Introduction: The Clinical Trials Market—A View from Europe

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Clinical Trials Today and ICH GCP

Since the 1960s, both the US and the EU have made significant clinical trial regulatory updates and numerous laws and regulations have been introduced.

The now well-known Declaration of Helsinki was developed by the World Medical Association (WMA) in 1964. Physicians and other participants in clinical trials that involved human subjects should abide by guidelines laid down in these ethical codes, which remain the foundation of ethical research to this day. The declaration was amended subsequently in 1975, 1983, 1996, 2000, 2001 and 2002, most notably in regards to the ethical use of placebo controlled trials.

In 1986, Great Britain, France, Germany, and the Scandinavian countries issued the Good Clinical Practice (GCP) recommendations. Three years later in 1989, they were ordered into the GCP recommendations of the European Community. In Europe, the EU-CTD was passed in 2001 in which the three compulsory criteria of quality, safety, and efficacy for the authorization of a medicinal product to be sold in the European Market were stated. The safety and efficacy criteria had to be demonstrated through the results of clinical trials.

With the continuing globalization of the pharmaceutical industry, globally acceptable guidelines were increasingly seen to be a necessity. The urgent need to rationalize and harmonize regulations was impelled by concerns over rising costs of health care, escalation of the cost of research and development and the need to meet the public expectations that there should be a minimum of delay in making safe and efficacious new treatments available to patients in need. In 1990, the International Conference on Harmonization (ICH) was constituted for just this intention. Representatives of the regulatory agencies and industry associations of Europe, Japan and the USA met, primarily, to plan an International Conference, but the meeting also discussed the wider implications and terms of reference of ICH. It was through this initiation that we now have the globally recognized ICH GCP guidelines, and

- To safety
- To be informed
- To chose
- To be heard
The country profiles that follow provide a description of clinical trial procedures in each of the EMEA Member States.

### 2.2. Austria

#### Country Description

<table>
<thead>
<tr>
<th>LAND AREA</th>
<th>83,870 km²</th>
</tr>
</thead>
<tbody>
<tr>
<td>POPULATION</td>
<td>8,205,533 (July 2008 est.)</td>
</tr>
<tr>
<td>GEOGRAPHICAL LOCATION</td>
<td>Central Europe, north of Italy and Slovenia. Bordering countries are Czech Republic, Germany, Hungary, Italy, Lichtenstein, Slovakia, Slovenia and Switzerland</td>
</tr>
<tr>
<td>POLITICAL SITUATION</td>
<td>Federal republic presidential election last held April 25, 2004 (next to be held in April 2010); Chancellor formally chosen by the President but determined by the coalition parties forming a parliamentary majority; Vice Chancellor chosen by the President on the advice of the Chancellor</td>
</tr>
<tr>
<td>MAIN RELIGION</td>
<td>75% Roman Catholic</td>
</tr>
<tr>
<td>MAIN CITIES</td>
<td>Vienna (capital), Salzburg, Innsbruck and Graz</td>
</tr>
<tr>
<td>HEALTH SERVICE BASIS</td>
<td>Government-funded National Health Service with private practice clinics alongside. System consists of local health care units headed by general practice doctors with some specialist services. If necessary, these units will refer patients to specialists in local or regional hospitals.</td>
</tr>
<tr>
<td>CLINICAL TRIAL POPULATION</td>
<td>Moderately large treatment-aware population</td>
</tr>
</tbody>
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European Clinical Trial Site Options: An Insider’s Analysis

Clinical Trials in Bosnia and Herzegovina—A Brief Overview and History

Bosnia and Herzegovina’s declaration of sovereignty in October 1991 was followed by a declaration of independence from the former Yugoslavia on March 3, 1992, after a referendum boycotted by ethnic Serbs. Bosnia was involved in the much publicized war between ethnic groups in the former Yugoslavia in the 1990’s. On November 21, 1995, in Dayton, Ohio, the warring parties initialed a peace agreement that brought to a halt three years of interethnic civil strife (the final agreement was signed in Paris on December 14, 1995). The Dayton Peace Accords retained Bosnia and Herzegovina’s international boundaries and created a joint multi-ethnic and democratic government charged with conducting foreign, diplomatic, and fiscal policy. Also recognized was a second tier of government, comprised of two entities roughly equal in size: the Bosniak/Croat Federation of Bosnia and Herzegovina and the Bosnian Serb-led Republika Srpska.

In Bosnia and Herzegovina it should be noted that there are two entities in every aspect, including health care and services. The health service is still in the development phase, and fragmented; it is described by the WHO in the following terms:

*The design of the health care system makes it difficult to achieve efficiency and quality. In the Federation of Bosnia and Herzegovina, health care is organized at the canton level and coordinated at the federal level. The cantons have had major operational difficulties in providing health services. Republika Srpska manages health institutions at both the entity level and the municipal level; it currently has two parallel systems of primary health care delivery—the former (pre-war) system and the new and reformed system based on family medicine.*

It is in this setting that each entity in Bosnia and Herzegovina has its own LECs and RA bodies, although the process and documents required are the same for both.

In this environment, it is surprising to see that the number of clinical trials continues to grow year after year. While there were only 8 clinical trials approved in 2003, this number had risen to 19 in 2006. The war and post war years significantly hindered the real initiation of clinical trials in Bosnia, and the running of trials according to ICH GCP guidelines. During October 2002 in the Federation of Bosnia and...
• CVs of all clinical trial sites’ staff, including investigators and additional specialists, in Russian or Ukrainian, providing experience in clinical trials: years, drugs/molecules, therapeutic area, signed and dated

• Originals of an application on behalf of a PI, head of medical and preventive treatment facility (hospital), head of medical institution (university) for inclusion of a clinical site to conduct a clinical trial, in Russian or Ukrainian

• Originals of cards of attestation of a clinical site, in Russian or Ukrainian (both for sites with single permission and sites accredited by HM of Ukraine)

• Copies of contracts on cooperation between heads of medical and preventive treatment facility and medical institution (if a chair of academic institution is involved as a clinical site)

• Copies of the GCP certificates of all clinical trial site’s staff in English, Russian or Ukrainian (if additional specialists are involved their qualification must be attested by appropriate certificates)

• Insurance (patients’ insurance and sites/sponsor indemnification policies need to be obtained from a local insurance company)

• Draft of a hospital agreement, without any study specific information, in English and Russian or Ukrainian

The documents can be submitted at the same time to both the State Pharmacological Center and CEC, with approval by both taking 10 weeks.

**Local Ethics Committee Submissions**

Following receipt of approval from both the State Pharmacological Center and CEC, a submission to the local site’s LEC is made. The documentation required is the same as required by the State Pharmacological Center and CEC, and the process for approval takes 1 to 4 weeks, depending on the LEC.

**Import/Export License**

After final approval of the study has been granted by the State Pharmacological Center and CEC, import/export licenses can be obtained from the State Pharmacological Center. This approval takes approximately 2 weeks.
Figure 5.1. Outcomes of FDA Inspections since 1994 by Region

<table>
<thead>
<tr>
<th>Region</th>
<th>Voluntary Action Indicated</th>
<th>No Action Indicated</th>
<th>Official Action Indicated</th>
</tr>
</thead>
<tbody>
<tr>
<td>United States</td>
<td>3.2%</td>
<td>56.7%</td>
<td>40.0%</td>
</tr>
<tr>
<td>EMEA Member States</td>
<td>4.3%</td>
<td>57.6%</td>
<td>38.1%</td>
</tr>
<tr>
<td>Non-EMEA European Countries</td>
<td>27.3%</td>
<td>63.6%</td>
<td>9.1%</td>
</tr>
<tr>
<td>Russia and CIS</td>
<td>2.4%</td>
<td>40.5%</td>
<td>57.1%</td>
</tr>
</tbody>
</table>

Number in center of pie chart = number of inspections recorded on the CLIIL database from January 1, 1994 to the April 14, 2008 update

Source: Insight Pharma Reports

FDA Inspection Detailed Findings: Site Deficiencies

For the inspections with an outcome of VAI or OAI, the findings are given a deficiency code depending on the nature of the objectionable condition (e.g., inadequate informed consent form, failure to report adverse drug reactions, inadequate and inaccurate records). Figure 5.2 shows the distribution of deficiencies recorded on the CLIIL database for all inspections conducted in each region during the January 1994 to April 2008 timeframe.

It is also informative to look at the average number of deficiencies per inspection: 1.26 for the US, 1.36 for the EMEA Member States, 1.00 for non-EMEA European countries, and 0.67 for Russia and the CIS. Interestingly, the deficiencies reported at the highest percentage level were the same regardless of region and are: failure to follow the investigational plan and inadequate and inaccurate records—a
Chapter 6

WHAT THE FUTURE HOLDS FOR EUROPEAN TRIALS, EMERGING MARKETS IN EUROPE

In order to look at the future of clinical trials in Europe, it is necessary to look at EMEA countries, non-EMEA countries and Russia and CIS countries separately.

6.1. EMEA Countries’ Future

EU CT Directive

The future for the EMEA countries is believed to involve a more cohesive and uniform following of the EU Directive by all members. At this time each country has been shown to have its own individual additional requirements for clinical trial submissions, but this should be phased out as harmonization between all the countries continues to evolve. The newer members of the EMEA who have recently adopted the EU CT Directive will catch up with the original members, alleviating many of the disparities and individualism that are seen at the moment.

Electronic Submissions

In the not too distant future, it is expected that all countries in the EMEA will be routinely requesting that SUSARs are submitted electronically. The list of countries requesting electronic SUSAR reporting is available on the EMEA website and is updated regularly. This change will speed up and equalize the reporting on such issues across the whole area.