceutical products and preparations (in tons), Poland, 2005-2011



Source: Central Statistical Office and EasyLink, 2013

29.2 Distribution of pharmaceuticals

29.2.1 Distribution structure – key distributors

More than 600 pharmaceutical wholesalers serving pharmacies, hospitals and the non-pharmacy segment operate in Poland. The three largest drug distributors (wholesalers) - Farmacol, Neuca, and Pelion – control approximately 70% of the market.

Leading distributors of pharmaceuticals, Poland, 2013

Company	Website	Profile
Farmacol S.A.	www.farmacol.com.pl	The leading distributor of drugs and medicine products; listed on the Warsaw Stock Exchange (WSE)
Neuca S.A.	www.neuca.pl	Publicly listed (WSE) distributor supplying mainly pharmacies; its market share is estimated at 30%
Pelion Healthcare Group S.A.	www.pelion.eu	One of the leaders in distribution of drugs; supply of pharmacies and hospitals via retail and wholesale
ACP Pharma S.A.	www.acppharma.pl	Part of Mediq NV; providing services in the field of distribution and logistics for drug manufacturers, pharmacy chains, and hospitals

Source: EasyLink, 2013

With regard to the distribution of OTC drugs, 96% are sold in pharmacies, while GSL sales (non-pharmacy) constitute only 4%. When it comes to dietary supplements alone, about 85% are sold in pharmacies, nearly 10% over the Internet, and the rest - in general store chains. Customers prefer to buy these products at the pharmacy, because they know that this type of distribution channel ensures the quality of the products and also the pharmacist can always provide information and advice.

The two key groups of drugs and supplements offered on the non-pharmacy market are analgesic/antipyretics and those for anti-gastric disorders (two-thirds of the market share of the non-pharmacy sector in terms of volume) and vitamins and mineral preparations. The products are delivered to non-pharmacy retail by pharmaceutical wholesalers, general wholesalers as well as by so called pre-wholesale, as large FMCG retail chains purchase medicinal products directly from manufacturers.

The largest share in retail of OTC medicines outside pharmacies is generated by small (24%) and medium-size (23%) grocery stores, followed by hypermarkets (17%) and supermarkets (12.%). The large area stores sell mostly vitamin supplements (mainly in soluble form), while small retail outlets focus on painkillers, and service stations on anti-gastric medicines. The biggest demand for drugs is observed in big cities, e.g. through drugstore chains such as Super Pharm, Rossman and Beauty Nature that offer a wide range of OTC drugs, cosmetics, food supplements, and personal hygiene products.

Among the other distribution channels (other than traditional pharmacies) trading via the Internet is becoming increasingly important for the pharmaceutical market. The other distribution channel that will grow rapidly over the next 12 months will be the direct distribution.

29.2.2 Key customers – pharmacies and hospitals

In Poland, there are over 13,000 pharmacies, of which 9,000 are associated in smaller or larger chains.

Currently, there are about 200 different pharmacy chains, which consist of just a few to several hundred retail outlets. Pharmacies are associated with wholesalers or create a form of a purchasing group. Pharmacies in the chain may belong to one owner or multiple owners, or share loyalty or affiliate programs. Joining the chains is a way for pharmacies to respond to changing market rules, including competitive struggle for the patient. Affiliated pharmacies adopting a common policy on purchasing and marketing benefit from economies of scale – i.e. incurring similar costs; they achieve much greater range and effectiveness during trade negotiations with suppliers, marketing campaigns or promotional activities.

The largest chain is DOZ (Dbam o Zdrowie – translation: I take care of Health), owned by the Polish Pharmaceutical Group. The number of pharmacies in this chain reaches nearly 1,500 (including franchise businesses).

Other major chains include Mediq (200 pharmacies) and Dr. Max (69 pharmacies).

According to the Central Statistical Office, the number of general hospitals in Poland reached 853 in 2011, of which 540 were public hospitals. The total number of in-patients exceeded 7.4 million in 2011.

29.3 End user analysis

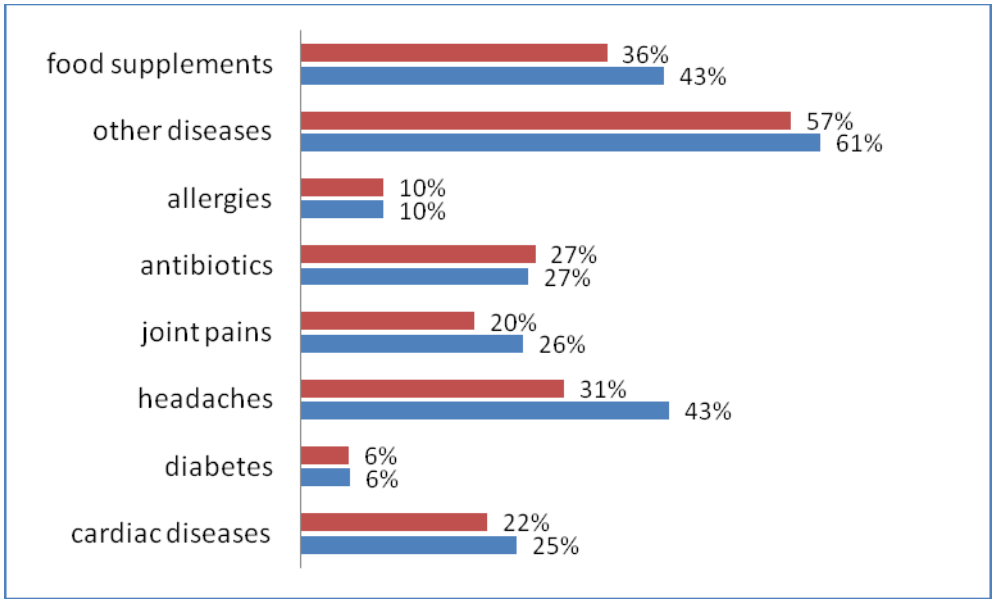
According to the Central Statistical Office, in the fourth quarter of 2010, more than 75% of Poles used various medicinal products; dietary supplements were the leading category (almost 40% of drugs) followed by drugs for headaches (38%) and antibiotics (27%).

Among all households, 90% bought drugs prescribed by a doctor, and almost 44% households drugs that were not prescribed, but recommended by the doctor. Almost 90% of households buy drugs from their own initiative, which still shows the common practice to use drugs without consulting a doctor.

In 2010, over 64% of the average monthly expenditure on health per capita in a household was spent on medicines and medical supplies, which amounted to PLN 33.73 (USD 10) per person. The highest spending on medicines was observed in households of the retirees where the expenses were almost twice higher compared to an average household. The level of expenditure on medicines and medical supplies per person varies depending on the place of residence of households; it is significantly higher in urban areas than in rural areas, and it also varies depending on the size of the city. The larger the city the higher the expenditure on medicines and medical supplies per person. In the largest cities, with a population of at least 500,000, the average spending (per person) for medicines and medical supplies was about 63% higher than in the countryside. At the same time in the group of households with the highest income, the average level of medicine expenditure was 2.5 times higher than in households with the lowest income.

When it comes to sex, more than 81% of women and 69% of men often take medicines and food supplements.

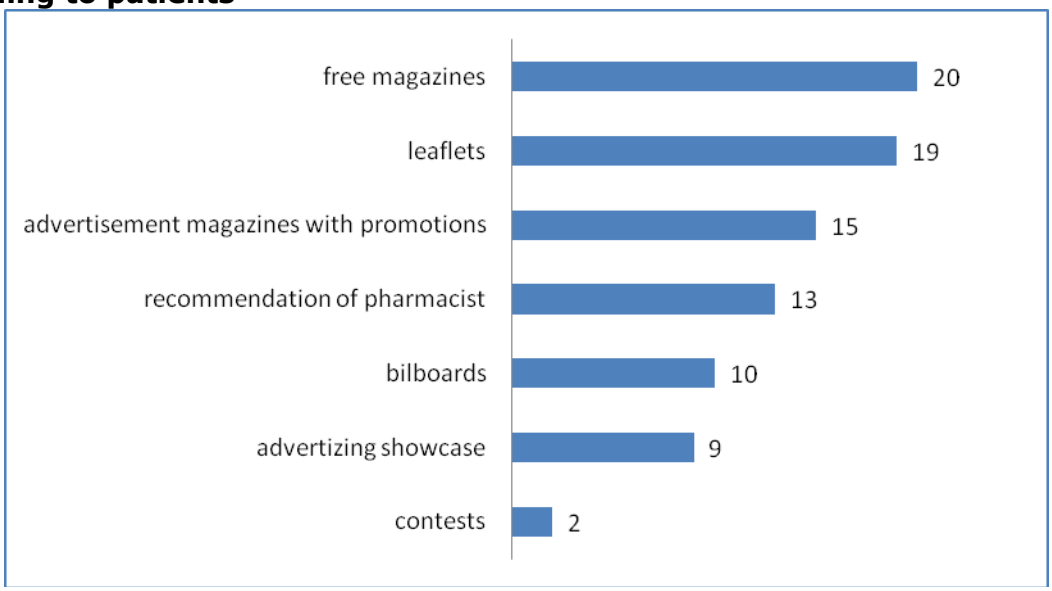
Breakdown by therapeutic category among people often taking medicines, Poland (%)



Source: Healthcare in Polish households, Central Statistical Office, 2010

According IMS Health, the average Polish household spends on OTC drugs around PLN 811 (USD 270) annually (2011 data include all OTC: drugs, food supplements, medical products, and medical cosmetics).

Effectiveness of marketing actions of OTC medicines taken by pharmacies according to patients



Source: Healthcare in Polish households, Central Statistical Office, 2010

Patients willing to buy new brands of OTC medicines (so-called innovators) represent 2.5% of customers. A group of people buying the drug following others (the first followers) already reaches 13.5%, while the early and later followers consists of almost 70% of customers.

30. ANALYSIS, STRATEGY & CONCLUSION

30.1 Obstacles and challenges

Chronic and unpredictable registration procedures and excessive bureaucracy still remain the leading barriers for further development of the clinical trials market in Poland. The average time of trial registration reaches about 65-75 days, depending on the complexity of project.

To register a clinical trial in Poland on average 31 documents have to be delivered to URPL and 22 documents to the bioethics committee. For comparison, in Canada, only 12 documents have to be submitted to the agency's Therapeutic Product Directorate.

Moreover, the attitude, approach and requirements of bioethics committees vary from region to region and Polish pharmaceutical legislation is still not fully compliant with EU directives, which can especially cause difficulties in early-phase clinical trials.

Market experts also see a need for a central registration system of the clinical trials. Implementation of such solution should result in patients feeling more safe (as it would give the government greater supervision over the trial) and it may help to capture the situation where a patient participates in two or three clinical trials, which sometimes happens and is totally inconsistent with good practice rules.

Another major problem is the low public awareness of clinical trials in Poland. Many media present trials stereotypically as the experiments to "guinea pigs". On the other hand, research participants believe that thanks to them they have better access to modern technology and a sense of better medical care. The society awareness could be improved through official publication of results and benefits from each trial carried in Poland, which altogether should be collected in the form of publicly available database of clinical trial summaries.

30.2 Market potential

According to the PwC report, Central Europe is a more attractive location for clinical research than CIS countries (e.g. Russia, Ukraine, Belarus, Kazakhstan, or Georgia), as the value for money here is much higher. The Polish accession to the European Union provided more predictable regulatory conditions under which a trial is conducted.

Poland is one of the major global markets. According to PwC, more than half of the pharmaceutical companies operating in the Polish market concluded that the research of 80% of all drugs introduced to the global market is conducted among others in Poland.

The key drivers of the clinical trials market in Poland are the size of the population, effective patient recruitment, high quality trials, and experience and high quality of medical staff.

Patients tend to be much more motivated to participate in a clinical trial in Poland where the level of the standard of medical care is rated lower than in Western Europe; participation in trials thus gives patients access to higher level of medical treatment.

Participation in clinical trials, especially in case of inpatient trials, often provide better service, faster access to treatment, and availability of expensive drugs at no cost to the patient. However, this advantage may cease to exist in the next few years, as the quality of medical care in Poland is approaching western standards.

Poland continues to run a relatively small number of clinical trials in comparison to the size of the Polish population. The development of this market in Poland depends mainly on the governmental decisions and regulations. If the legal and formal environment become more favorable, the number of clinical trials could still increase by 20% to 30%.

30.3 Route to market

A U.S. producer of pharmaceuticals and biotechnology products seeking to carry a clinical trial or register a medicinal product should **first appoint an in-market specialist** (a CRO or a company assisting with product registration).

In case of clinical trials, the company can select:

- Polish contract research organization
- Global CRO - branch office of one of the multinational CROs present in Poland

As the CROs operate in various markets (e.g. Polish CROs often work as subcontractors to other foreign CROs or contract CROs from other countries in the CEE region for cooperation), they can recommend the most cost effective country for a particular clinical trial (when provided sponsor's requirements on the therapeutic area and the number of patients).

RUSSIA

31. CLINICAL TRIALS

31.1 Country attractiveness and challenges

Various pharmaceutical companies started to conduct clinical trials in Russia in mid-1990s. At that time the barriers were so difficult that only the strongest players were able to overcome them. Since then the situation has changed dramatically.

The **key benefits** for carrying clinical studies in Russia include, but are not limited to the following:

- Highly concentrated urban population – 73% of the population live in metropolitan areas
- Centralized health care system
- High recruitment rates - patients are recruited between two and ten times faster in Russia than in the West
- Highly qualified investigators – GCP trained, experienced
- Willingness of patients to participate in the studies, refusals to participate are rare
- Low migration rate compared to other countries
- Large number of treatment-naive subjects, especially in oncology, HIV, and infectious diseases
- High prevalence and incidence of all major diseases
- Good data quality
- Robust investment of major pharmaceutical companies have set up good infrastructure, creating favorable conditions for sponsors-newcomers
- Legislation matching international standards

Medical centers specializing in oncology, cardiology, endocrinology, pulmonary, neurology, and other areas are located in all major cities, enabling to recruit high numbers of patients. It also reduces overhead and transportation costs.

The key **challenge** sponsors face in the Russian market is **a constantly changing legislation regarding clinical trials** (a number of amendments have been adopted and new ones are being discussed). The market experts point out the legislation must move in a way to make the market more transparent, attractive and accessible for both foreign and domestic sponsors.

Clinical trial limitations, Russia

Limitation	Exception
Pediatric study (up to 18 years)	Trial is necessary for strengthening children's health or prevention of infectious diseases in children; trial objective is to obtain data for better medication dosing in children; a trial on adults must precede the trial on children in all cases
IP is narcotic, psychotropic substances or their precursors	Import, logistic, and handling limitation are possible
Phase 1 studies on healthy volunteers	Allowed only for local manufacturers of IP

Source: Premier Research Russia, 2012

The Center for Drug Evaluation and Research (CDER) of the FDA approved 102 new drugs during 2012, and for 21 of them clinical trials were conducted in Russia.

During the fourth quarter of 2012 the Committee for Medicinal Products for Human Use (CHMP) of the European Medicine Agency (EMEA) gave positive recommendations on 87 new drug applications, out of which 48 were tested at Russian sites.

Russia provides high standard of clinical research. According to FDA, inspections revealed 56.9% of NAI (No Action Indicated) clinical trials and 41.1% VAI (Voluntary Action Needed) that could be compared to states with the same amount of trials conducted such as the United Kingdom (33.8% and 63.6% respectively) and Germany (39.3% and 58.9% respectively).

Six FDA inspections were conducted in Russia during Q1 and Q2 2012. Five inspections ended with NAI - no action indicated, and one inspection ended with VAI - voluntary action indicated.

31.2 Market size

31.2.1 Number of trials

The Ministry of Health of the Russian Federation approved **915 new clinical trials** including local and bioequivalence studies during 2012, up 61% compared to the previous year.

Structure of clinical trials, Russia, 2007-2012

	2007	2008	2009	2010	2011	2012
International multicenter	369	364	348	246	370	369
Local (foreign sponsors)	25	45	32	30	35	62
Bioequivalence (foreign sponsors)	5	5	8	6	19	107
Local (local sponsors)	101	133	112	123	80	165
Bioequivalence (local sponsors)	63	68	77	77	63	212
Total	*563*	*615*	*577*	*482*	*567*	*915*

Source: Association of Clinical Trials Organizations (ACTO), 2013

The number of approved clinical trials kept rising from 2005 to 2008, then declined by 6% in 2009 and 16% in 2010 to start rising again in 2011 (up 17%).

31.2.2 Number of patients

A total of **67,023 patients** enrolled in Phase I-IV trials launched in 2012; it translated into a 24% increase compared to 2011. **Approximately 75% of patients were enrolled for Phase III trials**, 12% for Phase IV, 11% for Phase II, and 2% for Phase I.

31.3 Structure of studies conducted

31.3.1 By type

Multinational multi-center clinical trials hold the leading position; their share in the total number of studies has varied quite significantly, it reached 65% in 2007, went down to 60% in 2008 and 2009, then dropped further to 51% in 2010 to climb back to 65% in 2011; a major drop followed in 2012 when they accounted for only 40%.

The number of bioequivalence and local clinical trials have grown dramatically - from 82 bioequivalence studies in 2011 to 319 in 2012 and from 115 to 227 local trials. Local and bioequivalence studies accounted for 25% and 35% of studies respectively in 2012.

In 2012, clinical trials in Russia were sponsored by companies from 38 countries. The highest number of trials (430) was initiated by Russian sponsors, followed by U.S. sponsors initiating 143 new studies, Swiss sponsors 52 trials, Israeli companies 47 new trials, and U.K. and French sponsors 40 and 24 studies respectively.

GlaxoSmithKline sponsored 29 new studies in 2012. It was followed by Roche and Novartis with 23 new trials each. The other top five sponsors included Teva and Bristol-Myers Squibb with 18 and 17 new trials in 2012.

Amongst domestic pharmaceutical producers the lead was held by Biocad, which sponsored 13 new clinical trials. The remaining top 5 players were Microgen (12 new trials), OOO FK Slavyanskaya Apteka (9), Materia Medica (8), and Veropharm (6)[10].

31.3.2 By phase

Phase III studies traditionally constitute **the largest proportion** of studies; their number increased 21% to 369 studies in 2012.

Phase II trials are the number two category, with 111 studies launched in 2012.

39 new Phase I clinical trials were started in 2012, down by 25 trials compared to 2011.

The number of Phase IV trials also decreased, from 75 studies in 2011 to 48 in 2012.

31.3.3 By disease

In 2012, **more than two thirds of new studies were initiated in eight leading therapeutic areas**:

- Oncology (110 studies)
- Pulmonology (65 studies)
- Endocrinology (61 studies)
- Musculoskeletal diseases (55 studies)
- Infectious diseases (45 studies)
- Cardiology (42 studies)
- Gastroenterology (35 studies)
- Psychiatry (32 studies)

31.4 Regulatory information

31.4.1 Regulatory institution

The **two regulatory institutions** in the field of clinical trials in Russia are:

[10] *Source: Synergy Research Group, www.synrg-pharm.com*

- **Ministry of Health** (MoH) – in charge of the implementation of the policy and defined executive responsibilities as stipulated by the Act "On Circulation of Medicines"
- **Federal Service on Surveillance in Healthcare** - executes the control and enforcement of the regulation of medicines for humans and medical devices.

COMPANY NAME	**Federal Service on Surveillance in Healthcare and Social Development (Roszdravnadzor)**
Address	4 Slavyanskaya Ploshchad, bld. 1
Address (city)	Moscow
Address (ZIP)	109074
Telephone	+7 495 698 45 38
Web site	www.roszdravnadzor.ru
PROFILE	Federal body of executive authority under the Ministry of Health
Description	Performing 46 state functions and more than 100 administrative procedures Involved in: • Surveillance • State control – including of pre-clinical and clinical trials of medicines and meeting of rules for laboratory and clinical practice • Licensing • Registration • Pharmacovigilance • Permissions

The legislative framework pertaining to clinical trials comprises:

- Act "On Circulation of Medicines" and it's amendments
- Order no. 266 from 19 June 2003 on "Rules for clinical practice in RF" (defined parts only), and the list of Governmental Decrees and Executive Orders
- GOSTP52379-2005 (National standard of GCP in RF)

31.4.2 Procedure

The following four steps have to be taken to obtain a permission to start a clinical trial in Russia[11]:

Step 1: Submitting the required study documentation to the Ministry of Health

Article 38 of the Act "On Circulation of Medicines" defines:

1. For what purposes clinical trials may be conducted to:
    - Establish safety and/or tolerance of medicinal products for healthy volunteers, except for the trials of medicinal products manufactured outside the Russian Federation

[11] *Source: Cooperation in the field of clinical trials report by EPRD Office for Economic Policy and Regional Development*

- Select optimal dosages of medicinal product and course of treatment for patients with specific disease, optimal dosages and vaccination schemes of immune-biological medicinal products for healthy volunteers
- Establish safety and efficacy of a medicinal product for patients with specific disease, prophylactic efficacy for immune-biological medicinal products for healthy volunteers
- Study the possibility to widen the indication for medical use and identify earlier unknown side effects of registered medicinal products

2. Only defined organizations are entitled to organize clinical studies:
   - "Developer of the medicinal product", i.e. a drug developing entity; private persons intending to develop a drug need to be authorized by a developer, i.e. a company/firm
   - Defined "educational institutions"
   - Research Centers
3. Clinical trials can be conducted only at clinical sites, which have been accredited by the Ministry of Health. Accreditations are issued for a 5-year period and can be renewed.
4. Clinical trials must be conducted by following the "Rules on clinical practice". Failure to follow the "Rules on clinical practice" will be subjected to legal actions.

In Russia drug manufacturing licenses are issued by the Ministry of Industry and Trade (Decree no. 684), not by the drug regulatory authorities (or the RZN)

Step 2: Checking the supplied documentation (Time limit is 5 working days)

The Department of State Regulation of Drug Circulation checks the submitted documents for completeness and issues a written acceptance notification to the applicant within 5 working days.

Step 3: Review by the "Ethics Council" and the "Expert Organization" (Time limit is 30 working days + 5 working days for issuing the preliminary notification letter)

Both subordinated organizations review the documents and the Ethics Council gives its favorable approval and the Expert organization its expertise.

This step must be finished within 30 working days plus there are additional 5 working days for sending a preliminary approval notification to the applicant. The Ethics Council's decision is limited to a favorable opinion (approval) or rejection: a conditional approval is not foreseen. Rejected applications must be re-submitted after correction of the stated flaws, i.e. the entire process starts again. This holds true also for rejected applications from the Expert organization.

Step 4: Final approval notification of the applicant (Time limit is 5 working days)
In total, a time limit of 45 days is set by the legislation for an application to conduct a clinical trial.

31.5 Key players

31.5.1 Key contract research organizations

There are **approximately 100 contract research organizations in Russia, about 25 of them are global players.** The share of clinical trials carried out by global CROs is estimated at **40%.** The largest global CRO working in Russia are Parexel, PPD, PRA, PSI, and Quintiles.

According to the Association of Clinical Trials Organizations (ACTO) of the Russian Federation, in late 2000s every year up to five new CROs – local and global - appeared in the market.

Global CROs have entered the market via establishment of a wholly owned subsidiary or acquisition of an established business from a local CRO or another international CRO. Some global CROs operate via local subcontractors. Most companies open their first office in Moscow, the second office in St. Petersburg, and the third in Novosibirsk.

The number of local CROs has been steadily growing. They now offer a wide range of services by using their own resources and international outsourcing. The prices are competitive and depend on a company's size and services. The quality of service local CROs provide is usually proven by the growing number of contracts with international sponsors. In the past, sponsors considered local CROs primarily as a source of clinical research associates. Today, local CROs manage international trials, including project management, data management, and biostatistics.

An overview of the leading CROs active in Russia has been provided in chapter 13. RUSSIA starting on page 35. Profiles of the key players follow below (employment and revenue figures are not publicly available in Russia).

A U.S. company seeking to identify a suitable CRO to run a clinical trial in Russia or other CEE countries shall contact the Authorized Trade Representative in Central Europe with specific requirements and expectations on the partner organization (see section 34.3 Route to market).

COMPANY NAME	**Association of Clinical Trials Organizations**
Address	4, Malaya Dmitrovka Str., App. 5
Address (city)	Moscow
Address (ZIP)	127006
Telephone	+ 7 (495) 956 13 87 + 7 (495) 699 41 98
Web site	http://acto-russia.org
PROFILE	Non-commercial organization of companies, legal entities and clinical research community involved in clinical trials in Russia
Description	Its members are 26 pharmaceutical companies and contract research organizations: Almedis, Amgen, Arterium, Bayer HealthCare, Boehringer Ingelheim, Bristol-Myers Squibb, ClinStar, Covance, Cromos Pharma, Eastern Clinical Trials, Eli Lilly Vostok S. A., ICON, inVentiv Health Clinical, Janssen Pharmaceutica, MB Quest, Medpace, Novartis, Novo Nordisk, Parexel, Pfizer, PPD, PRA International, PSI, Quintiles, Servier, Worldwide Clinical Trials (WCT).
Year of establishment	2007

COMPANY NAME	**PAREXEL**
Address	23 Osenny bulvar
Address (city)	Moscow
Address (ZIP)	121609
Telephone	+7 495 781 39 09
Web site	www.parexel.com
PROFILE	Extensive experience in more than two dozen key therapeutic areas, with particular expertise in Cardiovascular, CNS, Infectious Disease, and Oncology
Description	In Russia, it is represented by PAREXEL International (RUS) LLC (PAREXEL Russia AS representative office was operating in 1998-2006). Services provided include: • clinical trials - Phase I-IV • drug development consulting • data management • biostatistics and programming • quality assurance • proposal and contracts • processing data and preparing a final report
Year of establishment	1998
Ownership structure	LLC
Number of employees	170 (in Russia)
Turnover	n/a

COMPANY NAME	**PPD**
Address	Shevchenko Street, 65B
Address (city)	Smolensk
Address (ZIP)	214020
Telephone	+7 4812 207 500
Web site	www.ppdi.com
PROFILE	Leading global contract research organization
Description	Involved in/serving as: • Phase I clinic and Phase II-IIIb trial management and monitoring • Bioanalytical labs • Biomarker services • Biostatistics and programming • cGMP labs • Clinical supplies • Data management, including EDC • Device development services • Global central labs • Epidemiology: pharmacoepidemiology and health outcomes • Observational studies • Phase IIIb-IV trials • Registries • Processing data and preparing a final report
Year of establishment	1988
Ownership structure	LLC
Number of employees	n/a
Turnover	n/a

COMPANY NAME	**PRA**
Address	ul. Smolnaya 24/D Tower "Meridian"
Address (city)	Moscow
Address (ZIP)	125445
Telephone	+7 (495) 234-57-51
Web site	www.praintl.com
PROFILE	One of the world's leading global clinical development organizations with more than 3,000 employees worldwide
Description	The company services include: • Clinical trials - Phase I-IIa • Clinical trials - Phase II-III • Late phase services • Safety and risk management • Therapeutic expertise • Processing data and preparing final reports
Year of establishment	1983
Ownership structure	LLC
Number of employees	Over 3,000 worldwide
Turnover	n/a

COMPANY NAME	**PSI**
Address	19/21 Dostoyevsky Street
Address (city)	Saint-Petersburg
Address (ZIP)	191119
Telephone	+7 812 320 3820
Web site	www.psi-cro.com
PROFILE	PSI has strong presence in Central and Eastern Europe
Description	The company conducts Phase I-IV clinical trials. Involved in: • Clinical data management • Clinical supply management • Clinical trial feasibility • Regulatory support • Trial support services • Processing data and preparing a final report
Year of establishment	1995
Ownership structure	LLC
Number of employees	450 (in Russia)
Turnover	n/a

COMPANY NAME	**Quintiles**
Address	Leningradskiy prospekt 37A, bldg.14
Address (city)	Moscow
Address (ZIP)	125167
Telephone	+7 495 721 19 64
Web site	www.quintiles.com
PROFILE	Offering Phase I-IV clinical trials in a number of countries in Europe, including Russia
Description	The company offers a wide range of services, including: • Product development strategy • Early clinical development • Phase I-IIa Clinical Trials • Phase II-III Clinical Trials • Interventional phase IIIb/Phase IV Clinical Trials • Observational research and observations • Product launch and management • Processing data and preparing a final report
Year of establishment	1982
Ownership structure	LLC
Number of employees	n/a
Turnover	n/a

31.5.2 Key trial sites – hospitals/universities

The number of facilities able to carry clinical studies decreased dramatically during the last two years because of changes in norms that allow medical institutions to conduct the studies. Prior to 2010 the number of trial sites in Russia was steadily growing, with approximately 60 new centers every year. The growth took place in the regions and not the key cities of Moscow and St. Petersburg.

According to expert estimates, there are around 500 accredited trial sites in Russia, and the number is increasing, as more and more hospitals and universities are obtaining the accreditation.

Among the sites, hospitals in large cities, such as Moscow and Saint-Petersburg, provide an opportunity to carry trials in various areas.

Selected key trial sites, Russia

Organization	Website	Profile
I.M. Sechenov First Moscow State Medical University	http://www.mma.ru/en/	One of the leading medical universities in Russia
Kazan State Medical Academy	http://kgma.info	The largest medical academy in central part of Russia
N.A. Semashko Railroad Hospital	http://en.semashko.com/	One of the major multiservice hospitals in Russia
Pirogov Russian National Research Medical University (RNRMU)	http://rsmu.ru/home_en.html	One of the leading medical universities in Russia
Siberian State Medical University	http://www.ssmu.ru/	The largest medical academy in Siberia
Sklifosofsky Research Institute of Emergency Medicine	http://www.sklifos.ru	One of the largest multi-disciplinary medical institutions in Russia

According to ACTO there are over 9,500 hospitals with a total capacity of 1.6 million beds and about 22,800 outpatient clinics capable of screening 3.6 million potential trial subjects per day.

32. PRODUCT REGISTRATION

Medicinal products **must be registered in Russia before their launch** on the local market.

The registration procedure consists of 4 sequential stages:

1. Creation of a Registration dossier including documents necessary for clinical study initiation, and submission of the Registration dossier to the Ministry of Health of the Russian Federation
2. Obtaining a permission for the conduct of a clinical study in the Russian Federation
3. Drug quality evaluation and evaluation of the expected benefit to possible risk ratio which is done after the clinical study of a drug; the third stage may be divided into 2 sub-stages:
    a. 3a. Drug quality control at the FSBI SCEMP's laboratory and approval of a Normative document (specification and analytical procedures)
    b. 3b. Evaluation of the expected benefit to possible risk ratio and approval of Instruction for medical use of a drug
4. Decision by the Ministry of Health on registration of the pharmaceutical product, it is entered in the State Register of pharmaceutical products and marketing authorization issuance.

Industry experts still regard the process of the state registration of medicinal drugs as one of the most problematic aspects of the current Act "Concerning the Circulation of Medicinal Drugs". The introduction of the new legislation brought about a fundamental revision and re-allocation of the operating procedures and functions of executive bodies in the field of healthcare. In particular, the responsibility for the state registration of medicinal products was transferred from the Federal Service for Healthcare Supervision to the Ministry of Health.

32.1 Registration authority

Registration is a state procedure of a product quality, efficacy and safety evaluation to obtain an approval for medical use of a drug in the Russian Federation. The Department of state regulation of pharmaceutical product circulation at the Ministry of Health of the Russian Federation is in charge of registration of new medicines and circulation of already registered medicines. Foreign and Russian medical products undergo the same registration procedure.

32.2 Types of registration

The following pharmaceutical product categories are subject to state registration:

- original pharmaceutical products
- generic pharmaceutical products
- new combinations of earlier registered pharmaceutical products

- pharmaceutical products registered earlier but manufactured in other pharmaceutical forms, new strengths

The following products are not subject to state registration:

- medicinal products made by pharmacies, individual entrepreneurs licensed to conduct pharmaceutical business, made under drug prescriptions and on requests of medical institutions, veterinary institutions
- medicinal (herbal) plant raw materials
- medicinal products purchased by physical entities outside the territory of the Russian Federation and intended for personal use
- medicinal products intended for export
- radiopharmaceutical medicinal products made in medical institutions directly

The state registration is not allowed for:

- different pharmaceutical products under the same trade name
- one pharmaceutical product made by one and the same manufacturer under different trade names

For generics exceptions apply; "Accelerated procedure for expert examination of Medicines" is in place. Due to the fact that the Russian pharmaceutical market is dominated by generics, this provision is of high importance.

32.3 Key legislation for human medicines

The key legislation includes:

- FZ-61 "On circulation of medicines" from April 12, 2010
- Order 1413 of the Ministry of Health and Social Development of the Russian Federation „On approval of the Guidelines for contents and execution of documents required for creation of the Registration Dossier for a pharmaceutical product for medical use for the purpose of its state registration" from November 23, 2011.

For marketing authorization in Russia clinical trials are not required provided:

- IMCTs have been conducted at clinical sites in Russia
- medicinal products have been in use in Russia for more than 20 years (in the same indication)

The reform of healthcare and pharmaceutical legislation, which began in 2010, continued in 2011 and 2012. The past year witnessed the implementation of a number of weighty legislative initiatives, including the entry into force of important provisions of the Federal Law "Concerning the Fundamental Principles of Public Healthcare in the Russian Federation" as of 1 January 2012. Numerous debates continue over the need for amendments to the Federal Law "Concerning the Circulation of Medicinal Drugs". The new legislation "Concerning the Fundamental Principles of Public Healthcare in the Russian Federation" establishes and regulates, among other things[12]:

- fundamental principles of public healthcare
- power of state authorities
- rights and obligations of citizens
- organization of healthcare

[12] *Source: Ernst & Young, Survey of the pharm industry in Russia*

- activities of medical/pharmaceutical workers and medical organizations
- rules governing free medical care for citizens
- procedure for the financing of the healthcare sector
- supervision in the healthcare sector

Reform of the pharmaceutical market is far from complete, and further changes are expected in the future. As of January 1, 2014 it will be compulsory to comply with international Good Manufacturing Practice standards. The President's program also requires executive bodies to develop a drug reimbursement system with a view to implementation in 2016.

The market experts predict that the state will continue to encourage foreign pharmaceutical manufacturers to establish production enterprises in the Russian Federation. It only remains to be hoped that the Government will opt for a policy of granting preferences and concessions to Russian manufacturers rather than taking prohibitive measures against foreign companies.

On 22 August 2012 the Protocol of Accession of the Russian Federation to the World Trade Organization entered into force. Under the Protocol the level of import duty rates were to be gradually reduced beginning from 2013. In particular, import duty rates for medicinal drugs will come down from their existing level (10-15%) to 5-6.5% (no later than 2016), while rates for medical devices will fall on average from 5% to 3% (no later than 2014). Another condition of Russia's membership of the WTO was the improvement of intellectual property protection, including by means of the creation of specialized intellectual property courts.

32.4 Key players - companies assisting with registration

In absence of official databases or rankings of companies assisting with product registration, the consultant had to depend on references by experts in the pharmaceutical sector. Below are profiles of selected leading companies assisting with registration of medicinal products.

COMPANY NAME	**Expert Group "RegMed prof."**
Address	Vernadsky Prospect, Building 2, Construction 37
Address (city)	Moscow
Address (ZIP)	
Telephone	+7 495 938 95 65
Web site	www.en.regmed.biz
PROFILE	Providing registration services for pharmaceuticals
Description	Involved in: • Preparation of documents for registration of medicines, medical equipment, biologically active dietary supplements, perfumes and cosmetics products and diet food • Representation of producers' interests in state registration agencies of units designed for medical application • Organization of clinical tests • Organization of sanitary and epidemiological expertise • Execution and formalization of licenses for import/export of products • Execution and formalization of licenses for pharmaceutical activity • Certification in GOST R system • Certification in the system of sanitary and epidemiological control
Year of establishment	1998
Ownership structure	LLC

COMPANY NAME	**RusClinic**
Address	Kutuzovsky Prospect, 24
Address (city)	Moscow
Address (ZIP)	121151
Telephone	+7 495 981 06 35
Web site	http://rusclinic.ru/eng/main
PROFILE	Involved in registration, marketing, and distribution of pharmaceutical products
Description	The company provides a wide range of services, including registration (medical products, perfumes and cosmetic products, personal hygiene items, disinfecting agents etc.) as well as marketing and distribution services related to pharmaceutical products.
Year of establishment	2000
Ownership structure	Closed Joint Stock Company

COMPANY NAME	**PharmaReg**
Address	Pervomayskaya St. 58B, Building 1, Office 204
Address (city)	Moscow
Address (ZIP)	105043
Telephone	+7 495 645 78 27
Web site	http://pharmareg.ru
PROFILE	The company provides assistance in the area related to the state registration of pharmaceutical products, pharmaceutical substances and food supplements.
Description	Involved in: • Preparation of documents for registration of pharmaceutical products • Representation of producers' interests in state registration agencies • Cooperation with the State Authorities in the field of registration of pharmaceutical products • Translation of medical documentation
Year of establishment	2007
Ownership structure	LLC

COMPANY NAME	**SIA AFC**
Address	Lodochnaya St., 6
Address (city)	Moscow
Address (ZIP)	125363
Telephone	+7 495 9264836
Web site	http://siaapi.ru/about/
PROFILE	Subsidiary of one of the largest distributors of pharmaceuticals in Russia, SIA
Description	The company offers a complete range of services related to registration of pharmaceuticals.
Year of establishment	2005
Ownership structure	LLC

33. MARKET ENTRY STRATEGY

33.1 Market overview

33.1.1 Market size and breakdown

The Russian pharmaceutical market placed as one of top 10 markets in the world in 2011; it grew by 12% in 2011 compared to the previous year, amounting to RUB 824 billion (USD 28 billion) (including VAT) at end consumer prices. The Russian pharmaceutical market is forecasted to reach USD 75 billion by 2020, according to Cegedim Relationship Management aggregated opinion from industry experts, government employees, and analysts.

The market is import-oriented, as 76% of pharmaceuticals (in value) are produced abroad, while domestic pharmaceuticals are dominating by volume, holding a 63% share[13].

The main market trend of 2011 was a decrease in sales of low-cost drugs (less than USD 1.7 per package) and an increase in sales of expensive drugs (more than USD 16.7 per package)[14].

Market players continue to see unfavorable legislation as the main threat to the industry. Both Russian and foreign companies name corruption as one of the most dangerous threats to the market. Another challenge is a shortage of skilled staff. At the same time, despite the difficult economic climate, market players are not experiencing substantial shortages of financial resources needed to support and develop their activities.

On January 1, 2012 the new federal legislation on public health protection came into force. It aims at modernization of the health service through decentralization and the empowerment of regions to make decisions regarding both reimbursement and treatment protocols. The act also imposes fairly strict rules on the interaction between the pharmaceutical industry and healthcare professionals in order to levy far greater control over the promotion and prescription of drugs, trying to minimize the risk of corruption and to ensure that patients have access to the right medicines. Prior to introduction of this legislation, pharmaceutical companies could not only entertain healthcare professionals and offer gifts legally, but also pay to encourage prescribing. Now, such activities are forbidden; the government has tried to fundamentally change the conditions under which representatives and healthcare professionals can interact.

[13] *Source: DSM Group report*

[14] *Source: Ernst & Young, Survey of the pharma industry in Russia*

33.1.2 Local production

Currently, there are **about 350 producers of pharmaceutical products in Russia**. The top 20 players generate 70% of all revenues of domestic producers.

Industry experts claim that locating drug manufacturing to Russia will be the main trend over the next few years.

The Russian government is taking efforts to stimulate production of pharmaceuticals by Russian companies to substitute imported products, as Russia remains import-oriented: as stated above, 76% of all pharmaceutical products (by revenue) consumed in Russia are imported.

In October 2009, the Ministry of Industry and Trade adopted "Pharma Strategy 2020"; it is aimed at development of the pharmaceutical industry, which is under the jurisdiction of the Department of Chemical Technology Complex and Bioengineering Technologies of the Russian Ministry of Industry and Trade. The main objectives of Pharma Strategy 2020 are - "Creation of necessary conditions for the enhancement of innovative development of Russian pharmaceutical production, which should increase the availability of medicines for the Russian population, health care system, defense sector and other federal services and the supply up to the average European level in natural and value terms". The Strategy will improve the competitiveness of the Russian pharmaceutical sector and its production capacity to substitute up to 50% of imported products by locally produced ones, 80% of which is planned to be innovative.

The first phase of Pharma 2020—from 2009 to 2012— aimed to locate drug manufacturing and development in Russia. This resulted in many foreign companies announcing that they will build production facilities or launch joint development projects with Russian partners. The second phase (from 2013 to 2017), is set to boost the production of pharmaceuticals—both generic and innovative — by domestic companies. Various companies and institutions have announced projects to develop many new drugs during this period. In the final phase, 2018–2020, Russian pharmaceutical companies are due to start a new phase of pharmaceutical exports.

According to the IHS report meeting the Pharma 2020 goals causes concern; insufficient funding and structural deficiencies are likely to be the key obstacles.

The largest Russian producer is Pharmstandart; with a 3.5% share it ranks among top 5 pharmaceutical producers in Russia. No other Russian producer is included in top 20.

Foreign producers, such as Gedeon Richter, KRKA, Sanofi-Aventis, Servier, STADA CIS and Polpharma, have all established local production in Russia, and a number of other companies plan to develop local production. For instance, AstraZeneca began to construct a production facility. Some producers, including Pfizer, Roche, GlaxoSmithKline will offer technology transfer.

33.2 Distribution of pharmaceuticals

33.2.1 Distribution structure – key distributors

The combined share of the six largest distribution companies - Protek, SIA International, Katren, ZAO Rosta, Alliance Healthcare Rus, and R-Pharm - reaches almost 60%. Protek, the leader, controls 13.73% of the market; it is followed by Katren (13.18%) and ZAO Rosta (11.36%).

Largest distributors of pharmaceuticals, Russia, 2012

Company	Website	Profile
Alliance Healthcare Rus	www.alliance-healthcare.ru	Present in over 50 cities of Russia; part of international pharmaceutical group Alliance Boots
Katren	www.katren.ru/?lang=eng	Its logistics and distribution system operating nationwide
Protek	www.protek.ru/en	National distribution company, with a wide network of offices throughout Russia; distributing products of many leading producers, including Bayer, Novartis, Sanofi Aventis etc.
R-Pharm	http://r-pharm.com/en/	Carrying products of e.g. Eli Lilly, Pfizer, AstraZeneca, Sanofi, and others
SIA International	www.siamed.ru	One of the largest distribution companies in Russia
ZAO Rosta	www.rostagroup.ru	National distribution company; working with about 400 suppliers from 44 countries

Source: EasyLink Business Services and company websites, 2013

33.2.2 Key customers – pharmacies and hospitals

Retail sales increased by 11% in 2012, and chains of pharmacies drove the growth. The Russian government is discussing the possibility of allowing general retail chains to sell OTC drugs, as well as banning ads for OTC drugs. Both measures may significantly change the retail market in Russia.

Largest pharmacy chains (with a market share above 1%), Russia, 2012

Pharmacy Chain	Website	Market share, %
Rigla	www.rigla.ru	2.41
UMG	http://u-m-g.ru	2.26
A5 Group	http://a5group.ru	2.24
Apteki 36.6	http://366.ru	2.20
Alfega Apteka	www.alliance-healthcare.ru	1.90
Pharmacor	www.pharmacor.ru	1.29
Implozia	www.implozia.ru	1.27
Pharmaimpex	http://www.farmaimpex.ru	1.21

33.3 End user analysis

The most demanded products by end users are from the ”digestive tract and metabolism” ATC group, making up for 19.6% of sales (by value). Almost 18% of sales in this group come from the vitamins sub-group, with the most popular brand being Milgamma.

The second largest category are drugs for nervous system that generate 12.7% of sales. The leading sub-group are analgesics; the most popular brand is Theraflu.

According to DSM Group sales of drugs for the treatment of coronary heart diseases and respiratory disorders constitute slightly over 12% each.

According to industry experts, the nutritional supplements market in Russia may grow by 30% within 5 years. In 2011, over 300 million packages of supplements were sold. In terms of value, the increase equaled to 13% compared to 2010. The leading exporters to Russia include Germany (17% share), followed by USA (14%) and Denmark (13%). The leading producer among German companies is QUEISSER PHARMA GMBH & CO.KG (Doppelherz brand). The most popular US brand is Laveron from ULTRA HEALTH PRODUCTS, and the leading brand among Danish producers is Bifiform from FERROSAN AG.

34. ANALYSIS, STRATEGY & CONCLUSION

34.1 Obstacles and challenges

According to Ms. Svetlana Zavidova, executive director of the Association of Clinical Trials Association, the process of obtaining permission for trials from government authorities currently takes 116 days instead of approximately 60 days stipulated by the Russian government.

Also, the Russian legislation on clinical trials is considered to be more strict than in many EU countries.

It shall be pointed out that:

- Except of international multicentre clinical trials (IMCTs) and post-registration studies, applications for conducting a clinical trial in Russia can only be submitted in the course of a registration process
- "Local registration studies" on safety and efficacy (except for IMCTs) trials need to be repeated (so-called confirmatory trials) in the marketing authorization process

The major problems slowing down the development of the clinical trials market in Russia involve the following:

- Clinical trials can be conducted only for pre-defined purposes. Clinical studies need to include the aspect of research and must be scientifically sound
- Direct contacts of an applicant with the Ethics Council or the Expert Organization are not allowed. This differs from the EU where a dialogue between an applicant and drug regulatory authorities and Ethics Committees is considered beneficial.
- (Principal) investigators must have a 5-year experience in the conduct of clinical trials in order to be eligible as investigators in a clinical trial.
- The law provides very strict rules concerning the conduct clinical trials on defined vulnerable persons, exceeding those in the EU.
- Clinical trials involving healthy volunteers, i.e. in Phase I studies, with "medicinal products manufactured outside the RF" are prohibited, but for local sponsors they are permitted. Also Phase I studies with foreign drugs involving patients are possible.

Removing the above outlined barriers would harmonize Russian legislation with the legislation in various EU countries, plus it would also limit the excessive administrative barriers; thus, it would further raise the investment attractiveness of Russia for international trial programs.

34.2 Market potential

The Russian pharmaceutical market, including the clinical trials segment, is one of the most attractive in the world.

The key factors include:

- growing economy over the past several years and expectations of further growth of Russian GDP
- growth of middle class and overall increase of purchasing power in Russia
- high level of instauration of the Russian population's needs in medicine, especially in regions
- growing professional skills of Russian specialists in the pharmaceutical industry

In 2012, the Ministry of Health issued 915 approvals to conduct clinical trials, up by over 60% compared to 2011. **The pace of annual growth in the number of clinical trial approvals can be maintained during the upcoming years**, as the pharmaceutical market in Russia grows further.

34.3 Route to market

A U.S. producer of pharmaceuticals and biotechnology products seeking to carry a clinical trial or register a medicinal product in Russia should **first appoint an in-market specialist** (a CRO or a company assisting with product registration).

A large number of international CROs already operate in Russia, plus there are many Russian CROs as well. Local players tend to focus on a smaller range of therapeutic areas; however, they might provide assistance in other areas as well, depending on their niche of expertise.

UKRAINE

35. CLINICAL TRIALS

35.1 Country attractiveness and challenges

Ukraine is the second most populous country after Russia in **Central and Eastern Europe**; it is the **fifth largest market for clinical trials** in this region. Ukraine's GDP per capita equals to just about one quarter of the level in the Czech Republic.

According to the "Clinical trials in CIS countries 2012 — Russia, Ukraine, Belarus and Georgia, Development forecasts for 2012–2014" report by PMR, the CIS countries clinical trials market grew 19% to reach USD 597 million in 2011. Russia held a 63% share of the market and was followed by Ukraine with 33%.

The public health care system in Ukraine still follows a very similar structure as was developed during the Soviet Union times, which positively affects the clinical trials sector and patient recruitment.

The key advantages for carrying clinical trials in Ukraine include:

- Highly centralized "vertical" health-care system organized according to therapeutic hierarchies, with only minimal competition for patients among various centers
- Clinical research associates and monitors are usually physicians in contrary to those found in other regions of the world
- Qualified and enthusiastic investigators
- Lower costs – e.g. costs per patient are by 28% lower than in Western Europe and by 47% below those in the U.K.
- Large number of CT-ready patients
- The population of Ukraine in general is much less mobile than residents of Western countries, allowing for an easier long-term follow-up
- High patient recruitment rate
- Low drop-out rate
- Genetic diversity and high urban proportion
- Availability of comprehensive, often lifelong patient records
- Comparatively few, but large, specialized medical centers, which leads to lower screening failure and premature withdrawal rates
- Legislation matches international standards and practice (including ICH-GCP standards)
- Ukraine is the only PIC/S member (Pharmaceutical Inspection Cooperation Scheme) (www.picscheme.org/members.php) among CIS countries – this international system aims to facilitate networking between participating authorities, exchange information and experience in the field of GMP and related areas, and training of GMP inspectors. On March 1, 2013 Ukraine started the pharmaceutical import licensing procedure.

- The average site productivity (measured as patients enrolled per site and per month) in Russia, Ukraine, and the Balkans is more than twice the productivity found in Western Europe and the USA. The figures were based on data from 50 multinational Phase II and III clinical trials for which enrollment data per center and per month were analyzed[15].

Clinical trial limitations, Ukraine

Limitation	Exception
Pediatric study (under 18 years)	Clinical trials have to be designed to minimize pain, discomfort, fear and risk; no incentives or inducements except compensation in the event of a clinical trial-related injury; specific documents required e.g. a written agreement by both parents
Narcotic products, psychotropic substances or their precursors	Import, logistic, and handling obstacles are expected
Phase 1 and bioequivalence studies	Allowed only at health-care institutions that comply with special requirements
Placebo-controlled studies	Studies with placebo-control only are not welcome

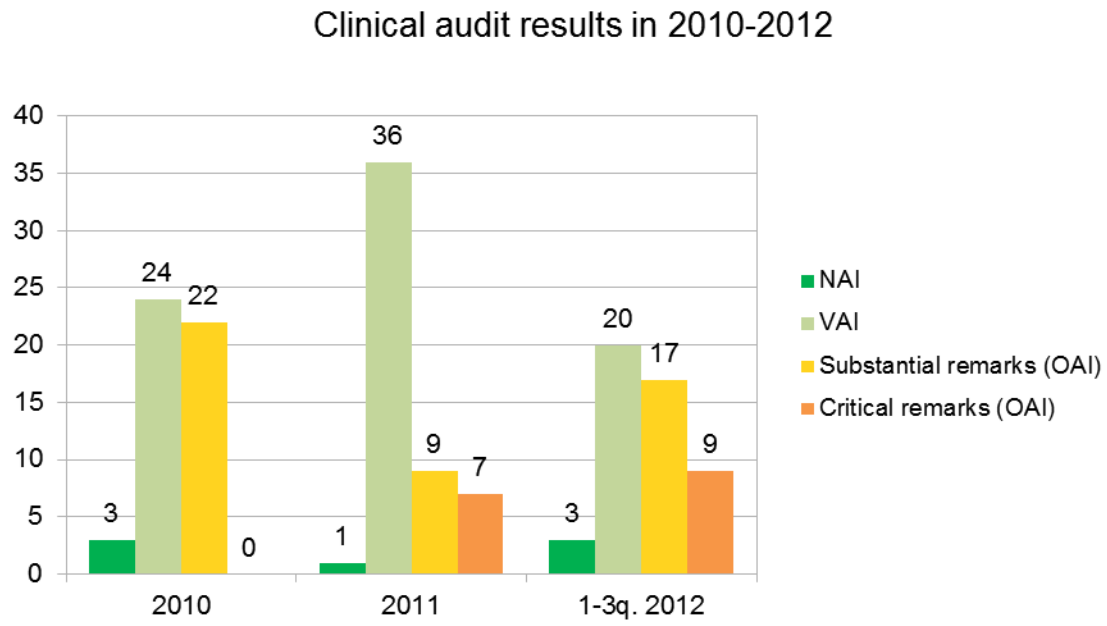
Source: Clinical Trials in Russia and Ukraine: Regulatory, Operational and Clinical Aspects Report, Premier Research Russia, 2012

According to FDA Data Audit site inspections between 1997 and 2008 just 5 trials were inspected in Ukraine, of which 4 were NAI (80%) and 1 VAI[16].

According to the report by Preclinical and Clinical Trial Department of State Expert Center (Ministry of Health of Ukraine) between 1999 and Q3 2012, a total of 597 clinical audits (inspections) were done, out of which 43 clinical trials (7%) were suspended and 7 (1%) were stopped.

For the period of 2010 to 2012 the State Expert Center report breaks the audit results into 4 categories: NAI, VAI and OAI, which is further divided into substantial remarks and critical remarks. The number of critical remarks OAI actions increased from 0 in 2010 to 7 in 2011 to 9 in the first three quarters of 2012.

[15] *Source: Why (not) go east? Comparison of findings from FDA Investigational New Drug study site inspections performed in Central and Eastern Europe with results from the USA, Western Europe, and other parts of the world*
[16] *Source: Clinical Trial Magnifier Magazine (April 2009 vol.2 iss.4)*

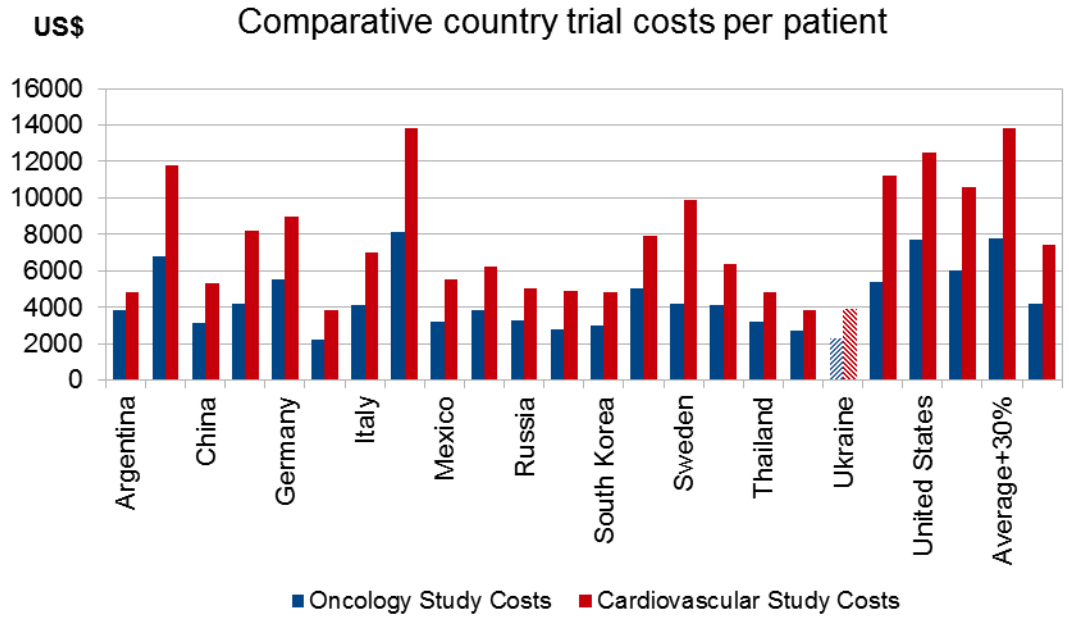


Low costs are often used as one of the key advantages for carrying a clinical trial in Ukraine; however, it is a very misleading argument, as cost items in clinical trial budgets are quickly catching up with those in Western Europe. For instance, investigator fees, regulatory costs, project management and monitoring costs do not differ much, while other costs, e.g. those related to import/export procedures, might be even higher in Ukraine.

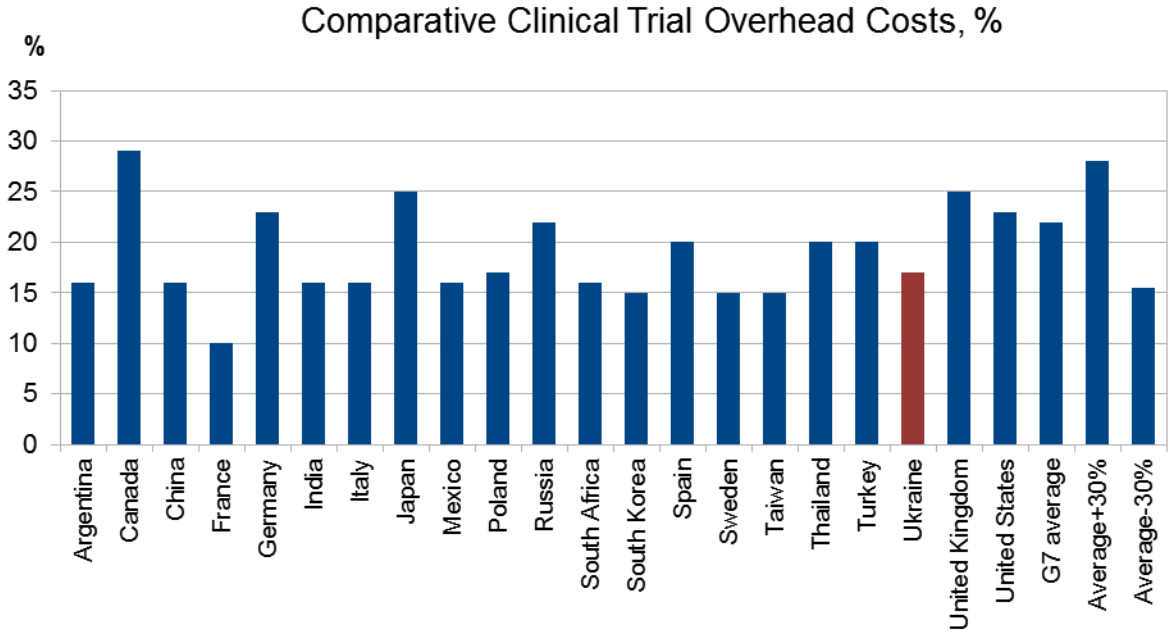
The cost advantages of Ukraine come when comparing costs per patient, rather than general budget per country. In this respect Ukraine with its high patient recruitment and low drop-out rates has a significant advantage, allowing sponsors to save up to 50% of their clinical trial budget compared to that in Western Europe.

Multi-country comparison of oncology and cardiovascular clinical study costs per patient show Ukraine to offer the lowest costs of about USD 2,300 and USD 3,900, which corresponds to figures for Turkey and India only. For comparison, the average costs for G7 countries reach as high as USD 6,000 and USD 10,600 respectively[17].

[17] *Source: Canadian Clinical Trial Summit, September 15, 2011*



At the same time overhead costs in Ukraine exceed those in many other countries, making about 17% of total study costs[18].



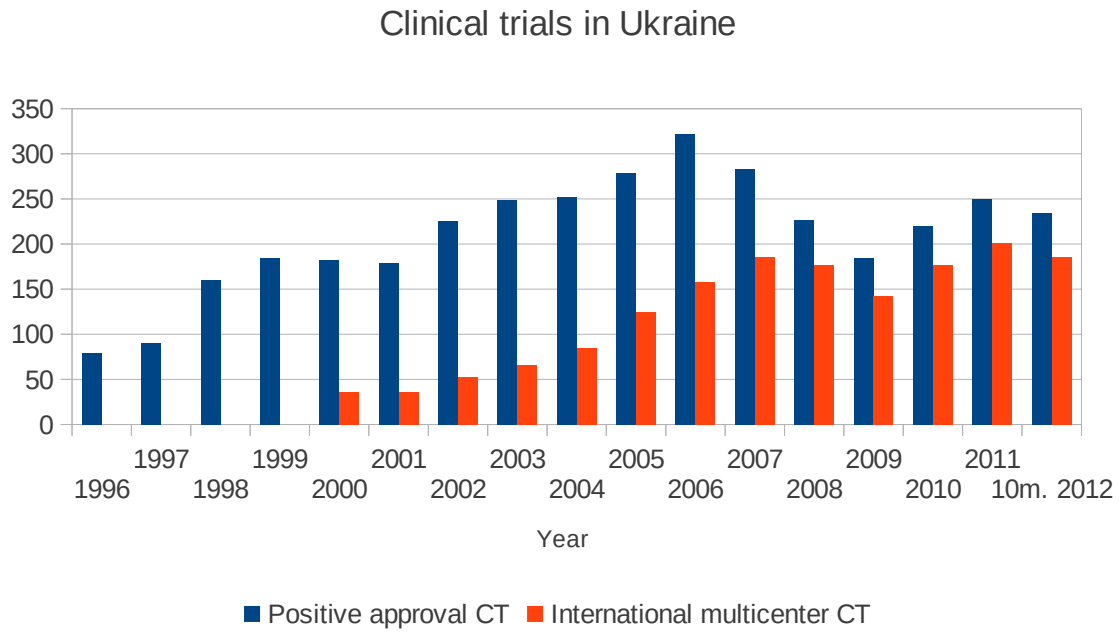
[18] *Source: Canadian Clinical Trial Summit, September 15, 2011*

35.2 Market size

35.2.1 Number of trials

Approximately 200-250 clinical trials are annually started in Ukraine.

In 2012, a total of **265 applications for clinical studies were approved** as stated by Ms. Nikolaeva, director of the Department of preclinical and clinical trials. More than **81% were multinational multicentric clinical trials**. The remaining 52 trials (22 comparison plus 30 bio-equivalence studies) were initiated by local producers. In 2012, a total of 357 studies (including those started prior to 2012) were conducted. No data is available on the percentage of denied/rejected applications for clinical trials.



Source: Preclinical and Clinical Trial Department report

35.2.2 Number of patients

A total of 278,621 patients were enrolled in 213 studies taking place in Ukraine during May 2013; the highest number of patients participated in Phase III studies.

Patient enrollment by phase, Ukraine, May 2013

Phase I	Phase II	Phase III	Phase IV	Phase not determined	Total
71	16,276	176,699	49,620	35,955	278,621

Source: ClinicalTrials.gov

35.3 Structure of studies conducted

35.3.1 By type

Up until 2005, foreign sponsors initiated just about 20-30% of clinical trials taking place in Ukraine; their share grew to about 50% by 2006; currently **multicentric commercial trials** account for as much as **80%** of clinical studies annually conducted in Ukraine.

The remaining 20% of trials are sponsored by the National Academy of Science of Ukraine.

Key sponsors of 213 currently open studies, Ukraine, May 2013

Sponsor	Number of clinical trials	Share, %
Janssen Research & Development, LLC	17	8.0
Hoffmann-La Roche	16	7.5
AstraZeneca	15	7.0
GlaxoSmithKline	15	7.0
Pfizer	13	6.1
Eli Lilly	8	3.8

Source: ClinicalTrials.gov

35.3.2 By phase

Phase II and III trials are the two most common in Ukraine; according to ClinicalTrials.gov data they combined for **92% of studies** conducted in Ukraine during May 2013.

Clinical trials by Phase, Ukraine, May 2013

Phase I	Phase II	Phase III	Phase IV	Phase not determined	*Total*
7	59	137	8	12	*213**
3%	28%	64%	4%	6%	*100%**

**Some trials have several phases, and thus the figures in the table do not add up to 213 (100%).*
Source: ClinicalTrials.gov

35.3.3 By disease

The **three leading therapeutic areas** include **oncology, psychiatrics, and neurology**; in 2012, 81 studies took place in the three areas. Other leading categories are pulmonology, rheumatology, and gastroenterology; studies in cardiology and endocrinology are conducted slightly less often. In 2010, Ukraine started to conduct clinical trials for AIDS (both adults and minors), but only a small number of studies have taken place.

35.4 Regulatory information

35.4.1 Regulatory institution

All procedures for commercial clinical trials are regulated by the Ministry of Health of Ukraine (MoH), specifically its State Expert Center (SEC), Department of preclinical and clinical trials.

COMPANY NAME	**State Expert Center of the Ministry of Health of Ukraine Department of Clinical and Preclinical trials**
Address	40 Ushinskogo street
Address (city)	Kiev
Address (ZIP)	03151
Telephone	+380 44 393-3190, +380 44 498-4352
Web site	www.dec.gov.ua/en
PROFILE	Administration body established by the Decree dated September 27, 2010; it falls under direct control of the Ministry of Health
Description	Its duties are: • Expert evaluation of materials related to the development, production, pre-clinical study, and clinical trials of medicinal products • Inspection of pre-clinical study and clinical trial sites and manufacturing sites of medicinal products, audits • Post-registration surveillance over medicinal products registered in Ukraine in collaboration with the State Inspectorate for Quality Control of Medicinal Products
Year of establishment	Tradition since 1989 as Pharmacological Commission
Ownership structure	State organization

Scientific trials are held independently by the National Academy of Science.

35.4.2 Procedure

In Ukraine the entire procedure of starting a clinical trial usually takes about 4.5 months.

Although a sponsor could possibly handle the entire process, **a CRO is usually appointed**. After a CRO is selected, test sites are selected based on the required patient enrollment quantity and insurance to be used.

An applicant shall submit to the State Expert Center the following documents:

- Cover letter
- Application form
- Protocol of a clinical trial of a medicinal product with all amendments
- Brief summary (synopsis) of the protocol in Ukrainian
- Case report form (except for international clinical trials)
- Investigator's Brochure that should include information stated in section 7 of Good Clinical Practice (GCP)

- Investigational medicinal product's dossier; the full dossier of a medicinal product to be investigated shall be submitted in a format given in Annex 4 to the Procedure if a medicinal product has not been registered in Ukraine. If a medicinal product has already been registered in Ukraine a sponsor has to submit a summary product characteristics as an investigational medicinal product dossier. For comparators and placebo the simplified dossier or summary product characteristics shall be submitted.
- Certificate for a batch (certificate of analysis, quality certificate) of an investigational medicinal product – a document issued by a manufacturer to accompany every batch of a medicinal product to verify its quality; if during the clinical trial another batch of an investigational medicinal product to be imported in Ukraine is used the applicant shall submit to the Center a certificate for the batch concerned together with a cover letter within 10 days after termination of an investigational medicinal product customs clearance.
- In case a clinical trial to be conducted in Ukraine only (with the purpose of their further registration in Ukraine) the conclusion of SEC accredited laboratory for pharmaceutical analysis regarding quality of each batch to be used for clinical trials shall be attached
- Results of previous expert evaluations and/or SEC conclusions concerning a pre-clinical study and clinical trial of a medicinal product (if any)
- List of authorized competent authorities of other countries where applications for the clinical trial are also submitted, and detailed information on their decision taken (if any)
- Letter of authorization by a sponsor with clearly specified granted powers if a clinical trial applicant differs from a sponsor
- Draft informed consent and other written information to be provided to a patient (healthy volunteer) (in Ukrainian or in officially recognized language of international communication). The draft should envisage a patient's consent to use his personal data for processing the study results.
- Brief data on all ongoing clinical trials conducted with the use of an investigational medicinal product concerned (if any)
- Expert evaluation of the clinical trial issued before (if any)
- Application from the responsible investigator according to a form given in Annex 5 to the Procedure
- Information on HCS and a clinical trial site by the time of submission of documents (materials)
- Information on responsible investigator/investigator (Curriculum vitae) should contain the following details: full name, year of birth, education, place of employment, position, record of service, degree, scientific works, previous participation in clinical trials
- Co-investigators' CVs should be submitted if doctors of different disciplines are to be involved
- Confirmation shall be issued for a medicinal product that operations at a manufacturing site or site involved in the manufacture of the medicinal product concerned are performed in compliance with good manufacturing practice providing a GMP certificate or a written official declaration of the Qualified person (of a manufacturer), or a copy of document issued by the State Administration of Ukraine on Medicinal Products that confirms the compliance of the manufacturing conditions with the Good Manufacturing Practice (GMP) requirements
- Sample labeling of a medicinal product in Ukrainian or officially recognized language of international communication

- Additional information on an investigational medicinal product (if applicable): viral safety studies; relevant documents for studies or medicinal products with specific properties (if any), a declaration on compliance of biological active substance with GMP requirements
- Copy of the insurance contract to cover an applicant's liability in case of harming subjects' life or health and a copy of insurance certificate to it
- Information on payments or compensations to subjects for participation in a clinical trial
- Sponsor's/applicant's information on measures to be taken by the investigator in case of events that may be considered as an insured accident during a clinical trial.

A sponsor must note that if a medicinal product to be investigated is a narcotic product, psychotropic substance or precursor, its clinical trial shall be conducted in compliance with requirements of the legislation related to narcotic products, psychotropic substances or precursors.

The SEC has 50 calendar days to study the materials and return a statement: positive or negative. Their decision must be approved by the Ministry of Health (MoH) during 10 days.

Assessment of ethical, moral, and legal aspects of a clinical trial is made by ethics committees at health care providers where a clinical trial is to be conducted. Positive opinion by an ethics committee shall be legalized by an appropriate protocol of its meeting. An applicant shall submit the following documents:

- Cover letter (the same as to SEC)
- Application form (the same as to SEC)
- Brief summary (synopsis) of the protocol in Ukrainian
- Investigator's Brochure that should include information given in section 7 of Good Clinical Practice (GCP)
- Copy of SEC conclusion approved by MoH (if any)
- Letter of authorization from a sponsor with clearly specified granted powers if a clinical trial applicant differs from a sponsor
- Draft informed consent and other written information to be provided to a patient (healthy volunteer) in Ukrainian or in officially recognized language of international communication)
- Information on subject recruitment procedures (information and promotional materials to be used for recruitment to a clinical trial (if any)
- Brief data on all ongoing clinical trials conducted with the use of the given investigational medicinal product (if any)
- Application from a responsible investigator
- Information on healthcare provider and clinical trial site valid at the time of submission of documents (materials)
- Information on responsible investigator/investigator (CV) should contain the following details: full name, year of birth, education, place of employment, position, record of service, degree, scientific works, participation in clinical trials in the past
- Co-investigators' CV should be submitted if doctors of different disciplines are involved in the clinical trial
- Information which defines the terms of inducements or compensations provided to subjects for participation in a clinical trial (if envisaged by a clinical trial protocol), which may be submitted in a cover letter with reference to the relevant document foreseeing this

- Sponsor's/applicant's instructions to responsible investigator/investigator concerning actions to be undertaken in the event which can be considered as an insured accident during the clinical trial in case of harm to subjects' health and life

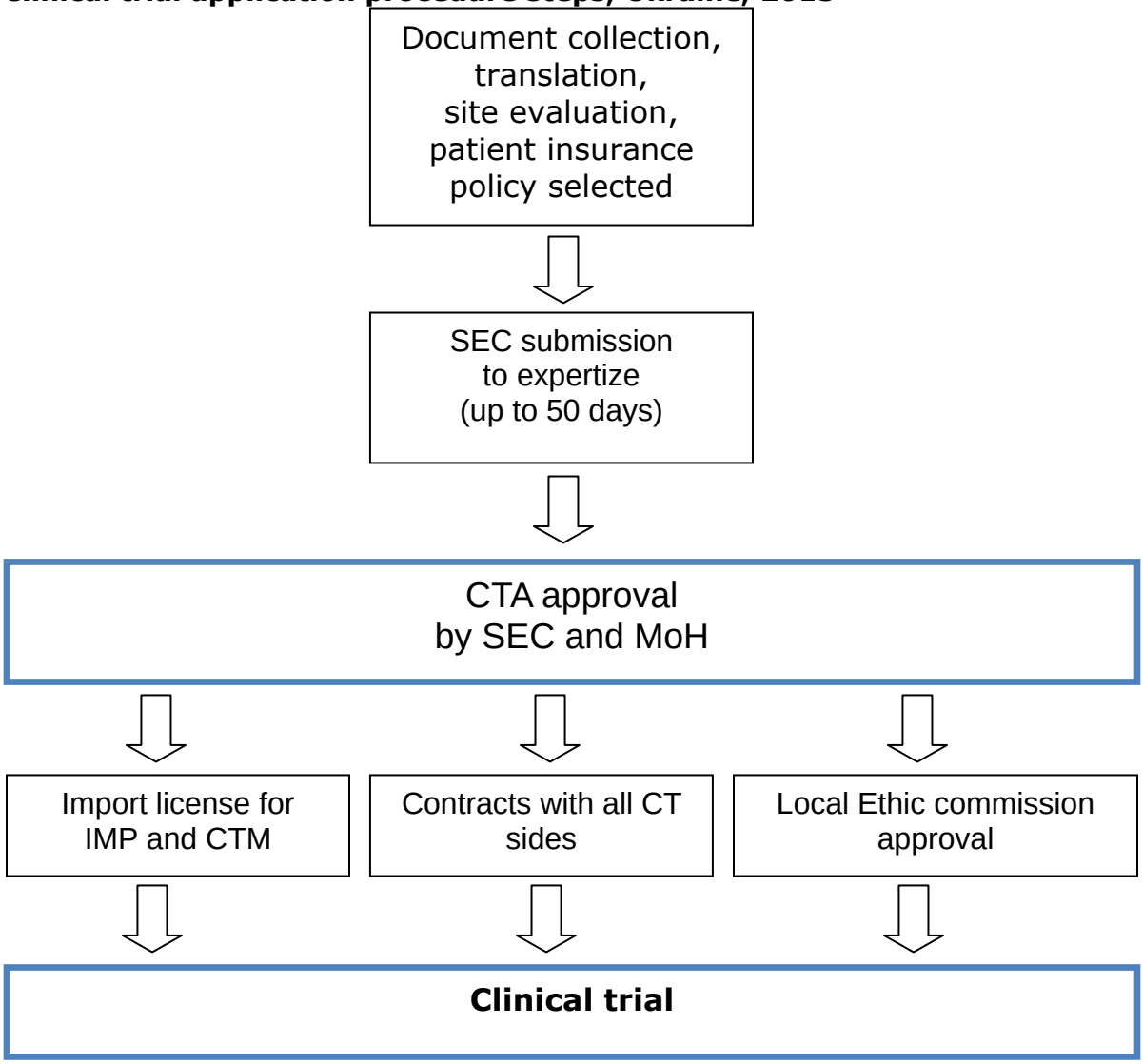
Clinical trials can start in every particular test site provided the following is ready:

- Positive Approval by State Expert Center (SEC)
- Approval by Ethics Commission at a Test Site
- Contracts with all sides conducting the clinical trial

Upon receiving a positive approval the applicant has to obtain all the required licenses to import Clinical Trial Materials (CTM) and Investigational Medicinal Products (IMP) to the territory of Ukraine. The license is a single import permit, so an import license must be received for every particular imported case. The same holds for exporting study materials. It takes approximately 2 weeks for the application for and receipt of permissions for importing and exporting study materials (import/export licenses) to go through.

When starting a clinical trial, during the process and when concluding the study a sponsor (CRO) must submit corresponding reports to the SEC.

Clinical trial application procedure steps, Ukraine, 2013



35.5 Key players

35.5.1 Key contract research organizations

Many multinational CROs already operate in Ukraine; they prevail in number over Ukrainian organizations.

Note: Financial data are not publicly available in Ukraine, and thus no objective ranking of the leading players is possible. Phone interviews with several CROs did not provide any additional insight as to who the leading players are; the managers were not open to share information on their rivals, and they all claimed to be "dynamically growing leaders".

Overview of selected leading contract research organizations, Ukraine, 2013

Company	Local vs global	Website	Activities	2011 Turnover (USD million)	Number of employees
Averion (Aptiv Solution)	Global	www.aptivsolutions.com	In Ukraine, it specializes mainly in oncology and cardiovascular diseases.	NA	NA
Axis Group Ltd (AXG)	Local	www.axis-group.com.ua/en/	Phase II–IV clinical trials, with experience in oncology, pulmonology, cardiology, vascular surgery, hematology, and psychiatry studies	NA	24
Chilltern	Global	www.chilltern.com	Phase I-IV, focus mainly on oncology, CNS-TBA, infectious diseases and vaccines, cardiorespiratory, ophthalmology, and pediatrics	NA	NA
Farmasoft CT	Local	www.farmasoft-ct.com.ua/en/	Phases II-IV studies, therapeutic areas covered: Cardiovascular, Endocrine and Metabolic, CNS, Pain, Inflammation, Urology, Sexual Health, Oncology, and Ophthalmology	NA	17
Parexel	Global	www.parexel.com	Phase I-IV, cardiovascular, CNS, infectious diseases, and oncology	NA	NA

Company	Local vs global	Website	Activities	2011 Turnover (USD million)	Number of employees
PRA International	Global	www.prainternational.com	Providing clinical development services across multiple therapeutic areas for Phase II-III	NA	NA
PSI	Global	www.psi-cro.com	Involved in multiple therapeutic areas of clinical trials, Phase I-IV	NA	NA

A Pennsylvania company seeking to identify a suitable CRO to run a clinical trial in Ukraine or other CEE countries shall contact the Authorized Trade Representative in Central Europe with specific requirements and expectations on the partner organization (see section 38.3 Route to market).

The following leading **global CROs** operate in Ukraine:

COMPANY NAME	**Averion (Aptiv Solution)**
Address	50 Artema street, office 7A
Address (city)	Kiev
Address (ZIP)	04053
Telephone	+380 44 284-0434 fax: +380 44 284-0435
Web site	www.aptivsolutions.com
PROFILE	Full-service CRO
Description	• In Ukraine, it specializes mainly in oncology and cardiovascular diseases. • Headquartered in Southborough, Massachusetts, with European operations based in Basel, Switzerland, it also has offices in France, the Netherlands, the United Kingdom, Poland, Russia, Israel, Germany, Austria, and Ukraine and operation centers in the Czech Republic, Slovakia, and Hungary.
Year of establishment	2008
Number of employees	850, operating out of 26 offices

COMPANY NAME	**Chiltern**
Address	18-22 Metalistiv Street, block 7
Address (city)	Kiev
Address (ZIP)	03057
Telephone	+380 44 593-6590, +380 44 593-6591
Web site	www.chiltern.com
PROFILE	Global Contract Research Organization, UK-based
Description	• The company focuses mainly on oncology, CNS-TBA, infectious diseases and vaccines, cardiorespiratory, ophthalmology, and pediatrics. • Extensive experience in the management of Phase I-IV clinical trials across a broad range of therapeutic areas and contract staffing solutions.
Year of establishment	1982
Number of employees	1,500 employees in more than 40 countries

COMPANY NAME	**Parexel (Parexel Ukraine LLC)**
Address	9, Moskovsky avenue, Building 2, Office 204
Address (city)	Kiev
Address (ZIP)	04073
Telephone	+380 44 490-7454, +380 44 496-2784 Fax: +380 44 490-9557
Web site	www.parexel.com
PROFILE	Global full-service CRO, USA-based
Description	• The company conducts Phase I-IV studies incorporating the full range of services from clinical study design to bioanalytics to peri-approval and post-marketing services, with an emphasis on First in Man and Proof of Concept studies. • Focus mainly on cardiovascular, CNS, infectious diseases, and oncology
Ownership structure	Limited Liability Company
Number of employees	14,400 employees through 78 locations in 52 countries

COMPANY NAME	**PRA international**
Address	10/14 Radischeva Street, Irva Business Center, Bld. B, 1st floor
Address (city)	Kiev
Address (ZIP)	03680
Telephone	+380 44 594-5555, +380 44 594-5556
Web site	www.prainternational.com
PROFILE	Global full-service CRO
Description	• Experienced in pharmaceutical and biotech industries • In Ukraine, the company is represented by ClinStar, a CRO acquired by PRA in 2013, it provides clinical development services across multiple therapeutic areas for Phase II-III.
Year of establishment	1976
Number of employees	5,000 employees in over 30 countries

COMPANY NAME	**PSI (PSI Company Ltd)**
Address	4 Ivana Lepse blvd., Silver Center
Address (city)	Kiev
Address (ZIP)	03067
Telephone	+380 44 492-8560
Web site	www.psi-cro.com
PROFILE	Global full-service CRO, Switzerland-based
Description	• Involved in multiple therapeutic areas of clinical trials, Phase I-IV • The largest office and the operational headquarters are in Russia, Ukraine, Romania, Bulgaria, Poland, Estonia, the Czech Republic, Switzerland and the USA. The parent company, PSI CRO AG, is based in Zug, Switzerland.
Year of establishment	1976
Ownership structure	Limited Liability Company (in Ukraine)
Number of employees	1,300 employees across Europe and North America

The following **local CROs** operate in Ukraine:

COMPANY NAME	**Axis Group Ltd (AXG)**
Address	16 V. Chaiky Street
Address (city)	Chaiky, Kiev-Sviatoshynsky district, Kiev
Address (ZIP)	08130
Telephone	+380 44 593-3950
Web site	www.axis-group.com.ua/en/
PROFILE	Middle-size independent Contract Research Organization
Description	• Focus on Phase II–IV clinical trials • Experience in oncology, pulmonology, cardiology, vascular surgery, hematology, and psychiatry studies • Involved in 25 ongoing studies • 4 completed clinical trials with successful audits and sponsor awards
Year of establishment	2005
Ownership structure	Private company
Number of employees	24 (16 clinical trial specialists)

COMPANY NAME	**Farmasoft CT**
Address	14 Polovetska Street
Address (city)	Kiev
Address (ZIP)	04107
Telephone	+380 44 353-4891, fax:+380 44 220-1377
Web site	www.farmasoft-ct.com.ua/en/
PROFILE	Clinical Research Organization offering a complete portfolio of services necessary to conduct clinical trials in Ukraine
Description	• Focus on Phases II-IV studies • Therapeutic areas covered: Cardiovascular, Endocrine and Metabolic, CNS, Pain, Inflammation, Urology, Sexual Health, Oncology, and Ophthalmology
Year of establishment	2006
Ownership structure	Limited Liability Company
Number of employees	17

35.5.2 Key trial sites – hospitals/universities

Up until 2009 medical centers (called healing and prophylactics organizations - LPU) had to have an accreditation from the Ministry of Health to be able to conduct a trial. Now, any LPU can host a clinical trial, if it can prove that it is able to fulfill all requirements and collect all necessary documents.

Mrs. Nikolaeva, director of Department of preclinical and clinical trials, estimates that there could be around 2,000 LPUs in Ukraine, including separate departments of hospitals on all regional levels.

Selected key trial sites, Ukraine, 2013

Organization	Website	Profile
Alexandrovsky Hospital Kiev	www.okl.kiev.ua	The largest hospital in Ukraine for cardiology; over 40 clinical research studies since 2000
Donetsk regional anti-tumor center	www.dopc.com.ua	One of the largest medical centers in Ukraine; in 1998, it became a clinical base of the Ministry of Health; at the end of 2012 the center run 56 active clinical trials
Institute of Endocrinology and Metabolism, named after Komissarenko	www.iem.net.ua	Clinical research base for endocrinology
Institute of Otolaryngology named after Kolomiychenko	www.iol.com.ua	One the largest medical centers in Ukraine; it specializes in inflammatory and allergic diseases of the upper respiratory tract and ear infections in adults and children
Kiev City Clinical Hospital # 1		One of the largest hospitals in Kiev; it specializes in pulmonology, gastroenterology, rheumatology, and cardiology
Lugansk Regional Clinical Oncology Center	www.locod.lg.ua	One the largest medical centers in Ukraine; it is a clinical base of the department of oncology, radiology and transfusion of Lugansk State Medical University

36. PRODUCT REGISTRATION

36.1 Registration authority

Registration of medications is regulated by the Ministry of Health of Ukraine and the State Expert Center (SEC, www.dec.gov.ua/en).

36.2 Types of registration

Only medications registered in Ukraine are permitted. The registration procedure is based on the Decree by Cabinet of Ministers of Ukraine #376 "On approval of state registration (re-registration) procedure of medicinal products" from 2005.

There is just one type of medication registration – **State registration**. Every medicine (except of those made in pharmacies by prescription or on a medical facility request) must pass State registration and receive an approval.

An applicant must submit an application form and a registry document set (registry dossier) according to the Decree #426 "On approval of Procedure of medicines registration materials expertise". Documents can be in Ukrainian, Russian or English language. In case English is selected, some documents still have to be translated into Ukrainian or Russian.

The dossier consists of the following administrative and medical documents:

- Dossier resume
- Chemical, pharmaceutical, biological documents on a medicine
- Pharmacological and toxicological documentation
- Pre-clinical trial reports
- Clinical trial reports

Also an applicant submits samples of a medicine and its package.

The exact list of documents to be submitted depends on the type of medicine.

MoH passes the application form and document dossier to SEC that does all expertise required. An applicant has to sign a contract with SEC for expertise and if required for additional pre-clinical and clinical trials.

The expertise procedure includes the following steps:

- Initial application expertise
- Preliminary expertise
- Specialized expertise
- Additional expertise, if required

SEC makes an expertise related to the efficacy, safety and quality of a medicinal product and recommends state registration of such product or refuses it. SEC has the right to initiate additional expertise.

During the first 14 days from the start of the expertise procedure SEC makes a preliminary expertise and returns a written answer to the applicant. In case of dossier problems an applicant has 90 days to correct them. When the preliminary expertise phase is passed, specialized expertise starts.

The entire expertise process lasts 210 days in case of a registration and 90 days for re-registration. This period does not include the time needed for correction of the applicant's dossier and conduct of additional trials.

Based on the SEC conclusions and recommendations the Ministry of Health rules on the registration of a medicinal product or refusal of the registration within a 30-day term.

In case of a positive decision the applicant receives a registration certificate valid for 5 years. Upon the end of the term the applicant could apply for a re-registry of the product.

The fee for the state medicinal product (re-)registration is EUR 100 (USD 139) for each drug form, EUR 10 (USD 14) for each next dose or each next drug package. The state (re)registration fee for radioactive medicinal products, diagnostic agents and some other products is EUR 25 (USD 35) for one name, EUR 5 (USD 7) for each next dose or each next drug package.

The costs charged for the expertise are based on the type of application.

Medical product registration procedure, Ukraine, 2013

#	Stage description	Duration limit, working days	Total expertise duration limit, calendar days	Total registration procedure duration, calendar days
1	Registration dossier translation and preparation for submitting to state bodies		210	Up to 240
2	Submitting Application form to Ministry of Health			
3	Registration fee payment			
4	Application form examination by MoH	3		
5	Initial application expertise	7		
6	Contract for expertise between SEC and applicant signing			
7	Preliminary expertise	14		
8	Specialized expertise			
9	Additional expertise, if required			
10	MoH registration approval	30 calendar days		
11	Registration certificate issuing			

According to Ukrainian legislation Ukrainian medical product manufacturers must conform to GMP standards as of 2010. As of February 2013, this is required for imported products as well; until February 2013 an importer had to submit a GMP certificate issued by the country of origin. Now an importer must get a special GMP certificate in Ukraine or confirmed international GMP certificate.

36.3 Key legislation for human medicines

The following legislation pertains to human medicines, including clinical trials:

- "Bases of legislation of Ukraine on health act" from 1992
- Act of Ukraine "On medicines" from 1996
- Decree by Cabinet of Ministers of Ukraine #376 "On approval of state registration (re-registration) procedure of medicinal products" dated 2005
- MoH Decree #426 "On approval of Procedure of medicines registration materials expertise" from 2005
- Decree by Cabinet of Ministers of Ukraine #902 "Procedure of State control of imported to Ukraine medicine product quality" from 2005
- Decree #690 "About the procedures of clinical studies of medical products and expertise of materials for clinical studies and regulations on ethics committees" amended by Decree #523 from June 12, 2012
- Decree "On approval of the Procedure for conducting additional studies of medicinal products during expert evaluation of registration materials" from April 17, 2007
- MoH Decree #237 "Procedure of import to the territory of Ukraine of non-registered medicines, standard samples and reagents" from 2011

36.4 Key players - companies assisting with registration

A rather small umber of companies in Ukraine specialize in the registration of medicines. Usually this service is provided as part of a wider range of services by companies offering marketing services or clinical research.

The following companies belong to the leading players.

COMPANY NAME	**Farm-ROST LLC**
Address	18, Chigorina st., office 520
Address (city)	Kiev
Address (ZIP)	01042
Telephone	+380 44 284-5117 +380 44 284-7211
Web site	http://en.farmrost.com.ua
PROFILE	Marketing company
Description	Involved in marketing, outsourcing, and promotional services for the Ukrainian pharmaceutical market, also assisting with product registration
Year of establishment	2003
Ownership structure	Private company
Number of employees	About 10 managers, 120 professional medical representatives

COMPANY NAME	**GFMG**
Address	14 Polupanova street, off. 5
Address (city)	Kiev
Address (ZIP)	04114
Telephone	+380 44 239-2641
Web site	www.gfmg.com.ua/en/
PROFILE	Marketing company
Description	Promotion and distribution of medicinal products and medical goods of foreign and domestic manufacturers It delivers full service in the area of market introduction of products: • Development of market entry strategy • Selection of market positioning • Promotion and clinical application of products • Development of product image • Marketing through wholesale and retail chains of pharmacies • Logistics • Registration of medicines and medical equipment
Year of establishment	2003
Ownership structure	Private company

COMPANY NAME	**Intermedical**
Address	7 Goloseevskaya street, Build 2
Address (city)	Kiev
Address (ZIP)	03309
Telephone	+380 67 507-0050, 44 570-5760
Web site	www.intermedical.com.ua
PROFILE	Providing services in medication registration
Description	The company assists with state registration of drugs, medical devices and equipment, special food products, and cosmetics.
Year of establishment	Over 10 years ago
Ownership structure	Private company

COMPANY NAME	**Megacom**
Address	195 B, Klochkovska street
Address (city)	Kharkiv
Address (ZIP)	61145
Telephone	+380 57 719-5905, 57 701-3752 (53,54)
Web site	www.megacom.com.ua/eng/
PROFILE	Marketing company
Description	The company offers: • Development of marketing strategy • Marketing analysis • Preparation of documents and registration • Team of medical representatives: formation, training and management • Storage and distribution
Year of establishment	1996
Ownership structure	Private company

COMPANY NAME	**Sona-Pharm LTD**
Address	4 Mykoly Grinchenka
Address (city)	Kiev
Address (ZIP)	03680
Telephone	+380 44 495-1014 Fax: +380 44 495-1015
Web site	www.sonapharm.com.ua/eng/
PROFILE	Marketing company
Description	• Registration/re-registration of products in the CIS • Marketing strategy development • Wholesale network development
Year of establishment	2005
Ownership structure	Private company

37. MARKET ENTRY STRATEGY

37.1 Market overview

The pharmaceutical market remains one of the few growing sectors of the economy of Ukraine. In 2012, the rate of growth of the pharmaceutical market even surpassed optimistic expert forecasts; it grew by 16.9% in local currency and 4.5% in volume. Nevertheless, the market size still has not return back to the pre-crisis level enjoyed in 2007, despite stable growth between 2008-2012.

37.1.1 Market size and breakdown

In 2012, the medicinal products market amounted to USD 3.97 billion, out of which retail generated USD 3.4 bn or 85.5% and the hospital segment 14.5%. For 2013, the market is forecasted to reach USD 3.5-3.7 billion.

Medicinal product market breakdown and dynamics by sales value, Ukraine

Year	Medicines			Medical devices		Cosmetics		Food supplements	
	Sales, USD mil.	Δ, %	Share, %	Sales, USD mil.	Share, %	Sales, USD mil.	Share, %	Sales, USD mil.	Share, %
2010	2,481	—	83.9	248	8.4	146	4.9	82	2.8
2011	2,891	16.5	84.7	281	8.2	146	4.3	94	2.8
2012	3,386	17.1	85.1	317	8.0	164	4.1	112	2.8

Source: Proxima Research

Medicinal product market breakdown and dynamics by packages sold, Ukraine

Year	Medicines			Medical devices		Cosmetics		Food supplements	
	Sales, mln. pcs.	Δ, %	Share, %	Sales, mln. pcs.	Share, %	Sales, mln. pcs.	Share, %	Sales, mln. pcs.	Share, %
2010	1,186	—	63.3	598	31.9	56.7	3.0	33.7	1.8
2011	1,201	1.3	64.0	584	31.2	54.3	2.9	35.8	1.9
2012	1,267	5.5	64.6	595	30.3	56.4	2.9	42.4	2.2

Source: Proxima Research

The shares of product groups have remained stable during the last three years with slow growth in the share of the segment of medicines (from 83.9% to 85.1%).

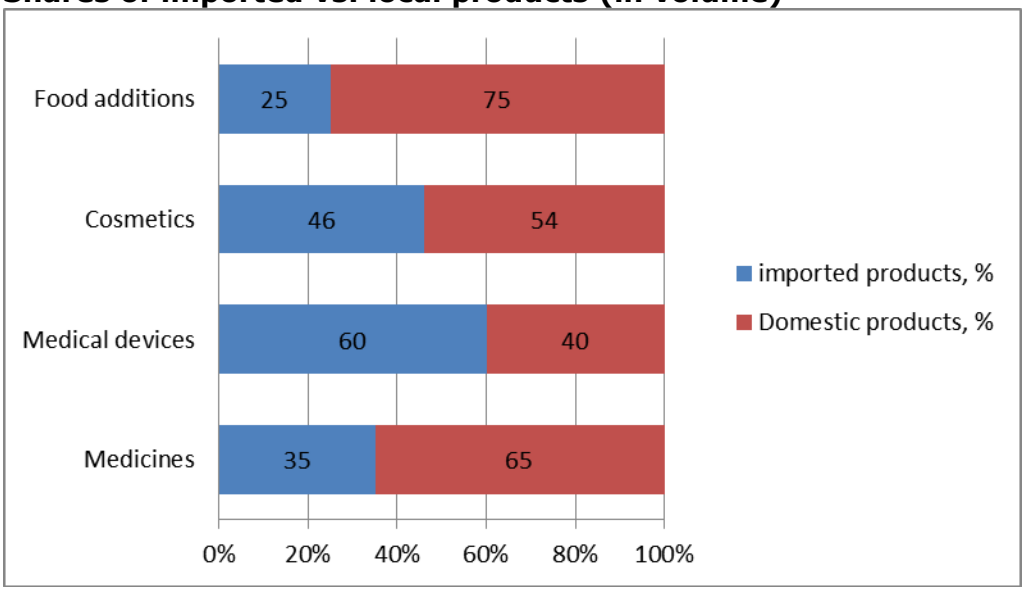
37.1.2 Local production

Before the 2008 economic crisis imported products held a major share of the market. Abrupt strengthening of foreign currencies and weak purchasing power of Ukrainian population created an opportunity for local manufacturers (who were able to offer products at lower prices) to strengthen their positions over the past 5 years. The average living standard of local consumers is quite low, they have no government support, and health insurance system does not work well; they are self-supported in prevention and treatment of diseases.

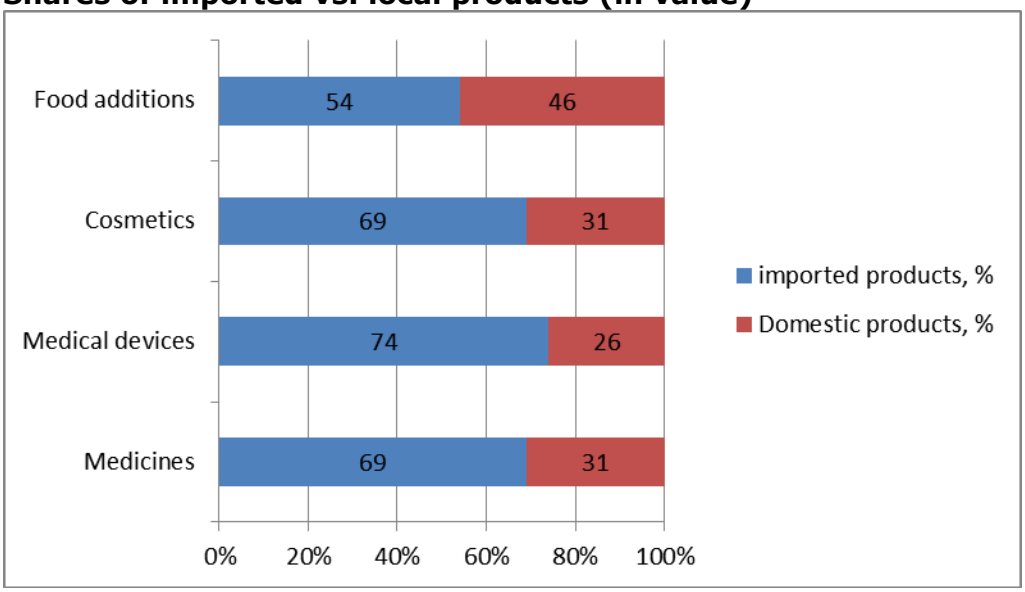
In 2011, Ministry of Health published the concept of a state program "The development of import substitution manufacture in Ukraine and substitution of imported medicines with domestic including biotech drugs and vaccines for 2011-2021". The initiative aims to stimulate local drug manufacture over the next 2 years; it is already changing the market.

Imported products prevail in terms of sales values, while local products lead in the volume of sales. The only exception are medical devices where imported products prevail altogether. On average, the ratio of foreign to Ukrainian products is 67:33 in money terms and 41:59 in quantity.

Shares of imported vs. local products (in volume)



Shares of imported vs. local products (in value)



Leading local manufacturers, Ukraine, 2013

Company	Web site	Profile
FARMAK	http://farmak.ua/en	The largest local manufacturer (18% share of Ukraine's drug manufacture) and the leader on the pharmaceutical products market for the past two years; exporting to over 20 countries: e.g. Russia, Uzbekistan, Kazakhstan, Belarus, Poland, Bulgaria, Germany, and Baltic countries
Darnitsa Pharmaceutical Company Private JSC	www.darnitsa.ua	One of the largest local pharmaceutical manufacturers; manufacturing solid dosage forms (tablets, coated tablets, capsule, sachet), solutions for injection in ampoule, drops (sterile and non-sterile), dosage forms (ointments, creams, gels, shampoos, topical solution), and sterile powder for solution for injection
Arterium Corporation	www.arterium.ua/en/	Manufacturing over 140 generic and several original drugs in 11 of 14 ATC groups
Zdorovye Pharmaceutical Company	www.zt.com.ua	Amongst top 5 manufacturers of medical products in Ukraine; the company has introduced 13 original medical products (e.g. Apiprost, Glutargin, Glutargin Alcoclean, Inflarax, Cardioarginin-Zdorovye, Artiphlex, HappyDerm plus, Plantaglucide-Zdorovye, Proalor, Fakovit, Phytolyt, Fladex, and Florised-Zdorovye).
Borshchahivskiy Chemical Pharmaceutical Plant PJSC (BCPP)	www.bhfz.com.ua/site/index.php?lang=en	The first pharmaceutical enterprise in Ukraine that fully implemented the European standards on quality (GMP, ISO 9001), distribution (GDP), environmental management (ISO 14001), health protection and labor safety (OHSAS 18001); a leader of original product

		sales among Ukrainian manufacturers; producing over 100 medicinal products of various pharmacotherapeutic groups such as tablets, capsules, granules, ampoules, lyophilized powders, syrups and sterile powders in vials.

Source: EasyLink Business Services and company websites, 2013

37.2 Distribution of pharmaceuticals

Local distributors have been major suppliers to the market for a long time, but their share in the segment of imported products is shrinking due to a more active position of direct importers; multinational pharmaceutical manufacturers have been increasing their share quite rapidly. Direct imports as percentage of total imports grew from 16% in 2007 to 41% by 2012.

37.2.1 Distribution structure – key distributors

A large number of Ukrainian distributors are present in the market; **top 10 players accounted for 93.7% of supplies to retail in 2012 compared to 91.3% in 2011** (top 5 players control about 90% of the market). The three leading distributors have maintained the same positions during the last 3 years.

Leading distributors of pharmaceuticals, Ukraine, 2013 (listed by market share)

Company	Web site	Profile
BaDM LLC	www.ooobadm.dp.ua	The largest distributor on the Ukrainian pharmaceutical market; long term contracts with over 190 leading foreign manufacturers
Optima Pharm Ltd	www.optima.kiev.ua	One of the leading pharmaceutical distributors; working with over 100 foreign and 70 Ukrainian manufacturers; 15 branches
Alba Ukraine PJSC	www.alba.kiev.ua	One of the largest wholesale traders of pharmaceuticals in Ukraine; 5 branches, covering the entire territory of Ukraine; over 100 direct contracts with suppliers
Venta Ltd	www.ventaltd.com.ua	Wholesaler of pharmaceutical products and medical devices; during the last 3 years it improved its position among national distributors from the 6th to the 4th place
FRA-M	www.fram.com.ua	Distributor working with all major domestic and most foreign pharmaceutical manufacturers

Source: EasyLink Business Services and company websites, 2013

Leading foreign producers of pharmaceuticals active in Ukraine, 2012 (by market share)

	Company
1	Berlin-Chemie Menarini Group, Germany
2	Takeda, Japan
3	Sanofi, France
4	Teva, Israel

5	Gedeon Richter, Hungary
6	Servier, France
7	KRKA, Slovenia
8	Sandoz, Switzerland
9	GlaxoSmithKline, UK
10	Actavis Group, Iceland

Source: EasyLink Business Services and company websites, 2013

37.2.2 Key customers – pharmacies and hospitals

85.5% of pharmaceuticals reach their end users via the retail channel while 14.5% are consumed in hospitals.

The following companies belong to the five largest pharmacy chains. Up until now the level of consolidation in the pharmacy sector has been very low, with the leading players holding just around 2 to 3% of the market each. Top 100 pharmacy chains control about 50% of the market.

Leading pharmacy chains, Ukraine, Q3 2012

Company	Website	Profile	Share, %
Drugstore-Magnolia (Low Prices Pharmacy)	-	Pharmacy chain operating nationwide	3.11
Med-service Group	www.med-service.com.ua	Consisting of 341 pharmacies in 119 cities/towns	2.18
Ukrainian Pharmacy Holding (Zdravitsa)	www.aptekaholding.com.ua	Over 170 pharmacies throughout the country	2.03
Arnica	www.arnika.dn.ua	Chain of pharmacies in Donetsk Region; 120 retail points	1.97
Pharmastore (Good Day Pharmacy)	www.drugstore.com.ua	National pharmaceutical chain "Pharmacy Good Day"; present in almost all regions of Ukraine with over 100 pharmacies	1.88

Source: EasyLink Business Services and company websites, 2013

In 2012, due to regulation of the sector, small pharmacy booths were closed, but the total number of retail points decreased insignificantly as many small pharmacies were replaced with bigger stores. In fact, this reduction hit mainly smaller towns and villages, as in large towns the number of retail points actually increased in number.

37.3 End user analysis

According to Proxima Research, medicines now generate about 85% of retail sales of medical products in Ukraine; medical devices constitute the second largest category (accounting for 8%), followed by cosmetics (4%) and food supplements (3%). The latter three product groups used to combine for 3-5% 15 to 20 years ago.

According to the Ministry of Health report the trend for domestic medicines preference is evident. For instance, as part of the state program for support of local manufacture the government has initiated price regulation of drugs for hypertonic disease; as a result, domestic drug sales grew both in quantity (up 44%) and value (29%) in 2012 compared to 2011.

Retail sales breakdown by ATC group (1st level), Ukraine

ATC Level 1	Share by sales value, %
Alimentary Tract and Metabolism	20.38
Respiratory System	13.82
Nervous System	13.27
Cardiovascular System	12.66
General Antiinfectives for Systemic Use	8.32
Musculo-Skeletal System	7.68
Genito-Urinary Systems and Sex Hormones	7.09
Dermatologicals	4.90
Blood and Blood Forming Organs	4.00
Antineoplastic and Immunomodulating Agents	3.55
Sensory Organs	2.20
Systemic Hormonal Preparations, excluding sex hormones	0.83
Various	0.73
Antiparasitic Products	0.57
Total retail	*100.00*

Source: Business Credit

38. ANALYSIS, STRATEGY & CONCLUSION

38.1 Obstacles and challenges

A pharmaceutical company wishing to carry a clinical trial or register a product in Ukraine shall be prepared to face a number of bureaucratic and logistic challenges:

- Ukraine remains a highly bureaucratic country; the bribery level, especially in state and municipal institutions, is one of the highest in Europe
- Imperfect legislation and complicated court system
- Long clinical trial authorization process
- Regulatory requirements and timelines
- Obligatory licensing of imported medications
- Barriers by the customs office affecting the import of study medication and export of biological samples
- Clinical trials, equipment and medication are subject to VAT (20%)

All business activities pertaining to clinical trials and registration are strictly regulated by the Ministry of Health of Ukraine; all procedures are not simple to pass and require understanding of the market specifics and the ways to solve the issues that might arise during the process. Thus, **a newcomer is highly recommended to appoint a locally experienced business partner**.

Ukrainian legislation has been constantly changing, which is something unusual for foreign companies. In order to conform to EU legislation, on March 1, 2013 medicine import licensing was introduced, which shocked all market players. Later the government softened the procedure and extended the complete transfer to a new licensing for 2013.

Clinical trial legislation was changed in June 2012.

Other challenges include the government program for support of domestic manufacturers and pilot projects on price regulation.

38.2 Market potential

In brief the Ukrainian clinical trial market could be characterized as heavily regulated - underdeveloped – dynamic – potentially very interesting.

The Ukrainian clinical trials market has been growing dynamically. Outsourcing clinical studies to Ukraine is attractive mainly due to lower trial costs per patient. Ukraine-based CROs and clinical centers carry all stages from Phase I to IV. Currently, Phase II and III combine for 92% of studies. This trend is not expected to change in the near future.

According to European Business Association data **Ukraine uses just about 10–15% of its clinical trials potential**. The "Clinical trials in CIS countries" report by PMR forecasts the Ukrainian **clinical trials market to grow by 10-20% annually during the next 3 years**.

The market is now restrained by official authority regulation and control and unclear approval procedures that usually take longer than stipulated. Ukrainian legislation starts to conform to EU rules, but local bureaucracy hinders the market growth.

The pharmaceuticals market belongs to just a few segments of the economy that have been enjoying permanent growth and interest by investors. According to European Business Association investments into clinical trials reach around UAH 1 billion (USD 123 million).

38.3 Route to market

A U.S. manufacturer of pharmaceuticals and biotechnology products seeking to carry a clinical trial or register a medicinal product in Ukraine should **first appoint an in-market specialist** (a CRO for a clinical trial; medicinal product registration is handled by CROs as well as specialized local marketing companies).

CROs operating in Ukraine are mostly **multinational** companies; many are based in the United States.

A **local CRO** could be contracted as well – they have international trial experience, are cheaper and offer quite high service quality, plus the companies are experienced in working with English speaking customers. Some local CROs have offices in Russia or in other CIS-countries.

Various CROs specialize in studies in different therapeutic areas. All CROs offer the most popular Phase II and III studies, while Phase I and IV studies can be carried by only some of them.

PART E: RECOMMENDATION

The Authorized Trade Representative (ATR) recommends that **a U.S. company wishing to outsource a clinical trial to or register and market a new product in any of the CEE markets first identifies and appoints an in-country specialist**, e.g. a contract research organization (selecting a local player over a subsidiary of a global company will result in cost savings), a regulatory consultant or a distributor. Their in-depth knowledge of the local legislative and administrative environment is essential, as each CEE country has several special expectations and requirements.

The Authorized Trade Representative in Central Europe can assist by identifying and approaching prospective partners based on client's requirements in order to confirm their qualification and interest in the service requested.

Then, the ATR can schedule conference calls or in-country meetings with the top candidates: qualified and with confirmed interest in collaboration.

The same service can be provided in all 15 countries subject to this study.