

DIRECTORATE-GENERAL FOR EXTERNAL POLICIES  
POLICY DEPARTMENT



**CLINICAL TRIALS  
IN DEVELOPING  
COUNTRIES:  
HOW TO PROTECT  
PEOPLE  
AGAINST UNETHICAL  
PRACTICES?**

DEVELOPMENT



EUROPEAN PARLIAMENT

DIRECTORATE-GENERAL FOR EXTERNAL POLICIES OF THE UNION

**DIRECTORATE B**

POLICY DEPARTMENT

STUDY

**CLINICAL TRIALS IN DEVELOPING COUNTRIES:  
HOW TO PROTECT PEOPLE AGAINST UNETHICAL  
PRACTICES?**



This document was requested by the European Parliament's Committee on Development

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## ABBREVIATIONS LIST

<b>AFSSAPS</b>	(French medicines agency)
<b>CHMP</b>	Committee for Medicinal Products for Human Use
<b>CIOMS Guidelines</b>	The International Ethical Guidelines for biomedical research involving human subjects of the Council for International Organisations of Medical Sciences
<b>CMD(h)</b>	Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human
<b>CRO</b>	Contract Research Organisation
<b>CTA</b>	Clinical trial application
<b>CTFG</b>	Clinical Trials Facilitation Group
<b>DG DEV</b>	Directorate-General Development, European
<b>DoH</b>	Declaration of Helsinki
<b>ECCJ</b>	European Coalition for Corporate Justice
<b>EDCTP</b>	European and Developing Countries Clinical Trials Partnership
<b>EMA</b>	European Medicines Agency
<b>EPAR</b>	European Public Assessment Report
<b>FDA</b>	Food and Drug Administration
<b>GCP</b>	Good clinical practice
<b>GCP IWG</b>	Good Clinical Practice Inspectors Working Group
<b>HMA</b>	Heads of Medicines Agencies
<b>ICH</b>	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
<b>ICMJE</b>	International Committee of Medical Journal Editors
<b>IFPMA</b>	International Federation of Pharmaceutical Manufacturers' Associations
<b>IMP</b>	Investigational medicinal product
<b>MAA</b>	Marketing Authorisation Application
<b>MEB</b>	Medicines Evaluation Board (Dutch medicines agency)
<b>MHRA</b>	Medicines and Healthcare products Regulatory Agency
<b>NCA</b>	National competent authority
<b>SAE</b>	Serious Adverse Event
<b>SOMO</b>	Center for Research on Multinational Companies
<b>WHO</b>	World Health Organization
<b>WMA</b>	World Medical Association

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## EXECUTIVE SUMMARY

European legislation regulating the marketing authorisation of medical products states that results from clinical trials that do not meet the ethical requirements of Good Clinical Practice, cannot legally be used by an applicant to justify its application, irrespective of whether the trial was done inside or outside the EU. However, earlier studies indicate that this legislation is not always properly observed: these studies identified trials with an unethical design that were part of approved EU marketing applications. Clinical trials that are no longer accepted by Western European ethics committees are approved by the local ethics committees in countries like India, China, Argentina and Russia. Once officially approved by an ethics committee, there are no obstacles to including the trial in the technical dossier of a marketing application. In particular the ethical principles which are of utmost importance for developing countries, as reflected in the Declaration of Helsinki, are ignored by companies and regulatory authorities.

The main objective of this paper is to provide the European Parliament with concrete recommendations, both at legislative and enforcement level, aimed to guarantee that trials conducted in third countries are done so in conformity with EU and international ethical standards.

In order to achieve the above objective, the study first established that the most appropriate standards for developing countries are the WHO guidelines on Good Clinical Practice (GCP), i.e. the WMA Declaration of Helsinki (DoH) and the elaboration of this in the CIOMS guidelines. However, the ICH Guideline on GCP is the leading guideline when generating clinical trial data intended to be submitted to regulatory authorities, also when they are generated in developing countries. The ICH guidelines are praised for the level of detail and the structures and formats provided by them that make clear what is expected. This in contrast to the DoH, which is a set of well described standards but has not been worked out in detail, making it difficult to work with in practice. An often voiced criticism of the ICH GCP guidelines is that some crucial ethical principles, relevant to developing countries and included in the DoH, are missing.

The top ten pharmaceutical companies in the world have committed themselves to the ethical standards of the Declaration of Helsinki, however, again the crucial ethical principles relevant to developing countries are not worked out according to the declaration or are sometimes missing entirely in these companies' policies.

The legal framework of clinical trials regulation in the European Community law is based upon the principle of good clinical practice. However, given the instruments used for verification, it is a challenge to ensure good clinical practice principles are respected when clinical trials take place outside the Community.

The main instrument used by the European Community legislation to enforce compliance of clinical trials with good clinical practice outside the Community is the mechanism of marketing authorisation. The marketing authorisation procedure requires the applicant to prove the efficacy and safety of the product with results of clinical trials. With the objective to ensure equivalent protection of trials subjects inside and outside the community, it is explicitly required that any clinical trials taking place outside the Community (i.e. in third countries) shall not be acceptable for the purposes of marketing authorisation when the requirements of the good clinical practice principles are not met. They shall be carried out in accordance with the ethical principles that are reflected, for example, in the Declaration of Helsinki. The applicant has to accompany his

application with a 'statement to the effect that clinical trials carried out outside the European Union meet the ethical requirements of the Clinical trials Directive (2001/20/EC)'. This statement by the applicant is one of the verification documents in the five modules of the technical dossier containing information about the ethics of trials. Another document is a short statement of an involved expert on the compliance of the trials in the dossier with GCP and there are the clinical trial study reports. Each trial has its own report and each report contains a section on ethics. Based on these documents, the regulatory authorities review the good clinical practice during the marketing authorisation procedure and one of the findings in this study is that it is rather impossible to really check compliance with GCP solely on the basis of this information in the technical dossier. Another finding is that only the pivotal trials (the decisive trials for approval) in a technical dossier are verified on GCP in more detail, and these are a mere fraction of all trials. Currently, about two thirds of the pivotal trials are conducted outside the EU, one third of which in non-traditional research areas such as Asia (11%), Latin America (11%), Africa, the Middle East and CIS countries (Russia, Ukraine etc.).

The second main instrument for enforcing the compliance of clinical trials with good clinical practice outside the Community is the GCP Inspection system, which is coordinated by the EMEA. Clinical trials inspected in third countries are always part of a Marketing Authorisation Application (MAA), because only those fall within the scope of the EMEA. Inspections can be triggered inspections (requested because there is a concern) or routine inspections. However, at the time trials are selected for inspection most of them had already been completed years ago, making it difficult to verify GCP afterwards; actually the verification should take place while a trial is still running. Another finding is that this instrument is not as effective as it could be because the constituency of subjects authorised to initiate the inspections is too narrow. In principle, the Commission, or the Member States, who are the only subjects authorised to initiate the inspections, are not always aware of the real situation or any infringements made during the clinical trial. Currently, GCP Inspections in third countries are increasing, but there is a strong appeal to increase this further. In 2008 (counted until November) 45 inspections were conducted (of 20 in the EU, 9 in the US and 16 in the rest of the world). In 2007, 38 GCP inspections were conducted. Typically per trial two investigator sites will be inspected. The sample is very tiny; bearing in mind that a full clinical trial development programme of a new product with a major indication and a big potential population like a cardiovascular might concern 100 trials and one trial can have dozens of investigator sites.

An important condition to protect trial subjects in developing countries is transparency on the existence of these trials, the study protocol and the results. Currently, the lack of information on running clinical trials in developing countries is a major obstacle. There should be a database that is accessible to the public; transparency is an important instrument for urging the sponsor or the investigator to carry out their research in accordance with the ethical principles. At present, EU legislation provides a public clinical trial database named EudraPharm, however, this database has no legal basis for including clinical trials (part of a MAA) conducted in third countries, but there is a strong appeal from various parties to create this. There has also been support for a proposal to copy the 'ICJME initiative' into EU legislation, which would mean that trials can only be part of an application if the trial is registered beforehand in the public European clinical trial registry, making registration mandatory. Additionally, the list of data fields to be made public, as published in February 2009, does (unfortunately) not include information on the ethics of the trials.

The penal mechanism is one of the important legal instruments by which compliance with the law can be enforced but is not put into practice nowadays.

The instruments used to enforce GCP in developing countries do not protect trial subjects sufficiently from inadequate reporting of Serious Adverse Events (SAEs).

Furthermore, the study analysed the more controversial provisions in the Declaration of Helsinki and the ICH GCP guidelines and how they have been incorporated in EU legislation. Different groups are lobbying either to have a harmonised reference to the ICH GCP as the EU standard in the EU legislation or to have a clear reference to the Declaration of Helsinki as the EU standard. In the US this dispute has been settled at the expense of the Declaration of Helsinki; in October 2008 a regulatory change of the FDA came into effect officially ending the requirement that clinical trials conducted outside the US have to comply with the Declaration of Helsinki. This development is now one of the many obstacles to achieving any clear reference to the Declaration of Helsinki. Therefore, it is recommended in this paper to not try to make the DoH hard law, but to make some crucial ethical standards of the declaration very explicit and to make sure that these standards become part of the practical guidelines for ethics committees, but also become part of the practical guidelines for the assessors of a marketing application and also for the GCP inspections. But to be able to do this, a discussion needs to take place first about these crucial ethical standards within the regulatory framework and with the industry to reach a common definition of the problem and to create a basis for solutions that are attainable. These guidelines should be applicable in relation to the clinical trials conducted outside the Community as well. This can be done within the current legislation.

One of the crucial principles in the DoH needed to be put on the agenda for discussion concerns unethical use of placebos. In reaction on the regulatory change of the FDA to leave out the DoH, critical journalists wrote this was done to allow the pharmaceutical industry to run international clinical trials in which patients in the control group (i.e. those who are not getting the experimental drug) can be treated with placebos instead of the best standard medical care. A significant danger is emerging from the misuse of placebos during clinical trials. Another problematic issue is the involvement of vulnerable poor trial subjects while the testing medicines will not be of any benefit of the population because the medicine will not be marketed in the country, or will not be affordable for the patients. Sometimes it concerns medicines for diseases that are not a major concern for the country. And there is the problem that in developing countries the end of the trial often also the end of the treatment opportunity is. If such cases are to be eliminated, detailed guidelines must set out principles explaining how to act.

The last part of the study presents an analysis of the legal instruments available to third country citizens who were subjects of unethical clinical tests conducted outside the European Union (EU), to sue pharmaceutical industries carrying out these tests. The aim of the analysis was to identify which instruments and strategies could be used by European legislature to improve such victims' access to justice. The study focuses on options available within the EU as the European legislation cannot directly influence a victim's position in third country litigation because of jurisdictional limitations.

The options available to victims of unethical clinical trials conducted outside the European Union are limited. They can sue pharmaceutical and clinical research companies who are domiciled in the European Union but not foreign companies unless there is no other appropriate forum available. The companies can be held liable only if they have been directly involved in managing or controlling the clinical trials in respect of issues that violate ethical standards. This might not

necessarily be the regular arrangement. Pharmaceutical companies taking the form of transnational corporations consist of many separate legal persons, who in principle do not share the legal obligations of the other members of the economic group.

These obstacles can be removed if legislation allocates civil liability for violations of ethical standards to the company seeking market authorisation of the medicinal product, or to the parent company of the transnational corporation which sponsored the clinical trial, and also extends jurisdiction of the courts of the Member State to parent companies which are domiciled outside of the European Union.

Material obstacles facing victims of clinical trials and keeping them from access to justice are a separate problem. These obstacles include lack of publicly available evidence, the financial costs of litigation as well as a large range of cultural and logistical issues. They can be addressed by specific reforms of the process - shifting the burden of proof, relieving the risk of cost recovery by the other party of the litigation, and collective means of redress.

Some last observations made in the study concern the fact that the execution of the European regulatory work is concentrated in five European countries; it should be further investigated whether this is a desirable situation. Only five EU countries (Germany, the UK, Denmark, the Netherlands and Sweden) are together responsible for 87% of the decentralised procedures and for 71% of the mutual-recognition procedure and four out of these five countries (the UK, Germany, Sweden, and the Netherlands) also deliver the highest number of rapporteurs and co-rapporteurs for the centralised procedure.

About 10% of the medicines entering the EU market is authorised by the EMEA which leaves about 90% of the medicines authorised through the mutual recognition and decentralised procedures by the national authorities. There were 90 centralised procedures in 2007 and for 2008 the estimation is more than 100. 1,034 decentralised procedures were initiated in 2007 and 397 mutual recognition procedures.

As far as the fee structure is concerned, the responsible authorities are highly dependent on the fees paid by the industry. For EMEA, the fees accounted for 67% of total revenue in 2007 (€ 108,579 million). The total revenue of the Dutch MEB is € 29,654 million, of which € 27,620 is third party revenue (93%) originating from fees from companies for delivery of services like marketing authorisation procedures. Generating income from the marketing authorisation is important for the Dutch MEB; their financial situation is at stake when not enough marketing authorisation procedures are submitted by pharmaceutical companies. However, there is no evidence to support the concept that fees alter the regulatory decisions of the EMEA or national authorities.

The European Commission and EU Member States should continue their supporting capacity building related to clinical trials in developing countries. They should continue to provide the resources needed to help to ensure that the regulatory bodies and ethical review committees in developing countries are able to function and that health workers are trained to carry out clinical trials to required standards and make sure that the different initiatives are coordinated. The EU capacity building projects should also involve adequate reporting of SAEs. Current activities taking place by the Commission and the EMEA concern the improvement of bilateral relations with third countries such as India, and training programs to increase expertise of EU and third country regulators, and the training of GCP inspectors within capacity building projects with WHO, the

Council of Europe and Unesco. These activities are very important and should continue; interviewees stressed that education and training in combination with inspections are key for improvements.

The most important recommendations in relation to the aforementioned four instruments to enforce Good Clinical Practice in developing countries (the market authorisation process, the GCP inspections, the public clinical trial database and the penalties) are defined as follows:

- **Marketing authorisation process:**

- 1) Issuing guidelines for responsible authorities on how to assess ethical standards: The Declaration of Helsinki needs to be made operational and assessors need to be provided with a checklist of which ethical aspects need to be assessed and how;
- 2) Investigate if and how the Good Clinical Practice verification can take place at an earlier stage than during the marketing authorisation phase;
- 3) Not only the pivotal trials should be verified in more detail on GCP, this should be done for a larger number of trials especially those carried out in third countries;
- 4) The verification process of GCP at the time of the evaluation of the MAA should become more transparent and should be described in the EPAR;
- 5) More coordinating efforts by the EMEA are needed to harmonise the application of ethical standards by the responsible authorities.

- **Inspections:**

- 1) Inspections should preferably take place during the trial instead of during the authorisation process, which is after the trials are completed;
- 2) Initiation of an inspection outside the marketing authorisation should be possible;
- 3) Initiation of an inspection by third parties (outside EMEA or NCA) should be possible (this requires a change in legislation);
- 4) Increase the number of inspections in third countries;
- 5) GCP Inspection should include post trial aspects, for example, checking whether patients are informed about the results of the trials they have participated in and checking post trial treatments, the SAE reporting system, and the compensation arrangement in the informed consent form;
- 6) It should be investigated if it is possible for the EMEA to set up regional offices in crucial third countries like India, Russia, Argentina and China;
- 7) Check procedures and structures (and declaration of conflicts of interest) of ethics committees in third countries and the ethical standards used systematically in GCP inspections.

- **Clinical trial database:**

- 1) Clinical trial database should include trials (part of MAA) conducted in third countries (requires a change in legislation);
- 2) Mandatory entry for trials that are part of EU marketing authorisation process (requires a change in legislation);
- 3) Penalise the submitting of misleading information for the database by sponsors, applicants or investigators (requires a change in legislation);

4) To provide a legal basis to include the clinical trials to test medical devices for the EU market in the database (requires a change in legislation);

5) The public clinical trial database EudraPharm should contain information about ethical considerations, for example a brief public statement from the involved ethics committee on their ethical review, including ethical considerations, e.g. the justification of placebo use, the justification of the use of vulnerable trial participants, explanation of the benefits for population, and the arrangements for post trial treatment.

- **Penalties:**

1) include unethical trials under definition of significant health implications for EU (requires change in legislation);

2) include underreporting of SAEs in third countries under definition of significant health implications for EU (requires change in legislation);

3) member states should take more responsibility to penalise applicants submitting misleading information;

4) personal liability for those submitting information for the marketing authorisation procedure representing the applicant, including the experts responsible for the summaries (requires a change in legislation).

## INTRODUCTION

### Context and aim

This research paper is the result of a tender of DG External Policies of the Union. From the beginning the intention of this study has not been to investigate the scope and the character of the problems related to the increasing number of clinical trials off-shored to countries outside the European Community (called third countries in jargon) to test medicines intended for sale on the European market. Those issues have been dealt with in earlier reports by SOMO and WEMOS (<sup>1</sup>). But to indicate the motive for this paper, one of the outcomes of these earlier studies is that European legislation regulating the marketing authorisation of medical products is not always observed properly. This legislation specifies that results from clinical trials that do not meet the ethical requirements of Good Clinical Practice, including those of the Declaration of Helsinki, cannot be legally used by an applicant to justify its application, irrespective of whether the trial was done inside or outside the EU. In practice double standards are applied to trial subjects from high income countries and from low income countries; clinical trials which are no longer accepted by Western European ethics committees are approved in countries like India, China, Argentina and Russia, where ethics committees can decide differently due to a number of reasons. This results in trials with an unethical design becoming part of EU marketing applications and not being filtered out because legally all the requirements are fulfilled.

Especially the ethical principles of main importance for developing countries as reflected in the Declaration of Helsinki are ignored by companies and regulatory authorities. These principles handle important issues such as the precondition of the beneficiary element and the affordability of the investigational medicinal products for the population, the right to arrangements for post trial treatment, and the obligation to test the investigational medicine against the best current proven intervention instead of testing against placebos (the standard of care discussion).

The main objective of this paper is to provide the European Parliament with concrete recommendations, both at legislative and enforcement level, aimed at guaranteeing that trials in third countries are conducted respecting EU and international ethical standards.

The request in the tender was to do this at two different levels, namely at the level of current EU legislation regulating the conduct of clinical trials and the marketing authorisation of medicines but also at the level of international law. The background of the latter is to find out what legal instruments and strategies could be used by European legislature to improve access to justice for third country citizens harmed by unethical trials, independent of the regulation of the marketing authorisation process. This is an interesting new aspect to bring into the discussion.

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<sup>1</sup> I. Schipper & F. Weyzig, Ethics for Drugs Testing in Low and Middle Income Countries. Considerations for European Market Authorisation (Amsterdam: SOMO:2008) and Wemos, A Bitter Pill. The Risks of Carrying Out Clinical Drug Trials in Developing Countries (Amsterdam: Wemos, 2008) and S. Sandhya Srinivasan, Ethical concerns in clinical trials in India: an investigation (Centre for Studies in Ethics and Rights: Mumbai, 2009).

## Description of the study

In order to achieve the above objective, the study starts with an overview of the relevant European legislation and international standards covering ethical standards for clinical trials. Subsequently, a selection of relevant documents and activities of governmental and non-governmental organisations is given. This study is focused on commercial sponsors and clinical trials intended to be part of EU marketing authorisation applications and not on biomedical research to combat poverty related diseases in public private partnership programmes, nor on projects in developing countries involving capacity building activities for ethics committees, regulators etc. Therefore no extensive overview is given of working groups in ethics guidelines (research ethics) in developing countries with governmental organisations like the WHO, the Council of Europe (Bioethics division), Unesco and the United Nations Inter-Agencies Committee in Bioethics. Similarly, guidelines that address more specific ethical questions, for example concerning stem cell research and biobanks, research on fertilised human eggs, participatory action research, research on HIV and AIDS, fall outside the scope of this study.

The first part of the study also includes a short analysis of the clinical trials ethics policies of the biggest pharmaceutical companies to see what ethical standards they commit themselves to. It ends with a description of the state-of-affairs at the European registration authorities.

Part two of the study – the research part – starts with a legal opinion on the applicability of international guidelines and EU legislation (including European Directive 2001/20/EG) in developing countries. This part elaborates on four instruments used by the community law to protect trial subjects in third countries: 1) the mechanism of marketing authorisation; 2) Inspections on Good Clinical Practice; 3) the clinical trials database; 4) and penalties.

Chapter 3 provides an interpretation of the present Community legislation on Good Clinical Practice compared with the Declaration of Helsinki and the ICH GCP Guideline.

Chapter 4 includes an analysis of legal instruments available to third country citizens who are the subject of unethical clinical trials carried out outside the European Union to sue pharmaceutical companies carrying out these tests. It focuses on options available within the EU as the European legislation cannot directly influence a victim's position in the litigation in third countries because of the jurisdictional limitations.

Chapter 5 includes an analyses of the mandate, organisation and functioning of the European Medicines Agency (EMA) responsible for the centralised marketing authorisation procedure and the national medicines agencies responsible for the decentralised or mutual recognition procedure.

Chapter 6 gives a final selection of recommendations on enforcement level and legislative level

Chapter 7 provides an assessment of the reaction of the industry.

## Methodology

For the legal part SOMO worked together with legal experts on the liability of multinational companies under international law who are members of the Legal & Policy Working Group of the European Coalition for Corporate Justice (ECCJ) for which SOMO has a coordinating role. These

legal experts, Filip Gregor and Jana Kravčíková - právnička (lawyer) are working for the Czech organisation Environmental Law Service. Filip Gregor is co-author of the report 'Fair Law – legal proposals to improve corporate social accountability for environmental and human rights abuses', published by ECCJ in 2008.

To analyse the medicine agencies, SOMO had several interviews with representatives of European medicines agencies and SOMO participated in an expert meeting on December 4, 2008 in Den Hague (NL) where the Dutch Medicines Agency was represented by Prof. dr. J.T. van Dissel, Vice president of the CBG and by Birthe van Elk. Also, the competent authority the Dutch Centre for Human Drug Research and Research Ethics Committee (CCMO) was represented by Mr. Adam Cohen, GlaxoSmithkline by Mr Jan Raaijmakers, AstraZeneca by Mr. Ad Antonisse and BioGen. And the following NGOs were present: WEMOS, SOMO, Farmacie Mondiaal and Health Action International (HAI). The expert meeting was organised by the Euro Parliamentarian of the Dutch Socialist Party (PvdA, Dorette Corbey). Additionally there was an extra meeting with SOMO and HAI and one with WEMOS.

We conducted interviews in the second week of January 2009 at EMEA office in London, interviewees were:

- Mr. Fergus Sweeney, Principal Scientific Administrator at the Inspections Sector of the EMEA and chair of the Good Clinical Practice Inspection Working group. Fergus Sweeney is closely involved with a recent EMEA strategy paper on the acceptance of clinical trials carried out in third countries and meant for marketing authorisation applications (October 2008);
- Ms. Maria Antonietta Antonelli, also working at the inspection sector of the EMEA and a former GCP inspector in Italy;
- Mr. Brian Davis, worked as head of the clinical trials section of the MHRA for 12 years, now member of the Clinical Trials Facilitation Group (CTFG) facilitated by the EMEA but also active in the working group responsible for the implementation of the regulation on the public register on clinical trials.
- Ms. Chantal Bélorgey-Bismut, head of Division on Evaluation of Special Status Medicinal Products and Clinical trials. She is also member of the CTFG-Clinical Trials Facilitation Group representing the French medicines agency AFSSAPS.
- Dr. Hartmut Krafft, Head of section, Clinical Trials at the Paul-Ehrlich-Institute which is the German federal agency for Sera and Vaccines.

## Part One

### OVERVIEW OF EXISTING DATA ON ETHICAL STANDARDS OF CLINICAL TRIALS IN DEVELOPING COUNTRIES

## 1 - STATE OF AFFAIRS

### 1.1 European legislation covering ethical standards for clinical trials in developing countries

Rules on the protection of clinical trial subjects are laid down in Community legislation and are based on Good Clinical Practice which is a set of internationally recognised ethical and scientific requirements which must be observed for designing, conducting, recording and reporting clinical trials that involve the participation of human subjects. Compliance with Good Clinical Practice should assure that the rights, safety and well-being of trials subjects are protected. The same rules apply for clinical trials carried out in third countries, which are all countries outside the Community including developing countries, if they are part of a marketing authorisation application under the centralised or decentralised procedure.

Therefore, the following EU legislation is also relevant for trials in developing countries:

- The '*Clinical trials Directive*' 2001/20/EC for setting standards for the conduct of clinical trials;
- The Commission Directive 2005/28/EC laying down principles and guidelines for Good Clinical Practice to implement Directive 2001/20/EC;
- Directive 2001/83/EC, as amended by 2003/63/EC, for regulating marketing authorisation of medicinal products for the European market;
- Regulation NO (EC) 726/2004 for establishing the EMEA and Centralised Procedure.
- EudraLex - Volume 10, Clinical trials guidelines 'The rules governing medicinal products in the European Union' contains guidance documents applying to clinical trials.

The Directives are supported by different guidances for proper implementation. Most of the guidance documents applying to clinical trials can be found in 'EUDRALEX Volume 10'. It contains, for example, an application form for request of authorisation of a clinical trial to the competent authorities and for an opinion of the ethics committee in the community, but also guidance for the preparation and the conduct of Good Clinical Practice Inspections. Besides these guidance documents, the guidelines of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) are just as important. Main aim of the ICH is the harmonisation in the interpretation and application of technical guidelines and requirements for successful product registration in the Europe, Japan and the United States. For the scope of this report the '*Efficacy*' guidelines are relevant, and more specifically guidelines ICH E3 (defining the structure and content of clinical trials study reports); E6(R1) Good Clinical Practice; and E10 (about the choice of control groups).

Regulators and the industry are relying on the above-mentioned legislation and guidelines to design their clinical trials according to Good Clinical Practice so that the clinical data will be accepted by the regulatory authorities in Europe, Japan and the United States.

Recently, on 4 February 2009, the guideline listing the data fields to be made public in the clinical trials database on medicinal products called 'EudraPharm' was published. The data will be extracted from EudraCT and made publicly available via the Web.

The question as to what current EU legislation exactly offers to protect trial subjects in third countries will be answered in detail in Part II of this research paper. (See also Table 1 in the ANNEX for more information on the relevant EU legislation and direct links to the texts.)

## 1.2 Overview of international ethical guidelines and developments

This paragraph offers a short overview of the most important international ethical guidelines for clinical trials.

- **The Nuremburg Code**, was the first international instrument on the ethics of medical research, promulgated in 1949 as a consequence of the trial of doctors who had conducted cruel experiments on prisoners during the Second World War.
- The Universal Declaration of Human Rights of the **United Nations** (1948), article 7, warrants voluntary consent.
- The Treaty on European Union as amended by **the Treaty of Amsterdam** in 1997, and in particular Article 6 (formerly Article F) of the common provisions, concerning the respect for fundamental rights;
- **The EC Treaty** and in particular Article 152 (formerly Art. 129) on public health;
- **The Charter of 28 September 2000 on Fundamental Rights of the European Union**, approved by the European Council in Biarritz on October 14th 2000, in particular Article 1 on 'Human dignity', Article 3 on the 'Right to the integrity of the person', which refers to the principle of 'free and informed consent' and Article 13 asserting freedom of research;
- The **Council of Europe's** Convention on Human Rights and Biomedicine, signed on 4th April 1997 in Oviedo, in particular Article 15 about freedom of research and Articles 16 and 17 about the protection of persons undergoing research: (**The 'Oviedo Convention'**).
- **The Declaration of Helsinki of the World Medical Association (DoH)**, 'Ethical Principles for Medical Research Involving Human Subjects' adopted in 1964 and revised in 1975, 1983, 1989, 1996, 2000, 2004 and 2008<sup>(2)</sup>. In short the 'Declaration of Helsinki', is a fundamental document in the field of ethics in biomedical research and is widely adopted by medical associations in various countries. It is a leading standard when it comes to the conduct of clinical trials in developing countries.
- The International Ethical Guidelines for biomedical research involving human subjects of the Council for International Organisations of Medical Sciences (**The CIOMS guidelines**) adopted in 1993 and revised in October 2002<sup>(3)</sup>. This standard was prepared by CIOMS in collaboration with the World Health Organisation (WHO). Together with the WHO guidelines, this is considered the most appropriate standard for clinical trials in developing countries. The disagreement regarding the 2002 revision concerned the placebo-controlled trials. Some participants questioned the ethical acceptability of the proposed exceptions to the general rule limiting the use of placebo-controlled trials. They argued

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<sup>2</sup> The world medical association, Policy, <<http://www.wma.net/e/policy/b3.htm>>

<sup>3</sup> CIOMS, International Ethical Guidelines for Biomedical Research Involving Human Subjects, <[http://www.cioms.ch/frame\\_guidelines\\_nov\\_2002.htm](http://www.cioms.ch/frame_guidelines_nov_2002.htm)>

that research subjects should not be exposed to risk of serious or irreversible harm when an established intervention could prevent such harm and that such exposure constitute exploitation <sup>(4)</sup>.

- **The Guidelines for Good Clinical Practice published by the International Conference on Harmonisation: The ICH GCP Guidelines/ CPMP/ICH/135/95** <sup>(5)</sup>. The ICH agreed in 1996 to adopt the same standards of GCP in pharmaceutical clinical trials in the EU, Japan, and the US, to facilitate the mutual acceptance of clinical data by the regulatory authorities in these high-income countries. These guidelines are said to be consistent with the principles that have their origin in the Declaration of Helsinki and are developed with consideration of the WHO.
- **WHO Guidelines for Good Clinical Practice for Trials on Pharmaceutical Products.** These were adopted in 1995<sup>(6)</sup>. It was developed as an administrative tool for use by WHO member states, to assure their compatibility with existing national and other provisions. It is not the intention of this document to replace existing national requirements or regulations. The objective is to provide a complementary voluntary standard that can be applied worldwide. Next to the guidelines the WHO is active with the development of registration standards on clinical trials results via the establishing of the International Clinical Trials Registry Platform (ICTRP) which aims to facilitate access to information about clinical trials and their results <sup>(7)</sup>.
- **The Pharmaceutical Research and Manufacturers of America (PHRMA) Principles on Conduct of Clinical Trials.** The principles, many of which reflect existing practices by the industry, became effective for trials begun after October 1, 2002. The first principle says that 'Clinical trials are conducted in accordance with all applicable laws and regulations, as well as recognised principles of Good Clinical Practice (GCP), wherever in the world trials are conducted.'
- In 2001, the **European Forum for Good Clinical Practice** has produced guidelines and recommendations for GCP to help European research ethics committees <sup>(8)</sup>.
- **UNESCO's** Universal Declaration on Bioethics and Human Rights, 19 October 2005, contains also a specific section on developing countries <sup>(9)</sup>.

The ICH guidelines are increasingly important. The secretariat is run by the business association IFPMA. The lobby for the ICH guidelines is strong and effective: the regulatory agencies of Central and Eastern Europe now automatically adopt ICH standards, and Canada has also adopted some. The ICH guidelines are also promoted throughout the developing world by the WHO. According to a report of the Joint CIOMS/WHO Working Group on implementing Good Clinical Practice guidelines in developing countries, the ICH GCP guidelines must be followed as a minimum and

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<sup>4</sup> An example of such exploitation is the case of the clinical trials in Cameroon in September 2004 of an anti-AIDS drug being tested on 400 sex workers who were free from infection from the virus. Half of them were given a placebo, while they were asked to have unprotected sex, at the end of the trial the women were due to be retested for HIV. The women who did become HIV positive did not receive any treatment.

<sup>5</sup> International Conference on Harmonisation, Guideline for Good Practice, June 1996, <<http://www.ich.org/LOB/media/MEDIA482.pdf>>

<sup>6</sup> World Health Organisation, Guidelines for good clinical practice (GCP) for trials on pharmaceutical products, 1995, <<http://www.who.int/medicinedocs/collect/medicinedocs/pdf/whozip13e/whozip13e.pdf>>

<sup>7</sup> World Health Organisation, WHO Technical Consultation on Clinical Trials Registration Standards, 25-27 April 2005, <[http://www.who.int/ictpr/news/ictpr\\_sag\\_meeting\\_april2005\\_conclusions.pdf](http://www.who.int/ictpr/news/ictpr_sag_meeting_april2005_conclusions.pdf)>

<sup>8</sup> EFGCP, European Guidelines on Auditing Independent Ethics Committees, 2001, <[http://www.who.int/ictpr/news/ictpr\\_sag\\_meeting\\_april2005\\_conclusions.pdf](http://www.who.int/ictpr/news/ictpr_sag_meeting_april2005_conclusions.pdf)>

<sup>9</sup> UNESCO, Universal Declaration on Bioethics and Human Rights, 19 October 2005, <[http://portal.unesco.org/en/ev.php-URL\\_ID=31058&URL\\_DO=DO\\_TOPIC&URL\\_SECTION=201.html](http://portal.unesco.org/en/ev.php-URL_ID=31058&URL_DO=DO_TOPIC&URL_SECTION=201.html)>

liaison with appropriate community leaders, charities, religious figures and health authorities, in compliance with local laws and practices, to ensure that trial participants are protected<sup>(10)</sup>.

The ICH guidelines have been criticised because some ethical principles, which are included in the DoH, are missing, and because regarding the placebo issue it leaves too many options open and gives research efficiency priority over ethical considerations. The ICH guidelines are praised for the level of detail and the structures and formats provided so it is clear what is expected. This in contrast with the DoH, which is a set of well described standards but not worked out in detail, what makes is difficult to work with in practice. One of the experts interviewed for this report called it *'a great theoretical exercise but not usable in practice'*.

It is important to note that at the end of April 2008, the US Food and Drug Administration (FDA) published a regulatory change ending the need for clinical trials conducted outside of the US to comply with the Declaration of Helsinki<sup>(11)</sup>. Critical observers say that this is a major victory for corporate interests which have sought to loosen the ethical standards for international clinical trials; 'In effect the FDA will now allow the pharmaceutical industry to run international clinical trials in which patients in the control group (i.e. those who are not getting the experimental drug) can be treated with placebos instead of the best standard medical care'<sup>(12)</sup>. As the US, an important endorser of the ICH GCP guidelines, formally rejects the DoH, it seems clear that the reference in the ICH GCP guidelines to the DoH has no meaning.

### **Conclusion concerning the international standards**

The WHO guidelines on Good Clinical Practice (GCP), the WMA Declaration of Helsinki and the elaboration of it in the CIOMS guidelines are the most appropriate standards for developing countries. These guidelines are endorsed by civil society organisations like Oxfam International, Health Action International and the Dutch organisation WEMOS.

The ICH Guideline of GCP is in practice the leading guideline when generating clinical trial data intended to be submitted to regulatory authorities, also when they are conducted in developing countries. The reference to the Declaration of Helsinki in the ICH GCP guideline has no binding status and has been officially abandoned by the US authorities.

### **1.3 European registration authorities**

Currently the European Medicines Agency (the EMEA) is very active in evaluating the clinical trial Directives in general but also especially in relation to the ethical standards required of clinical trials conducted in third countries and the verification of GCP.

At the request of the Commission, the EMEA organised a conference on the implementation of the EU legislation on clinical trials on medical products with the aim to evaluate the experiences to date and to provide an analysis of what works well and which aspects do not work, and to establish

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<sup>10</sup> CIOMS/WHO Working Group, Drug Development Research in Resource-limited Countries: How to succeed in implementation of Good Clinical Practice Guidelines, December 2005, <[http://www.cioms.ch/march2008\\_pv\\_in\\_rpc\\_final\\_14dec2005.pdf](http://www.cioms.ch/march2008_pv_in_rpc_final_14dec2005.pdf)> p.24

<sup>11</sup> FDA, 'Human Subject Protection; Foreign Clinical Studies Not Conducted Under an Investigational New Drug Application.' Federal Register, April 28 2008, Vol. 73, No. 82, Rules and Regulations, <<http://www.fda.gov/cber/rules/forclinstud.pdf>>. The official reasons as stated by the FDA to leave the DoH out is that the DoH has evolved considerably since 1989 and in the opinion of the FDA the ICH E6 is of good quality and includes many of the 1989 ethical standards. Next to this, the DoH does not provide guidance how to ensure proper conduct of trials and because the World Medical Association is independent from the FDA authority and continues to change the declaration, the FDA cannot take responsibility for it.

<sup>12</sup> The Social Medicine Portal, 'FDA abandons Declaration of Helsinki for International Clinical Trials', 1 June 2008, <<http://www.socialmedicine.org/2008/06/01/ethics/fda-abandons-declaration-of-helsinki-for-international-clinical-trials/>>

recommendations for future improvement<sup>(13)</sup>. In this report some of the observations made are relevant for the conduct of clinical trials in third countries.

Moreover, the EMEA has drafted a strategy paper on the acceptance of clinical trials in third countries for marketing authorisation applications (MAAs)<sup>(14)</sup>. The background for this *'is the growing concern both among regulators and in public debate about how well these trials are conducted from an ethical and scientific/organisational standpoint (including GCP compliance) and about the available framework for the supervision of these trials'*.

The EMEA anticipates that the trend of the increasing number of clinical trials conducted outside of the traditional Western Europe and North America research areas will continue. In 2007, the percentage of patients in *pivotal* trials (note that not all trials in an MAA are pivotal, it is a possible scenario for an MAA to include 50 trials of which 10% are pivotal) coming from EEA/Swiss sites is 30-35% and from US clinical sites also 30-35%. The contribution of Asia and Latin America has grown quickly; in 2007 about 11% of the patients came from Asia and 11% from Latin America. Significant numbers are also included by trial sites in Russia, Ukraine and other CIS countries. Smaller but growing numbers are also recruited in Africa and the Middle East. On the basis of the 2007 figures supplied by the EMEA it can be concluded that 65-70% of the pivotal trials in MAA concern trials conducted in third countries, of which 30-40% outside the traditional research areas, and this has only increased in 2008<sup>15</sup>. A system of routine GCP inspection has been in place since 2006 and two key factors in selecting sites are the presence of vulnerable populations and of investigator sites in developing countries. (See also Table 2 for EMEA inspection statistics.)

For more information on the coming activities of the EMEA in this area see Chapter 5.

A follow up on the October 2007 EMEA conference is the Impact on Clinical Research of European Legislation project (ICREL), funded by DG Research through the European 7th Framework Programme. This project aims to provide metrics and thus objective arguments for the need to adapt the current Clinical Trial Directive with the objective of making clinical research more competitive in the European Union whilst providing fair and equivalent protection to participants. The European Forum on Good Clinical Practice coordinates the project; one of the partners is the European Clinical Research Infrastructures Network (ECRIN). First results were presented in December 2008<sup>(16)</sup>.

#### 1.4 Governmental and non-governmental organisations

Here follows a selection of relevant documents and activities of governmental and non-governmental organisations.

<sup>13</sup> European Commission-European Medicines Agency Conference on the Operation of the Clinical Trials Directive (Directive 2001/20/EC) and perspectives for the future, Conference held on 3 October 2007 at the EMEA, London, Report on the Conference, London, 30 November, 2007, Doc. ref.: EMEA/565466/2007.

<sup>14</sup> EMEA, EMEA strategy paper: Acceptance of clinical trials conducted in third countries, for evaluation in Marketing Authorisation Applications, 12 February 2009, <<http://www.emea.europa.eu/Inspections/docs/22806708en.pdf>>

<sup>15</sup> For the period 2005-2008 the estimation is that one quarter of the patients in pivotal trials were recruited in countries in Latin America, Asia, Commonwealth of Independent States members and Africa. As the time period over which the data has been collected by the EMEA has been short, they can only be taken as illustrative at this stage, and not too much can be read into precise differences.

<sup>16</sup> EFGCP, 'ICREL Project', <<http://www.efgcp.be/icrel>>

- A very useful background paper is Opinion N° 17 ‘Opinion on the ethical aspects of clinical research in developing countries’, published in February 2003 by the European Group on Ethics in Science and New Technologies (EGE). This opinion was requested by the European Commission. This document gives an overview of the legal background, the work of the Council of Europe, CIOMS, National Bioethics Advisory Commission, Nuffield Council on Bioethics (UK), and includes a study on the ethical controversy over the use of placebos in clinical trials in developing countries and a study on industry funded clinical trials in developing countries.
- Another publication of EGE is the report on the conference (May 2007) ‘Ethics, Research & Globalisation: Europe and its partners building capacity in research ethics’<sup>(17)</sup>.
- A very useful article based on the outcomes of a Round Table held in France to formulate guidelines for clinical research in developing countries was published in 2007<sup>(18)</sup>.
- In 2005, the Council of Europe published the ‘Additional Protocol to the Convention on Human Rights and Biomedicine, concerning Biomedical Research’<sup>(19)</sup>. Currently the Council of Europe is preparing a new recommendation on ethics in clinical trials.
- In 2005, the Nuffield Council on Bioethics published ‘The ethics of research related to healthcare in developing countries: a follow-up Discussion Paper based on the Workshop held in Cape Town, South Africa 12–14th February 2004’<sup>(20)</sup>.
- In 2005, a report and recommendations of the National Bioethics Advisory Commission, ‘Ethical and policy issues in international research: clinical trials in developing countries’, USA, 2001.
- CIOMS has issued a report on Drug development research in resource-limited countries in 2005<sup>(21)</sup>. WHO has issued a complementary Handbook for Good Clinical Research Practice in 2002<sup>(22)</sup>.

One relevant conference report is still expected, namely of the Round Table on Biomedical Research in Developing Countries: the Promotion of Ethics, Human Rights and Justice, held in Rome, Italy on 15-16 December 2008 and organised by UNICRI, the United Nations Institute specialised in research and training in the areas of justice administration; human rights protection; and crime prevention and control together with the Italian Medicines Agency, GCP Promotion Unit, GCP and Pharmacovigilance Inspectorate. This International Round Table was about the protection of human participants in biomedical research<sup>(23)</sup>.

Organisations agree that registration of all clinical trials at the time of registration is fundamental to ensuring transparency in medical research and fulfilling ethical responsibilities. In 2006, the World Health Organisation (WHO) urged research institutions and pharmaceutical companies around the world to register all medical studies that test treatments on human beings, including the earliest phase of research, whether they involve patients or healthy volunteers. The initiative—known as the International Clinical Trials Registry Platform— adopted the International Committee of

<sup>17</sup> J. Houghton, Ethics, Research & Globalisation: Europe and its partners building capacity in research ethics, Brussels, European Communities, 2007.

<sup>18</sup> Muriel Vray, Francois Simon, Francois Bompard and the participants in Round Table N° 2, Giens XXII, Guidelines for clinical research in Developing Countries, Therapy 2007, Mai-Jun 62 (3),223-227.

<sup>19</sup> Council of Europe, Conventions, <<http://conventions.coe.int/treaty/en/Treaties/Html/195.htm>>

<sup>20</sup> Nuffield Council on Bioethics, The ethics of research related to healthcare in developing countries, February 2004, <[http://www.nuffieldbioethics.org/fileLibrary/pdf/HRRDC\\_Follow-up\\_Discussion\\_Paper001.pdf](http://www.nuffieldbioethics.org/fileLibrary/pdf/HRRDC_Follow-up_Discussion_Paper001.pdf)>

<sup>21</sup> CIOMS/WHO Working Group, Drug development research in resource limited countries: How to succeed in implementation of Good Clinical Practice Guidelines, December 2005, <[http://www.cioms.ch/march2008\\_pv\\_in\\_rpc\\_final\\_14dec2005.pdf](http://www.cioms.ch/march2008_pv_in_rpc_final_14dec2005.pdf)>

<sup>22</sup> WHO, Handbook for good clinical research practice (GCP): Guidance for implementation, 2002 <[http://www.who.int/medicines/areas/quality\\_safety/safety\\_efficacy/gcp1.pdf](http://www.who.int/medicines/areas/quality_safety/safety_efficacy/gcp1.pdf)>

<sup>23</sup> UNICRI, Biomedical Research in Developing Countries: the Promotion of Ethics, Human Rights and Justice, December 2008, <<http://www.unicri.it/wwd/analysis/clinical.php>>

Medical Journal Editors (ICJME) initiative and used their set of 20 'key details' that must be disclosed at the time a study begins. As a follow up on this there is now a new group working on what should be the world wide standard for the data fields of a CT registry. This group is called Health level 7, they are part of the American National Standards Institute and they work on the basis of 'The Clinical Trial registration and reporting project charter'. They started in January 2009 with the project RCRIM: Regulation Clinical Trial; research Information management. The EMEA will take part in this <sup>(24)</sup>.

The Dutch Foundation Wemos, which focuses on health issues in developing countries, published their '*Call for Ethical Clinical Trials in Developing Countries*' in February 2009. It represents a call to action for policy makers, regulators and pharmaceutical companies to protect vulnerable trial subjects <sup>(25)</sup>. In November 2007, they published a report on an expert meeting 'Clinical trials and protection of trial subjects in low-income and developing countries' in December 2007 <sup>(26)</sup>. For references to other publications of Wemos see the bibliography.

### 1.5 Company policies

Of the top 10 pharmaceutical companies of 2008, five are US companies. The others are UK companies (2), Swiss (2) and one French company. Looking at their policies on clinical trials and the ethical standards they endorse, we see that nine companies communicate that they follow the Declaration of Helsinki. That is a positive change compared with 4 years ago when half of them explicitly mentioned it. But at the same time it is wise to look at the formulations, because for example does '*all of those [ethical rules] contained in the Declaration of Helsinki and governed by the directives of the ICH*' mean that only the ethical rules of the Declaration that are governed by the ICH are followed? Then some crucial rules are missing. But the majority commit themselves very clearly: 'we have strict policy and standards which are in line with [...] the declaration of Helsinki'. And: '*all clinical trials are designed in accordance with ethical principles embodied in the Declaration of Helsinki*'.<sup>27</sup>

Subsequently, we looked at the commitments made relating to post trial treatment arrangements. GlaxoSmithKline (GSK) is concerned by the suggestion that research sponsors should be routinely obliged to provide treatments to participants post trial <sup>(27)</sup>. GSK says that in exceptional circumstances, when nationally licensed medicines are not funded through the normal healthcare infrastructure, the medicines may be funded by GSK but normally the responsibility for post trial provision of nationally licensed medicines used during a trials lies with governments. Pfizer is not very clear, the company says that '*potential participants are informed [in the informed consent process] if Pfizer anticipates that subjects may continue to receive control or investigational product after the study is completed and if so under what conditions. As the study processes, Pfizer updates subjects of any material changes in Pfizer's plan regarding post-study access to control or investigational product*'. That sounds like it is up to Pfizer to decide whether the trial subjects will receive post trial treatment or not and the subjects will know that in advance, however, it is also up

<sup>24</sup> Source: Interviews at EMEA, London, January 2009

<sup>25</sup> Wemos, Call for Ethical Clinical Trials in Developing Countries, February 2009, <[http://www.fairdrugs.org/uploads/files/Call\\_for\\_Ethical\\_Clinical\\_Trials\\_in\\_Developing\\_Countries.pdf](http://www.fairdrugs.org/uploads/files/Call_for_Ethical_Clinical_Trials_in_Developing_Countries.pdf)>

<sup>26</sup> Final report of the expert meeting 'Clinical trials and protection of trial subjects in low income and developing countries, Tuesday 6 November 2007, 'Wemos, December 2007 <[http://www.wemos.nl/Documents/report\\_expert\\_meeting\\_clinical\\_trials.pdf](http://www.wemos.nl/Documents/report_expert_meeting_clinical_trials.pdf)>

<sup>27</sup> GSK, 'Clinical trials in the developing world', Global Public policy issues, GlaxoSmithKline's position, April 2006, <<http://www.gsk.com/policies/GSK-on-clinical-trials-in-the-developing-world.pdf>>

to Pfizer to change the rules once the trial is started. You can call that an arrangement, but it is not a good one. Roche states in its position paper on clinical trial in the paragraph about developing countries that *'Continuity of drug supply following termination of the Roche Sponsored Clinical Trial will be assured for all Roche Sponsored Clinical Trial participants for as long as they continue to receive medical benefit from the Sponsored Clinical Trial medication, provided that the benefit-risk ratio for the product continues to support such use'* <sup>(28)</sup> which does sound like a good arrangement. The other 7 companies do not mention post trial treatments in their policies at all. Half of the companies have made a statement that the trials they conduct must be relevant for the host country's health needs.

In conclusion, one can say that the top ten companies in the world do commit themselves to the ethical standards of the Declaration of Helsinki but the difficulty lies in how to use these commitments to improve access to justice for third country citizens harmed by unethical trials. Because company codes of conduct are voluntary commitments, companies cannot be strictly held legally accountable for non-compliances. The only available option would to assess whether companies are breaching rules of the EC directive 2005/29/EC on unfair commercial practices, if it can be proved that a company has knowingly mislead consumer by making false statements.

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<sup>28</sup> Roche, Roche Global Position on Human Subject Research , February 2004, <<http://www.roche.com/pages/downloads/sustain/pdf/poshumsubres.pdf>>

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## Part Two

### RESEARCH PART OF THE STUDY

## 2 - APPLICABILITY OF EU LEGISLATION ON CLINICAL TRIALS CONDUCTED IN DEVELOPING COUNTRIES

### 2.1 Introduction chapter 2

This section provides an analysis of legal instruments used by the European Community law to protect human participants of clinical trials taking place outside the Community, including developing countries.

The legal framework of clinical trials regulation in the European Community law is based upon the principle of good clinical practice. This principle applies to clinical trials carried out within the Community as well as to those that take place in third countries. However, given the jurisdictional limitations, it is a challenge to ensure that good clinical practice principles are respected when clinical trials take place outside the Community. This chapter assesses the level of protection offered to trial subjects in developing countries by current EU legislation and explores what possibilities there are to improve these.

### 2.2 Marketing authorisation process

**Background:** The mechanism of marketing authorisation is the main instrument used by the European Community legislation to enforce clinical trials' compliance with good clinical practice outside the Community.

**Current situation analysis:** The pivotal Community legislation concerning marketing authorisation procedure is represented by Regulation (EC) No 726/2004 <sup>(29)</sup>, read in conjunction with Regulation (EC) No 1901/2006, and Directive 2001/83/EC <sup>(30)</sup> as amended by 2003/63/EC <sup>(31)</sup>.

In principle, anyone who wants to place certain medicinal products on the European market (the applicant) has to undergo the marketing authorisation procedure <sup>(32)</sup>. The applicant can choose whether he wants to submit his application for the marketing authorisation to the European Medicines Agency (formerly called the European Medicines Evaluation Agency, therefore the acronym EMA) according to regulation 726/2004 ('centralised procedure') or to the competent authority of any Member State of the Community according to the above-mentioned directive 2001/83/EC ('mutual recognition procedure', 'decentralised procedure' or 'national procedure'). However, there is a category of medicinal products for which the centralised procedure is mandatory: for biotechnology products, for medicines to treat AIDS, cancer, diabetes or

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<sup>29</sup> Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency, OJ L 136, 30.04.2004, p. 1

<sup>30</sup> Directive 2001/83/EC of the European parliament and of the Council of 6 November 2001, on the Community code relating to medicinal products for human use, OJ L 311, 28.11.2001, p. 67

<sup>31</sup> Commission Directive 2003/63/EC of 25 June 2003 OJ L 159 46 27.6.2003.

<sup>32</sup> Article 3 (1) of Regulation 726/2004 and Article 6 (1) of Directive 2001/83/EC.

Neurodegenerative disorder containing a new active substance and orphan drugs <sup>(33)</sup>. The EMEA is responsible for the centralised procedure which involves a single application, a single evaluation and a single authorisation allowing direct access to the single market of the Community.

The national medicines agencies are responsible for the national procedure, the mutual recognition procedure and the decentralised procedure. The national procedure allows selling a medicine on the national market only. If the manufacturer subsequently follows a mutual recognition procedure, the product can be marketed in more than one European country. The procedures for mutual recognition and the decentralised procedure are based on the adoption (or non-adoption) of a Member State's assessment by other EU Member States. The difference between the two procedures is that in case of the mutual recognition procedure one Member State has already granted a marketing authorisation for its national market, whereas in the decentralised procedure this only happens after the assessment has been completed. The country that has provided the initial assessment for the drug in question (the Reference Member State or RMS) makes its assessment report available to the other Member States (Concerned Member States or CMSs).

The marketing authorisation procedure requires the applicant, inter alia, to prove the effectiveness and safety of the product with results of clinical trials <sup>(34)</sup>.

To ensure equivalent protection of trial subjects inside and outside the community, it is explicitly required that any clinical trials taking place outside the Community (i.e in third countries) shall not be acceptable for the purposes of marketing authorisation when good clinical practice principles are not met. They shall be carried out in accordance with the ethical principles that are reflected, for example, in the Declaration of Helsinki <sup>(35)</sup>.

Following Article 6 (1) of Regulation 726/2004 and Article 8 (3) of Directive 2001/83/EC, as amended by Commission Directive 2003/63/EC, the applicant has to accompany his application with a 'statement to the effect that clinical trials carried out outside the European Union meet the ethical requirements of Directive 2001/20/EC <sup>(36)</sup>' (hereinafter 'the statement by the applicant'). Directive 2001/20/EC and complementary Commission Directive 2005/28/EC <sup>(37)</sup> are the key Community legislation concerning good clinical practice and all clinical trials shall be conducted in accordance with the principles spelled out by them.

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<sup>33</sup> See Annex to Regulation (EC) No 726/2004 'Medicinal products to be authorised by the Community'

<sup>34</sup> Article 6 (1) of Regulation 726/2004 and Article 8 (3) of Directive 2001/83/EC.

<sup>35</sup> Point no. 8 of the Annex to the Commission Directive 2003/63/EC of 25 June 2003 amending Directive 2001/83/EC of the European parliament and of the Council on the Community code relating to medicinal products for human use (OJ L 159, 27.6.2003, s. 46), 'Introduction and general principles', states that: '[...] To be taken into account during the assessment of an application, clinical trials, conducted outside the European Community, which relate to medicinal products intended to be used in the European Community, shall be designed, implemented and reported on what good clinical practice and ethical principles are concerned, on the basis of principles, which are equivalent to the provisions of Directive 2001/20/EC. They shall be carried out in accordance with the ethical principles that are reflected, for example, in the Declaration of Helsinki.'

<sup>36</sup> Directive 2001/20/EC of the European parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use, OJ L 121, 1.5.2001, p. 34

<sup>37</sup> Commission Directive 2005/28/EC laying down principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use, as well as the requirements for authorisation of the manufacturing or importation of such products, OJ L 91, 9.4.2005, p. 13

The statement by the applicant, regardless of the type of marketing authorisation procedure, shall be presented in accordance with the requirements set out in the Annex to the Commission directive 2003/63/EC amending Directive 2001/83/EC (hereinafter 'the Annex')<sup>(38)</sup>.

The centralised procedure starts with the validation process of the EMEA guaranteeing that the technical dossier consisting of 5 modules<sup>(39)</sup> is a legally complete dossier, if this is the case the appointed rapporteurs will receive the dossier. The technical requirements for the dossier are the same for all procedures; the mutual recognition, the decentralised, the national and the centralised procedure (except for some administrative burdens).

#### The 5 modules are:

Module 1 regional information (different requirements per region, e.g. Japan, US, EU)

Module 2 summary of expert reports

Module 3 data on quality manufacturing data

Module 4 non-clinical data

Module 5 all clinical trial study reports with the results<sup>(40)</sup>.

Based on these documents, the regulatory authorities review the good clinical practice during the marketing authorisation procedure. In this regard, under point no. 7 of the Annex, all information relevant to the evaluation of the medicinal product concerned, shall be included in the application, whether favourable or unfavourable to the product.

However, it is not clear whether applications must be refused if the statement by the applicant, other documents submitted to support the clinical trials results, and subsequently the particulars submitted in accordance with the requirements of the Annex are *misleading*. In the case of particulars and documents that must be included in each application for the marketing authorisation, Regulation 726/2004 and Directive 2001/83/EC state the same requirements. However, the regulation of the refusal of the application differs. According to the Article 26 of Directive 2001/83/EC, '*Authorisation shall likewise be refused if any particulars or documents submitted in support of the application do not comply with Articles 8, 10, 10a, 10b and 10c.*' On the other hand, Regulation 726/2004 in Article 12 states that '*Authorisation shall likewise be refused if particulars or documents provided by the applicant in accordance with Article 6 are incorrect [...]*' This Regulation explicitly sets out the obligation to refuse the application if the documents provided (including the statement by the applicant) are incorrect. On the contrary, the text of the Directive could be strictly interpreted in an unfavourable way. Interpreted strictly, the application in the mutual recognition procedure, the decentralised procedure or the national procedure fails to comply with this obligation only if the statement by the applicant and the relevant documents are not submitted, not if they just are misleading<sup>(41)</sup>.

<sup>38</sup> According to point no. 1 of the Annex, all particulars and documents accompanying an application for marketing authorisation pursuant to Articles 8 and 10 (1) of Directive 2001/83/EC shall be presented in accordance with the requirements set out in this Annex and shall follow the guidance published by the Commission in 'The rules governing medicinal products in the European Community, Volume 2 B, Notice to applicants, Medicinal products for human use, Presentation and content of the dossier, Common Technical Document (CTD)'. This applies as well to the statement by the applicant submitted under the centralised procedure as the Article 6 (1) of Regulation 726/2004 fully refers to documents listed in Directive 2001/83/EC.

<sup>39</sup> 'The rules governing medicinal products in the European Community, Volume 2 B, Notice to applicants, Medicinal products for human use, Presentation and content of the dossier, Common Technical Document (CTD)', [http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-2/b/update\\_200805/ctd\\_05-2008.pdf](http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-2/b/update_200805/ctd_05-2008.pdf)

<sup>40</sup> Note for guidance on structure and content of clinical study reports (CPMP/ICH/137/95)

<sup>41</sup> More thoroughly, Article 116 of Directive 2001/83/EC states that „ An authorisation shall also be suspended, revoked, withdrawn or varied where the particulars supporting the application as provided for in Article 8 or Articles 10, 10a, 10b, 10c and 11 are incorrect'.

**Improvement MAA 1:**

Because this lack of a clear legal mandate might be steering national authorities away from looking into ethical issues, Directive 2001/83/EC could be amended in favour of legal certainty and protection of clinical trials participants so it explicitly states that the marketing authorisation application should be refused in the case of misleading statements being provided by the applicant.

It is also possible to enforce refusals of applications in such cases by issuing guidelines that would force the national authorities to look into the ethical issues more thoroughly when evaluating the marketing authorisation applications. This way merely checking the presence of the statement by the applicant would no longer be possible.

In principle, the marketing authorisation procedure has the potential to enable regulatory authorities to effectively and legally exclude clinical trials conducted outside the European Community from marketing applications when they do not meet the standards of Good Clinical Practice and ethical principles as reflected in the Declaration of Helsinki. However, some important obstacles prevent it from being truly effective to this end. First of all, the standards of Good Clinical Practice and ethical principles as reflected in the Declaration of Helsinki are not clear enough. There is an ongoing debate if a clinical trial can be legally excluded when it does not comply with all ethical principles as reflected in the Declaration of Helsinki: this means that the Declaration of Helsinki needs to be made operational in for example the assessment guidelines for regulatory authorities evaluating the marketing authorisation applications. To be able to develop consensus guidance on specific ethical issues, the debate about some controversial ethical principles as in the Declaration of Helsinki needs to be held inside the regulatory framework, for example about post trial treatment. There is also a need to put more coordinating efforts into harmonising the application of ethical standards; this was a conclusion at the EMEA conference on the operation of the clinical trials Directive held in October, 2007. Secondly, it is difficult for regulatory authorities to effectively verify if ethical principles were observed in clinical trials conducted in third countries, based on the technical dossier, or, moreover, based on the statement by the applicant; this concerns desk research at the end of the process. It would be good if the good clinical practice verification can take place in an earlier stage, at the time the clinical trial is actually conducted. However, to do that, the regulatory authorities need to have an overview of all trials potentially part of a marketing authorisation application (MAA) and a system to filter out the most risky trials to check at random. Therefore, you need a compulsory database registering trials at the time patients are recruited and this database has to include the trials conducted in the developing countries. But more than this, you need the possibility to initiate GCP inspections outside the marketing authorisation procedure.

### 2.3 GCP Inspections

**Background Inspections:** One of the criteria for making a decision on a MAA is the assessment of the clinical trial documentation and this can lead to a request for a GCP inspection to determine whether a trial was conducted according to the applicable regulatory requirements<sup>(42)</sup> or to provide answers to questions arising from the assessment process or to determine whether the data submitted in the dossier are credible and accurate. The legal basis for GCP inspections concerning MAAs is to be found in article 57(a)(i) of Regulation (EC) No. 726/2004. To facilitate a higher level of protection for clinical trial participants in developing countries, it is important to

<sup>42</sup> CPMP.ICH/135/95 Note for Guidance on GCP, Directive 2001/83/EC as amended and local regulations and ethical standards.

carry out the inspections at the time the clinical trial takes place, as it allows for more effective review of clinical practices and is better aligned with the precautionary principle; necessary measures shall be preferably taken at the time they can effectively protect the clinical trial participants.

**Current situation analysis:** clinical trials inspected in third countries are always part of a Marketing Authorisation Application (MAA), because only those fall inside the scope of the EMEA. Inspections can be triggered inspections (requested because there is a concern) or it can be routine inspections and these are usually requested earlier during the validation phase of the technical dossier (<sup>43</sup>). However, at the time trials are selected for inspection most of these trials have already been completed. In general, the present legislation allows inspections to take place at the time when the clinical trial is actually running, sometimes with long term studies this is the case (<sup>44</sup>).

Looking for other possibilities for 'real time inspection' one option may be to involve other groups overlooking a clinical trial, such as the Data Monitoring Committees (DMC), Ethics Committees, Steering Committees, and the Study Team. All these groups are involved with monitoring tasks at the time the trial is running. Maybe there are ways to extend their tasks and include monitoring of GCP and reporting of non-compliance with GCP. A problem is that neither a DMC nor a Study Team is independent from the sponsor. There are financial interests as well as non-financial conflicts of interests. Another option is to make members of these groups personally liable for reporting non-compliance with GCP.

#### **Improvement GCP inspections 1:**

The role of groups overlooking a clinical trial at the time a trial is running, such as the Data Monitoring Committees (DMC), Ethics Committees, Steering Committees, and the Study Teams should be investigated to see if they can play a role in monitoring of GCP and reporting of non-compliance with GCP.

Article 15 of Directive 2001/20/EC, empowers the Commission and Member States to propose that a trial site and/or the sponsor's premises and/or the manufacturer established in a third country undergo an inspection. *'Subject to any arrangements which may have been concluded between the Community and third countries, the Commission, upon receipt of a reasoned request from a Member State or on its own initiative, or a Member State may propose that the trial site and/or the sponsor's premises and/or the manufacturer established in a third country undergo an inspection. The inspection shall be carried out by duly qualified Community inspectors.'* This instrument is not as effective as it could be because the constituency of subjects authorised to initiate the inspections is too narrow. In principle, the Commission or the Member States, as subjects authorised to initiate the inspections, are not always aware of the real situation and the infringements made during the clinical trial.

#### **Improvement GCP inspections 2:**

The legislation should be changed to make it possible:

- to initiate GCP inspections outside the marketing authorisation procedure.

<sup>43</sup> Procedure for coordinating GCP inspections requested by the EMEA (INS/GCP/1-Corr).

<sup>44</sup> vide Article 15 of Directive 2001/20/EC; also, in accordance with Article 23 (1) of Directive 2005/28/EC, good clinical practice inspections may be carried out before, during or after a clinical trial, as a part of the verification of an application for marketing authorisation or as a follow-up to the granting of authorisation.

- for anyone to initiate inspections through the Commission. Such person should only have to produce reasonable evidence of a risk that good clinical practice principles have been violated during the clinical trial outside the Community (preferable registered in a compulsory clinical trial database). That means the Commission should examine the given evidence, and if it concludes that good clinical practice principles may be violated during the clinical trial, it should initiate the inspection itself.

In order to enforce the observance of good clinical practice principles, it is advisable that the inspections cover the highest possible range of conducted clinical trials within the bounds of possibility (evidently, this partly depends heavily on political will and available resources). There has also been a call for an increased number of inspections during the 'Conference on the operation of the clinical trials directive' as well <sup>(45)</sup>.

**Improvement GCP inspections 3:**

The number of GCP inspections should be increased. Enforcement of this recommendation can be reached within the present legislation.

Another issue is the question of compensation for any harm experienced by a trial subject related to their participation in a trial. There are examples of companies insufficiently insuring their clinical trials <sup>(46)</sup>.

**Improvement GCP inspections 4:**

The EMEA as well as the GCP inspectors should check the provisions made for compensation in the informed consent form as part of the verification of GCP compliance.

## 2.4 Clinical trials database

**Background:** As already indicated in the previous paragraphs, there is a significant need for a comprehensive database of clinical trials that includes those conducted outside the Community. It was analysed that inspections could be more effective when performed at the time the clinical trial takes place. The lack of information on running clinical trials is a major obstacle to accomplish this goal. Within this context, it was also implied that this database should be widely accessible to public. Not only is this a vital prerequisite for the proposed mechanism of publicly triggered inspections, transparency is also an important instrument for urging the sponsor or the investigator to carry out their research in accordance with the ethical principles.

**Current situation analysis:** As to the present Community law, in order to exchange information among the Member States, Directive 2001/20/EC states, in article 11, that Member States shall enter listed pieces of information into the European database (EudraCT). However, the way the database is designed cannot match the requirements relevant for the protection of clinical trial participants in developing countries. Several major problems feature in this respect.

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<sup>45</sup> Report on the European Commission-European Medicines Agency Conference on the Operation of the Clinical Trials Directive (Directive 2001/20/EC) and Perspectives for the Future Conference, held on 3 October 2007 at the EMEA, London, Doc. ref.: EMEA/565466/2007, p. 41

<sup>46</sup> Ibid note 18

First and most importantly, this database is intended only for information concerning clinical trials conducted within the territory of the Community, as the obligation to enter information about a given clinical trial is only imposed upon the Member State in whose territory the clinical trial takes place. Therefore, the database does not include information about clinical trials taking place in third countries.

Second, information on the ethical issues is very limited. According to Article 11 of Directive 2001/20/EC, the database includes the favourable opinion of the ethics committee and a reference to the inspections carried out in conformance with good clinical practice. What is missing is information proving compliance with good clinical practice principles (e.g. the justification of placebo use, the justification of the use of vulnerable trial participants, the arrangements for post trial treatment).

Ultimately, the EudraCT database is accessible only to the competent authorities of the Member States, to the European Medicines Agency and to the Commission. The data never becomes available to the public or to the ethics committees. This lack of transparency results in low patient and clinical trial participant awareness, as well as a lack of information for the public, the ethics committees and the regulatory authorities (especially in regard of the 'real time' inspections).

Apart from the EudraCT database, Article 57 of Regulation (EC) No 726/2004 provides for the European Medicines Agency to establish a publicly accessible database on medicinal products authorised in the Community, which should also (where appropriate) include references to data on clinical trials currently being carried out or already completed that are contained in EudraCT database. Currently, there is an ongoing process by which the 'EudraPharm' database is being created and implemented. However, the guideline listing the data fields to be made public in the clinical trials database 'EudraPharm' does not include data on clinical trials in third countries or information proving compliance with good clinical practice principles<sup>(47)</sup>.

**Improvement clinical trial database 1:**

A comprehensive database on clinical trials taking place outside the Community should be established. The existing database EudraCT (or EudraPharm, under construction) can be improved to meet the necessary requirements, or a separate database for clinical trials taking place outside the Community can be established<sup>(48)</sup>. In any case, this database should:

- be open to information about all clinical trials conducted outside the Community relating to medicinal products intended for use in the Community,
- insist on mandatory entry of reports, including the registration of the clinical trial before it actually starts (as a condition of the later acceptability of its results for the marketing authorisation procedure in the Community),
- penalise the failure to submit documents and statements by sponsors, investigators or applicants, and the submission of misleading or inaccurate documents and statements by sponsors, investigators or applicants,
- contain more information about ethical issues and
- be accessible to the public.

<sup>47</sup> OJ, C 168, 03/07/2008 P. 0003 - 0004 <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:C:2008:168:0003:01:EN:HTML> [4.2.2009]

<sup>48</sup> It is also possible to refer to another existing international database if it meets the listed requirements.

## 2.5 Penalties

**Background:** The penal mechanism is one of the important legal instruments by which compliance with the law is enforced. In order to increase the efficacy of the whole mechanism as proposed in this report, the appropriate sanctions must be integrated into all instruments (the marketing authorisation procedure, inspections, and the clinical trials database).

**Current situation analysis:** A financial penalty can be imposed in cases where *'the infringement concerned may have significant public health implications in the Community, or where it has a Community dimension by taking place or having its effects in more than one Member State, or where interests of the Community are involved.'*<sup>(49)</sup>

It is important to note that the instruments mentioned so far (the marketing authorisation process, GCP inspections, a public clinical trial database) do not protect trial subjects in developing countries sufficiently from inadequate reporting of Serious Adverse Events (SAEs). There are various reasons for this inadequate reporting of SAEs; insufficient institutions for recording and processing; investigators that are more interested in efficacy than safety; patients that are reluctant to report SAEs in the fear that they will be cut off from a treatment that they perceive as a lucky chance; or even as a result of the patient's respect for the physician<sup>(50)</sup>. The inadequate reporting of SAEs in developing countries is a serious problem and needs further investigation as it can affect the health problems of patients in the EC. EU capacity building projects should involve adequate reporting of SAEs.

### Improvement penalties 1:

This point should be cleared up and defined. Preferably, the Commission Regulation (EC) No 658/2007 would explicitly state that the interests of the Community are involved:

- in case of a breach of good clinical practice principles occurring while conducting clinical trials in developing countries. This requirement results from the fact that the Community's international reputation is affected by the way it approaches the problems with infringements on human rights during the clinical trials conducted outside its territory.
- in case of inadequate reporting of SAEs in third countries.

Article 84 (3) of Regulation 726/2004 states that 'At the Agency's request, the Commission may impose financial penalties on the holders of marketing authorisations granted under this Regulation if they fail to observe certain obligations laid down in connection with the authorisations' (under the centralised procedure). However, the majority of applications are submitted under Directive 2001/83/EC to the competent authority of a Member State, imposing adequate penalties in such cases fall within the authority of Member States (decentralised procedure). Directive 2001/83/EC states, *'the applicant or the holder of a marketing authorisation shall be responsible for the accuracy of the documents and the data submitted.'* Because the determination of the type and level of the criminal penalties that should be applied does not fall within the Community's sphere of competence<sup>(51)</sup>, it is not possible to provide cogent regulation

<sup>49</sup> Article 1 of Commission Regulation (EC) No 658/2007

<sup>50</sup> Ibid note 18

<sup>51</sup> Judgment of the European court of justice of 23 October 2007 in case C-440/05: *Commission v Council* [2007] OJ C 315, 22.12.2007, p. 9

on the Community level. However, Member States can be addressed more directly this point. The 'Penalties Regulation'<sup>52</sup> was adopted in June 2007.

#### **Improvement penalties 2:**

The statement 'the applicant or the holder of a marketing authorisation shall be responsible for the accuracy of the documents and the data submitted.' should be amended to the effect that Member States must take all appropriate measures to ensure that the applicant who submits misleading documents and data is subject to 'effective, proportionate and dissuasive penalties'.

#### **Improvement penalties 3:**

As mentioned in regard to the mandatory database on clinical trials, as the database's integrity depends on receiving accurate information appropriate penalties should be imposed for the submission of misleading documents and statements by sponsors, investigators or applicants, as well as for the lack of submitting them at all. Also, the marketing authorisation should not be granted in such cases. In addition, natural persons representing the sponsor, the investigator or the applicant who submit the information, as well as any other responsible corporate officer who controls the submitting of the information, should be personally liable for the accuracy of the reported information. If the reported information is misleading or inaccurate, this person should be subject to financial sanctions or other 'effective, proportionate and dissuasive penalties'. This would function as an incentive to report accurate information.

#### **Improvement penalties 4:**

The same mechanism should apply with respect to the documents and particulars submitted under the marketing authorisation procedure. Aside from not granting the marketing authorisation and imposing the penalties on the applicant, natural persons representing the applicant who submit the documents and particulars, as well as any other responsible corporate officer who controls such submissions, should be held personally liable for their accuracy. Further, the experts who draft and sign the expert reports (detailed summaries which must accompany the documents and information concerning the results of the clinical trials submitted within the marketing authorisation procedure; vide supra) should be held personally responsible for their accuracy and thoroughness. If the expert reports are misleading, inaccurate or incomplete, these persons should be subject to financial sanctions or other 'effective, proportionate and dissuasive penalties'.

The background of establishing personal liability, is that in case of directors or other persons being in conflict of interest, there should be an incentive to prevent submitting misleading information. The proposed solution is to require them to act in a diligent way or face penalties.

### **Summary of improvements:**

#### **Marketing authorisation process:**

1) To repair the shortcoming in the legislation for the national marketing authorisation procedure, or the mutual recognition or decentralised procedure, as, according to this legislation, the

<sup>52</sup> Commission Regulation (EC) No 658/2007 of 14 June 2007 concerning financial penalties for infringement of certain obligations in connection with marketing authorizations granted under Regulation (EC) No 726/2004 of the European Parliament and of the Council <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2007:155:0010:0019:EN:PDF>

authorities can only check the presence of the statement by the applicant and they cannot refuse the marketing authorisation application in the case of the statement by the applicant being misleading.

2) Issuing guidelines for regulatory authorities on how to assess ethical standards. To be able to do this, the debate about some controversial ethical principles in the declaration of Helsinki needs to be held inside the regulatory framework.

### **Inspections:**

1) Inspections should preferably take place at the time that the trial is running instead of during the authorisation process when the trials are completed,

2) Initiation of an inspection outside the marketing authorisation should be possible,

3) Initiation of an inspection by third parties (outside EMEA or NCA) should be possible,

4) Increase the number of inspections in third countries,

5) check the provisions made for compensation in the informed consent form as part of the verification of GCP compliance.

### **Clinical trial database:**

1) Clinical trial database should include trials conducted in third countries;

2) Mandatory entry for trials should be part of EU marketing authorisation process;

3) Penalise the submission of misleading information by sponsors, applicants or investigators; 4) the clinical trial database should contain the ethical considerations made, and

5) it should be a public database.

### **Penalties:**

1) include unethical trials under definition of significant health implications for EU,

2) include underreporting of SAEs in third countries under definition of significant health implications for EU

3) member states should take more responsibility to penalise applicants submitting misleading information,

4) natural persons representing the sponsor, the investigator or the applicant who submit the information should be personally liable for the accuracy of the reported information for the database,

5) personal liability for those submitting information for the marketing authorisation procedure representing the applicant, including the experts responsible for the summaries and groups capable of overlooking a clinical trial at the time a trial is running, such as the Data Monitoring Committees (DMC), Ethics Committees, Steering Committees, and the Study Teams.

### 3 - SUBJECT-MATTER ANALYSIS ON GOOD CLINICAL PRACTICE

This chapter analyses the way the present Community legislation on good clinical practice principles refers to international ethical guidelines, or to be more precise, to the Declaration of Helsinki and the ICH GCP Guideline. Additionally, a brief comparison will be made between the more controversial provisions of the two documents.

As indicated in chapter 1.2, 'Overview of international ethical guidelines and developments', the pharmaceutical industry as well as representatives of European regulators perform a strong lobby in favour of the ICH GCP guidelines wanting to have a harmonised reference to the ICH GCP as the EU standard in the EU legislation. At the same time concerned civil society organisations lobby for a clear reference to the Declaration of Helsinki as the EU standard in the EU legislation. In the US this dispute has been settled at the expense of the Declaration of Helsinki; in October 2008 a regulatory change of the FDA came into effect, officially ending the need for clinical trials conducted outside the US to comply with the Declaration of Helsinki. To give insight on the ethical issues causing the debate a short overview of the most common ethical violations in developing countries is in order:

- Trial subjects not being well informed in advance about the nature of the trial and the risks involved, or not even being informed that they participate in a clinical trial at all;
- Trial subjects not being guaranteed continuing treatment when the trial ends;
- Failure to have the ethical aspects of the research proposal approved by a local ethical review committee prior to the start of the trial;
- The experimental drug being tested against a placebo instead of the current proven intervention thus exposing trial subjects to additional risks of serious or irreversible harm;
- Failure to ensure that the population involved in the trial benefits from the results of the research<sup>(53)</sup>.

The last point implies that patients and their communities should be informed about the conclusions issuing from the research, because the legitimacy of conducting a drug trial on a disease which will not benefit from a local healthcare programme is (at best) questionable<sup>(54)</sup>.

#### 3.1 Legal basis of good clinical practice principles in the Community

**Background:** The Community legislation concerning the clinical trials issue is based upon the principle of good clinical practice, regardless whether the clinical trial takes place within the Community's territory or in third countries.

**Current situation analysis:** Directive 2001/20/EC and Commission Directive 2005/28/EC are the key pieces of Community legislation concerning good clinical practice during clinical trials for medicinal products intended for human use.

Regarding good clinical practice, Directive 2001/20/EC sets out rules concerning several issues, including clinical trials on minors and incapacitated adults, ethics committees and the procedure for conducting the clinical trial. Furthermore, Article 1 (3) of Directive 2001/20/EC postulates that

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<sup>53</sup> Idem note 25

<sup>54</sup> Idem note 18

the principles of good clinical practice and detailed guidelines in line with those principles shall be adopted, and these detailed guidelines shall be published by the Commission.

As a result, Commission Directive 2005/28/EC, applying these provisions, was issued. Within the explanatory note of 2005/28/EC (the 'where as clauses' point no. 8), there is a reference to the Guideline for Good Clinical Practice, adopted by The International Conference on Harmonisation (ICH GCP Guideline) in 1995, with the objective of providing a unified standard for the European Union, Japan and the United States <sup>(55)</sup>. Further, Article 3 states 'Clinical trials shall be conducted in accordance with the Declaration of Helsinki on Ethical Principles for Medical Research Involving Human Subjects, adopted by the General Assembly of the World Medical Association (1996)'. This reference in 2005/28/EC is made to the 1996 version of the Declaration of Helsinki. The 'where as clause' (2) of 2001/20/EC also refers to the 1996 version of the Declaration of Helsinki. Annex 1 of Directive 2003/63/EC (amending Directive 2001/83/EC) includes the following statement in the 'Introduction and general principles section' (8): 'To be taken into account during the assessment of an application, clinical trials, conducted outside the European Community, which relate to medicinal products intended to be used in the European Community, shall be designed, implemented and reported on what good clinical practice and ethical principles are concerned, on the basis of principles, which are equivalent to the provisions of Directive 2001/20/EC. They shall be carried out in accordance with the ethical principles that are reflected, for example, in the Declaration of Helsinki'. In this part there is no reference to the 1996 version, however, the interpretation of these provisions regarding the way that the latest available version of the Declaration of Helsinki should be used is challenging (because of the reference to Directive 2001/20/EC which does mention the 1996 version). And because of the evasive language, e.g. the phrase 'the ethical principles that are for example, in the Declaration of Helsinki' or the phrase 'as for instance reflected in the 1996 version of the Helsinki Declaration', prevents making it hard law. Only Article 3 of Commission Directive 2005/28/EC specifically states 'in accordance to' the 1996 version and can be therefore defined as the Directive providing the highest standard of protection for clinical trial participants.

Considering that the ethical principles are applied primarily by ethics committees, it is the ethics committees' task to consider, based on the way it is designed and reported, whether the conduct of a clinical trial can begin. However, the good clinical practice principles essentially determine only general rules. To ensure a high level of protection for clinical trial participants, as well as consistency in ethical review, practical guidelines for ethics committees should be issued at the Community level. These guidelines should further elaborate on the more controversial provisions (e.g. in relation to use of placebo and post trial treatment arrangements). The need for such guidelines was clearly stated during the Conference on the operation of the clinical trials directive <sup>(56)</sup>. The Community legislation should also refer to these guidelines with regards to the clinical trials conducted outside the Community so that the ethics committees established in these nations will follow them.

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<sup>55</sup> 'The International Conference on Harmonisation (ICH) reached a consensus in 1995 to provide a harmonised approach for Good Clinical Practice. The consensus paper should be taken into account as agreed upon by the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency, hereinafter 'the Agency', and published by the Agency'.

<sup>56</sup> Report on the European Commission-European Medicines Agency Conference on the Operation of the Clinical Trials Directive (Directive 2001/20/EC) and Perspectives for the Future Conference, held on 3 October 2007 at the EMEA, London, Doc. ref.: EMEA/565466/2007, p. 27

## Concluding remarks

In view of the many obstacles, we are faced with the question whether it is worth the effort to try to change EU legislation in order to have a clear reference stating that all clinical trials that are part of EU are to be *in accordance* with the *current revision* of the Declaration of Helsinki. One of the obstacles is that the declaration is updated regularly by the World Medical Association (WMA) and that the WMA is free to put anything in their declaration. It is risky to make that hard law. Additionally, the Declaration of Helsinki does not make the ethical principles explicit enough, i.e. it is too vague to make it hard law. Therefore, it is recommended to make the crucial ethical standards of the declaration explicit and to make sure that these standards become part of practical guidelines for ethics committees, and also become part of the practical guidelines for the assessors of a marketing application and for the GCP inspections. But to be able to do this, a discussion about these crucial ethical standards needs to take place within the regulatory framework and with the industry, to reach a common definition of the problem and to create a basis for solutions that are attainable. In the next paragraph some of the controversial standards are discussed.

### Recommendation:

It is highly advisable to select those ethical standards from the Declaration of Helsinki that are crucial to protecting clinical trial subjects in developing countries and to elaborate on these in implementary guidances for ethics committees, the GCP inspectors and the EU assessors for marketing applications in cooperation with the European medicines agencies, the industry, intergovernmental and non-governmental organisations. These guidelines should be applicable in relation to the clinical trials conducted outside the Community as well. This can be done within the current legislation.

### 3.2 A brief comparison of the regulation of some controversial issues in the Declaration of Helsinki, ICH GCP Guideline, Directive 2001/20/EC and Commission Directive 2005/28/EC

**Background:** As demonstrated by several reports about the unethical use of placebos, a significant danger is developing out of the misuse of placebos during clinical trials. In some cases patients were put into serious danger by trials supplying them with a placebo instead of existing proven treatments or by taking seriously ill but stabilised patients off their treatment to measure the time to relapse and compare this with the experimental treatment. Some of these studies are done in third countries because the ethics committees in most Western European countries no longer approve this kind of trials due to the unethical aspects involved. However, pharmaceutical companies say that they are forced to conduct these kind of trials by the European authorities granting market authorisation because they require in principle placebo-controlled studies to prove efficacy<sup>(57)</sup>. Another problematic issue is the involvement of vulnerable and poor trial subjects while the testing medicines will not be of any benefit to the population because the medicine will not be marketed in the country, or will not be affordable for the patients. Sometimes it concerns medicines for diseases that are not of major concern for the country. And then there is the problem that in developing countries the end of the trial also means the end of the treatment. If such cases are to be eliminated, the legislation and detailed guidelines must set out principles explaining how to act.

<sup>57</sup> I. Schipper & F. Weyzig, Ethics for Drug Testing in Low and Middle Income Countries: Considerations for European Market Authorisation (Amsterdam: SOMO, February 2008)

**Current situation analysis:** The standard of protection for clinical trials participants varies within the different documents. In this section the Declaration of Helsinki, the ICH GCP Guideline, and Directive 2001/20/EC and Commission Directive 2005/28/EC will be compared on selected issues. In general, ICH guidelines are intended for use in combination with regional requirements. According to Article 2.1 of ICH GCP Guideline: *'Clinical trials should be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with GCP and the applicable regulatory requirement(s).'* Thus, adoption of the principles set out in the Declaration of Helsinki is unlikely to cause significant problems.

### Placebo-controlled trials

The Declaration of Helsinki, in Article 32, requires that the placebo or no-treatment use in clinical trials shall be restricted. It states that *'the benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best current proven intervention.'* An exception is allowed when no current proven intervention exists, or when on the basis of compelling and scientifically sound methodological reasons, the use of placebo is necessary to determine the efficacy or safety of an intervention and the patients who receive placebo or no treatment will not be subject to any risk of serious or irreversible harm. Under this exception, it is stressed that extreme care must be taken to avoid any abuses.

The 2001 ICH guideline on control groups states *'whether a particular placebo-controlled trial of a new agent will be acceptable to subjects and investigators when there is a known effective therapy is a matter of patients, investigator, and IRB judgement, and acceptability may differ among regions and (...) populations chosen'*.<sup>58</sup> This is considerably weaker than the DoH. In fact, it leaves many options open and gives research efficiency precedence over ethical considerations. According to point 2.1.3 'Ethical issues,' in cases where an available treatment is known to prevent serious harm, such as death or irreversible morbidity in the study population, it is generally inappropriate to use a placebo control. In other situations, it is generally considered ethical to ask patients to participate in a placebo-controlled trial (advisability depends on specific conditions). Compared to the Declaration of Helsinki, this protection of patients is weak.

Directive 2003/63/EC, Annex I, part I, section 5.2.5.1 states: *'In general, clinical trials shall be done as 'controlled clinical trials' if possible, randomised and as appropriate versus placebo and versus an established medicinal product of proven therapeutic value; any other design shall be justified. The treatment of the control groups will vary from case to case and also will depend on ethical considerations and therapeutic area; thus it may, in some instances, be more pertinent to compare the efficacy of a new medicinal product with that of an established medicinal product of proven therapeutic value rather than with the effect of a placebo.'* This makes clear that there is no obligation in the EU legislation to test against placebos as some companies feel. But the spirit of this text is different to that of the declaration; where in the declaration the placebo controlled trial is the exception to the rule, in the Annex of the Directive testing against a proven treatment is the exception to the rule.

The Declaration of Helsinki offers the best protection of patients (to all patients, not only those in third countries).

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<sup>58</sup> ICH Topic E 10, Choice of Control Group in Clinical Trials, Step 5, Note for guidance on choice of control group in clinical trials (CPMP/ICH/364/96), January 2001, published by the European Medicines Agency (EMA). Section 2.1.3 Ethical issues. <http://www.emea.europa.eu/pdfs/human/ich/036496en.pdf>

### Post trial treatment

In Article 14, the Declaration of Helsinki requires the research protocol (describing the design and performance of the clinical trial) to *'describe arrangements for post-study access by study subjects to interventions identified as beneficial in the study or access to other appropriate care or benefits'*. Furthermore, Article 33 explicitly states that clinical trial participants are entitled to be informed about the outcome of the study, and to share any benefits that result from it, such as access to an intervention identified as beneficial in the study or other appropriate care or benefits.

There is no provision equivalent to those included in the Declaration of Helsinki in the ICH GCP Guideline or in Directive 2001/20/EC and Commission directive 2005/28/EC that would establish the rights of the clinical trial participants to post trial treatment.

The right of clinical trial participants to post trial treatment is the ethically sound requirement. Thus it is necessary to effectively assert it. However, access to post trial treatment for clinical trials participants outside the Community is rarely provided<sup>(59)</sup>. Even when the clinical trial takes place within the Community, its participants are not always guaranteed cost-free continuation of a successful treatment at the end of a trial<sup>(60)</sup>.

### Vulnerable subjects

In Article 9, the Declaration of Helsinki gives the general definition of 'vulnerable population' with respect to clinical trials, that is, those who cannot give or refuse consent for themselves and those who may be vulnerable to coercion or undue influence. Furthermore, the article states that such people need special protection. In this regard, in Article 17 requires that *'medical research involving a disadvantaged or vulnerable population or community is only justified if the research is responsive to the health needs and priorities of this population or community and if there is a reasonable likelihood that this population or community stands to benefit from the results of the research.'*

The ICH GCP Guideline contains an extensively detailed definition of vulnerable subjects. However, it only requires, in Article 3.1.1, that the Independent Ethics Committee (or the Institutional Review Board), while safeguarding the rights, safety, and well-being of all trial subjects, pay special attention to trials that include vulnerable subjects. The guideline gives no rule concerning the justification for conducting clinical trials on these subjects.

Directive 2001/20/EC in Articles 4 and 5 sets out several protective rules focused on minors and incapacitated adults (i.e. the ban of incentives or financial inducement, relation to the subject clinical condition, benefit). However, special protective provisions for other vulnerable subjects, like poor trial subjects, are not detailed. This analysis shows that the protective scope of Declaration of Helsinki is the most favourable to clinical trial participants in developing countries.

### Obligation to register the trial

The Declaration of Helsinki states in Article 19 that every clinical trial must be registered in a publicly accessible database before the first subjects are recruited.

<sup>59</sup> Idem note 56, p.48

<sup>60</sup> Report on the European Commission-European Medicines Agency Conference on the Operation of the Clinical Trials Directive (Directive 2001/20/EC) and Perspectives for the Future Conference, held on 3 October 2007 at the EMEA, London, Doc. ref.: EMEA/565466/2007, p. 38

There is no obligation to give notice of when the clinical trial will begin, or to register information set out in the ICH GCP Guideline.

Directive 2001/20/EC only imposes an obligation to enter listed information into the European database on Member States whose territory relates to the clinical trial. As interpreted supra, this database does not make the information publicly accessible or provide information concerning clinical trials taking place outside the Community.

**Recommendation:**

Because the principles laid down in the Declaration of Helsinki provide the highest level of patient protection, they should be implemented and applied to ensure the effective protection of clinical trial participants, especially of those in third countries.

## 4 - ANALYSIS OF LEGAL INSTRUMENTS AVAILABLE TO THIRD COUNTRY CITIZENS

### 4.1 General situation

This section includes an analysis of legal instruments available to third country citizens, who were subjects of unethical clinical tests carried out outside the European Union (EU), to sue the pharmaceutical industries carrying out these tests. The aim of the analysis is to identify which instruments and strategies could be used by European legislature to improve such victims' access to justice. The study focuses on options available within the EU as the European legislation cannot directly influence a victim's position in the litigation in third countries because of jurisdictional limitations. These options are independent of regulation of the marketing authorisation process.

As pointed out by Günther Verheugen, Vice President of the European Commission, in response to the European Parliament interpellations, the EU law does not specify whether the sponsors of clinical trials in third countries are liable civilly or criminally for their actions<sup>(61)</sup>. The available options thus depend on the laws of the Member States, principles of the international law and incidental effects of general European law. As a result, third country victims' enforcement of remedies in Europe is extremely difficult, as noted by the European Parliament<sup>(62)</sup>. On their quest for justice, victims have to go through a cascade of legal obstacles. The layers of this problem will be addressed hereinafter separately to demonstrate what kinds of changes are necessary to mend the existing system.

### Jurisdictional Grounds

#### 4.1.1 Criminal liability

In principle, private subjects such as pharmaceutical companies and clinical research organisations can be exposed to civil or criminal liability. In criminal law, European states respect the territoriality principle. That means they exercise their jurisdiction only with respect to crimes that take place in their territory. There are some exceptions to this. A number of European states prosecute, at least in theory, the most serious abuses of human rights – crime of genocide, war crimes and crimes against humanity, regardless of where and by whom they have been committed<sup>(63)</sup>, and so does the International Criminal Court, although not against legal persons<sup>(64)</sup>. However, unethical clinical trials would not fit definitions of those crimes, unless their participants were coerced to take part in them by force. In other cases, criminal law of Member States does not provide victims with access to justice.

<sup>61</sup> European Parliament, Parliamentary questions, Answer given by Mr Verheugen on behalf of the Commission, (Question E-0777/2007), <<http://www.europarl.europa.eu/sides/getAllAnswers.do?reference=E-2007-0777&language=EN>>

<sup>62</sup> European Parliament Resolution of 13 March 2007 on Corporate Social Responsibility: A New Partnership (2006/2133(INI)), point 42: '[...] encourages the Commission to develop, in particular, mechanisms that ensure that communities affected by European companies are entitled to a fair and accessible process of justice'.

<sup>63</sup> For more on this subject see: O. Schutter, *The Role of EU Law in Combating International Crimes*, Louvain, 2006

<sup>64</sup> The International Criminal Court was established by the Rome Statute of the International Criminal Court, adopted on 17 July 1998 by the United Nations Diplomatic Conference of Plenipotentiaries on the Establishment of an International Criminal Court. The Rome Statute is an international treaty, binding only on those states that formally express their consent to be bound by its provisions. Today, 105 States have become parties to the Statute.

It doesn't appear feasible to expand Member States' criminal jurisdiction in this respect. First, jurisdictional limitations are a matter of public international law and international comity. Under these authorities, a state may not prosecute foreign nationals for conduct beyond the state's physical boundaries. This leaves a significant loophole in the regulation allowing implementation of clinical trials to be carried out by foreign persons. Second, neither the Treaty of the European Union nor the Treaty Establishing the European Community provides a strong basis for EU competence in this respect.

#### 4.1.2 Civil liability

More options are available to victims before European courts if they try to hold pharmaceutical companies liable in the sphere of private law. In cases of non-contractual obligations, the rules on the jurisdiction of Member States' courts are partly harmonised by Brussels I Regulation <sup>(65)</sup><sup>(66)</sup>. Accordingly, persons (legal or natural) may be sued in the courts of a Member State, in which they are domiciled <sup>(67)</sup>. In matters relating to tort, persons may be sued in the courts of the place where the harmful event occurred or may occur <sup>(68)</sup>. This means that victims of unethical clinical trials can sue sponsors of that trial in the court of a Member State if the latter is domiciled or has managed the trial from there.

If the sponsor is not domiciled in the EU, the national court hearing the case will decide whether it has jurisdiction in the matter based on its national law. This so-called residual jurisdiction (i.e. not harmonised by Brussels I Regulation) was analysed in a 2007 study by the European Commission, which revealed great diversity in the national rules of jurisdiction currently in force in the Member States <sup>(69)</sup>.

In tort matters, Member States determine the jurisdiction based on where the damage and/or event giving rise to it occurred <sup>(70)</sup>. This does not extend options for victims beyond Brussels regime but some states provide for additional exorbitant jurisdiction. The concept of exorbitant jurisdiction is generally understood as referring to a ground that does not guarantee 'a sufficient connection with the parties to the case, the circumstances of the case, the cause or subject of the action' <sup>(71)</sup>. The aforementioned study identifies <sup>(72)</sup> several such grounds used by various Member States <sup>(72)</sup>. These grounds include presence of the defendant or its assets in their territories, which provides victims with an additional venue to sue sponsors of unethical trials <sup>(73)</sup>. Majority of Member States recognising this jurisdictional ground limits this option by application of the *forum non-conveniens* doctrine, which allows courts to stay proceedings, if there is an **available** and more

<sup>65</sup> Non-contractual obligations represent law of tort, civil delicts or quasidelicts - depending on varying terminology of Member States' jurisprudence. English term of tort is used hereinafter.

<sup>66</sup> Council Regulation (EC) No 44/2001 of 22 December 2000 on jurisdiction and the recognition and enforcement of judgements in civil and commercial matters, OJ L 012, 16.1.2001, p. 1

<sup>67</sup> Ibid, Article 2

<sup>68</sup> Ibid, Article 5(3). According to the Judgment of the European Court of Justice of 30 November 1976 in case C-21/76: Bier v. Mines de Potasse d'Alsace [1976] ECR 1735 at paragraph 25 this definition should be interpreted to the end that the defendant may be sued, at the option of the plaintiff, either in the courts for the place where the damage occurred or in the courts for the place of the event which gives rise to and is at the origin of that damage.

<sup>69</sup> A. Nuyts, Study on Residual Jurisdiction (Review of the Member States' Rules concerning the 'Residual Jurisdiction' of their courts in Civil and Commercial Matters pursuant to the Brussels I and II Regulations) - General Report, The European Commission, 2007

<sup>70</sup> Ibid., p. 34

<sup>71</sup> C. Kessedjan, International Jurisdiction and Foreign Judgments in Civil and Commercial Matters, Preliminary Document No 7 of April 1997, Hague Conference of Private International Law, <<http://www.hccn.net>>. See also P. Struyven, Exorbitant Jurisdiction in the Brussels Convention, *Jura Falconis*, 1998-1999, p. 521 s.; De Winter, L.I.: *Excessive Jurisdiction in Private International Law*, 17 I.C.L.Q. 706 (1968). All in A. Nuyts, op. cit, page 58

<sup>72</sup> A. Nuyts, op. cit, page 58-66

<sup>73</sup> Countries recognising this kind of jurisdiction include England and Wales, Ireland, Malta, Cyprus, Poland, Finland, Scotland, Austria, Czech Republic, Denmark, Germany, Lithuania, and Sweden.

**convenient** forum where the plaintiffs can raise their claim <sup>(74)</sup>. The more convenient forum will usually be in the country where the damage occurred, the evidence is located or the victims can be found.

The *forum non-conveniens* doctrine cannot be applied if it would deprive any of the parties to the dispute of a fair trial <sup>(75)</sup>. However, the only known lawsuits brought by third country nationals against pharmaceutical companies in a developed country's courts were *Abdullahi v. Pfizer* <sup>(76)</sup> and *Adamu v. Pfizer* <sup>(77)</sup>. In both of these cases the U.S. courts dismissed the lawsuits of victims of a controversial clinical trial of Trovan antibiotics in the Nigerian town of Kano, concluding that Nigeria is an available alternative forum. This decision was based on case law from U.S. courts dictating that cases should be dismissed for *non-conveniens* reasons unless a very exceptional case arises. English courts are arguably more willing to examine whether alternative forum would indeed enable due process before applying the *forum non-conveniens* doctrine. Thus, the House of Lords ruled in *Connely v. RTZ* <sup>(78)</sup> and *Lubbe v. Cape plc* <sup>(79)</sup>, that Namibia and South Africa, respectively, did not, for various specific reasons, ensure that parties would be served with fair trial. It must be borne in mind though, that these decisions were based on specific circumstances of the cases and that it took years in each case just to settle this preliminary question.

Finally, 10 Member States apply the *forum necessitatis* doctrine, which enables their courts to hear cases if there is no available or appropriate forum abroad <sup>(80)</sup>. The general conditions are similar to those used by English and U.S. courts in applying *forum non-conveniens* doctrine, that is, that refusing to hear the case would lead to the denial of justice and that there is some kind of connection with the forum.

## 4.2 Corporate Veil

Pharmaceutical companies usually take the form of transnational corporations. They operate as a single economic entity, normally through the coordination of a number of separate legal persons. The twin concepts of separate legal personality and limited liability insulate each member of the corporation from the obligations, civil or criminal, of the other members of the economic group. This is a fundamental principle of company law, protecting entrepreneurs from financial risks connected with their operations beyond the sums initially invested, and hence encouraging investment. However, it can also preclude victims from successfully bringing a lawsuit against pharmaceutical corporations before courts of the Member States.

European law requires those who seek market authorisation of medicinal product to be established within the EU or be legally represented there <sup>(81)</sup>. According to the Brussels I Regulation, these persons can be sued in the courts of the Member States. However, they are not necessarily the

<sup>74</sup> *Forum non-conveniens* doctrine is applied by courts in England and Wales, Ireland, Malta, Cyprus, Scotland and Lithuania.

<sup>75</sup> See, e.g.: B. Sahni, Limitations of Access at the National Level: Forum Non Conveniens, 9 GONZ. J. INT'L L. 119, 2006, <<http://www.gonzagajil.org>>

<sup>76</sup> 2005 U.S. Dist. LEXIS 16126

<sup>77</sup> 399 F. Supp. 2d 495; 2005 U.S. Dist. LEXIS 26804

<sup>78</sup> *Connely v. RTZ* [1998] AC 854

<sup>79</sup> *Lubbe v. Cape plc*. [2000] 1 WLR 1545,

<sup>80</sup> A. Nuyts, op. cit., p. 63. These countries include Austria, Belgium, Estonia, France, Germany, Luxembourg, Netherlands, Poland, Portugal, and Romania

<sup>81</sup> Article 8(2) of Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use O. J. L 311, 28.11.2001, p. 67, and Article 2 of Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency, O. J., L 136, 30.4.2004, p. 1.

same persons who are legally responsible for ethical issues in the clinical trials such as sponsors of the clinical trials and/or the clinical research organisations to whom the pharmaceutical corporations might outsource the conducting of trials. In this case, the persons who seek market authorisation of medicinal product can be held liable for the unethical consequences of clinical trials when they clearly fail to adhere to their duty of care<sup>(82)</sup>, when they have authorised or abetted the violation, or when the corporate structure has deliberately been used to advance fraud or other illegal or wrongful purposes. However, the pharmaceutical corporation would not likely be held liable if it did not control the operation for which it is blamed, but it retained strategic control over the clinical research. In civil matters, wrongdoing must be proven by plaintiffs, which is very difficult in respect of the aforementioned given the fact that the necessary evidence would be normally be held by the defendant corporation.

It follows from the aforementioned that victims of unethical clinical trials can start a case in the courts of the Member States against person (legal or natural) domiciled within the EU who was actively involved in or orchestrated the unethical trials and this connection is proven by the plaintiffs. This is a serious obstacle in litigation. Victims have to resolve a question of liability within the enterprise before subject matter related questions of the case can be dealt with. The problem in this respect can be narrowed down to the fact that current legislation does not explicitly stipulate that liability for ethical issues belongs to any concrete person. Those who seek market authorisation of medicinal product are indeed liable for the clinical trials that have been carried out, as part of their application, in accordance with international guidelines under sanction of refusal of the application. This administrative liability, however, is without prejudice to the civil liability.

### **Recommendations to mitigate the Corporate Veil obstacle.**

Obstacles created by the corporate veil and jurisdictional limitations, as described above, should be addressed by new legislation containing the following requirements:

- 1.** Parent companies in enterprises that market medicine products should be held strictly liable, in the sphere of private law, for damage caused to the participants of the clinical trials carried out on behalf of these products. This arrangement provides for similar liability as pharmaceutical companies face for damages their products cause to patients and consumers. Furthermore, such requirements would enable victims to sue pharmaceutical enterprises that are domiciled within the EU.
- 2.** Persons seeking market authorisation should be jointly liable with the aforementioned parent companies. This rule would enable victims to sue pharmaceutical enterprises, with parent companies outside the EU, that benefit from unethical trials. The liability of the entity seeking market authorisation, however, would be limited to clinical trials used in the market authorisation procedure.

The proposed liability would be without prejudice to existing liability of persons who carried out the violations. Enterprises that are held liable for providing redress to victims of unethical clinical trials would be able to bring an action for damages against those persons. In other words, the

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<sup>82</sup> A duty of care can be recognised where the parent company knows about the violations and actually exercises direct and close control over its subsidiary's operations. Claims of failing such duties were raised in litigation in the United Kingdom, where a foreign direct liability of parent in United Kingdom was an central issue – *Connely v. RTZ* [1998] AC 854, *Lubbe v. Cape plc.* [2000] 1 WLR 1545, *Ngcobo v. Thor Chemical Holdings Ltd*, TLR 10 November 1995, *Sithole v. Thor Chemical Holdings*, TLR 15 February 1999. In France, *Tribunal de Grande Instance de Paris* (Court of First Instance of Paris) held oil company *Total* liable on analogous basis in criminal proceedings to pay compensations for impacts of Erika tanker disaster (Judgment of 16 January 2008). The case is currently under appeal.

proposed solution shifts litigation burden from the victims to those benefiting from the sale of tested products.

Currently there is no European legislation dealing with civil (nor criminal) liability for clinical trials. **The aforementioned proposals can be implemented in the EU law either as a brand new legislation in a form of a directive or regulation.**

### 4.3 Conflict of Laws

In civil matters, courts have to determine which national law is applicable to disputes they hear. Rules on applicable law in disputes about torts and delicts arising from non-contractual obligations is harmonised within the European Union by the Rome II Regulation<sup>(83)</sup>. This regulation generally rules out the possibility of application of European law in extraterritorial cases. According to Article 4 thereof, the courts shall apply the law of place, where the damage occurred, which in these cases will be a law applicable in the countries where the unethical clinical trials were conducted and where the victims of these trials suffered damage or encroachment of their rights.

This would not automatically lead to victims' deprivation of protection guaranteed to them by customary international law. International human rights law shall be applied by courts universally and irrespective of what is stipulated in the applicable national law. Given the lack of case law it is much less clear, though, to what degree this protection would include specific principles of ethical conduct of clinical trials as defined in soft law instruments such as the Declaration of Helsinki or the Nuremberg Code. As expressed by the New York Federal District Court in *Abdullahi v. Pfizer* 'non-consensual medical experimentation violates the law of nations'<sup>(84)</sup>. Nevertheless, this didn't prevent U.S. court from stating that from its perspective respective international law does not provide in this case for private cause of action. The position of other principles defined in the aforementioned documents is even more problematic. The practice of jurisprudence and courts would vary among the States and its analysis greatly exceeds scope of this study. For its purposes, it is sufficient to state that it cannot be guaranteed that victims are able to claim that their rights were violated.

Furthermore, the Rome II regime explicitly rules out an application of EU legislation regarding liability for the acts of another person, such as those proposed above<sup>(85)</sup>. In other words, if victims sued a pharmaceutical company domiciled or represented in the EU, courts would examine the liability of this company for the misconduct of its subsidiaries or clinical research organisations based on principles of law of the country where the trials were conducted.

### Recommendations Conflict of Laws

The obstacle to applicability of proposed legislation created by the conflict of laws and rules in the Rome II regulation can be addressed in two different ways.

1. The proposed legislation should include a provision specifying that the legislation must be applied by the courts of the Member States, irrespective of where the damage caused by

<sup>83</sup> Regulation (EC) No 864/2007 of the European Parliament and of the Council of 11 July 2007 on the law applicable to non-contractual obligations, O. J., L 199/40, 31.7.2007, p. 40

<sup>84</sup> Judgment of New York District Court of August, 9, 2005 in the case *Abdullahi v. Pfizer*, 2005 U.S. Dist. LEXIS 16126, page 7. Term 'law of nations' refers to the body of law known as customary international law. Flores, 406 F.3d 65, 2003 WL 24122601.

<sup>85</sup> See Article 15 (g) of Regulation (EC) No 864/2007 of the European Parliament and of the Council of 11 July 2007 on the law applicable to non-contractual obligations

infringement of the law occurs, and irrespective of the provisions of the Rome II Regulation. This is possible by virtue of article 16 of the Rome II Regulation.

**2.** The Rome II Regulation should be amended to enable a choice of applicable law to be made by the plaintiffs seeking compensations for damage they have suffered in the course of clinical trials. A similar exception is currently included in the Rome II Regulation allowing such claims based on environmental damage. Plaintiffs can choose to apply the law of the country where event(s) giving rise to the environmental damage occurred, e.g. mismanagement on the part of the parent company <sup>(86)</sup>.

#### **4.4 Material Obstacles to Access to Justice**

Previous sections focused on legal obstacles that prevent victims of unethical clinical trials from suing pharmaceutical companies or other responsible subjects in courts of Member States. Besides that, there are major material obstacles to litigation. This is especially true in cases of informational asymmetry and financial imbalance between parties, which is characteristic of disputes between people and transnational corporations. In the analysed subject matter the adverse effects of this imbalance are amplified by the fact that victims of unethical clinical trials are often recruited from vulnerable and very poor population groups and that the essential evidence concerning clinical trials and arrangements within the pharmaceutical corporations is not public.

The inferential problems include very concrete issues like lack of legal expertise and insufficient access to legal aid, poor access to evidence that is vital due to the burden of proof requirements, as well as other cultural and logistical issues preventing victims from litigation. These problems are not limited to cases of human rights abuses in developing countries. The legal framework of the EU and the Member States addresses them in several other areas, namely in environmental law, anti-discrimination law, and consumer protection law. Furthermore, in 2005 the Commission has issued a Green Paper on damages actions for breach of the EC antitrust rules in which it discusses a number of measures designed to improve position of the small competitors in civil litigation against large corporations who breached EC competition law <sup>(87)</sup>. Proposed measures, which are described below, build on these examples.

### **Recommendations Material Obstacles to Access to Justice**

#### **1. Access to evidence and burden of proof**

Actions against transnational corporations in human rights cases normally require the investigation of a broad set of facts. The particular difficulty with this kind of litigation is that often the relevant evidence is not easily available and is held by the party committing human rights violations. Access by claimants to such evidence is the key to making claims effective. This access can be facilitated by following measures.

(a) Once a plaintiff has set out in detail the relevant facts of the case and has presented reasonably available evidence in support of its allegations, the court should order the defendant party to allow the investigation to be carried out by the plaintiff on its premises and to disclose identified

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<sup>86</sup> Ibid., Article 7.

<sup>87</sup> Commission Green Paper on Damages actions for breach of the EC antitrust rules {SEC(2005) 1732}

evidence. Unjustified refusal by a defendant to turn over evidence should establish a presumption of proof.

(b) The burden of proof should be shifted in favour of the plaintiffs when they are able to present reasonable evidence in support of their allegations. Such rules could, to a certain extent, make up for the non-existent or weak disclosure rules available to the claimant <sup>(88)</sup>.

## 2. Collective actions

Very often victims of unethical clinical trials are not physically and financially able to start litigation. Their interests and law enforcement can be protected by collective actions or private enforcement of public law. Many states allow for citizens or victims to enforce public liabilities such as French penal law <sup>(89)</sup>, United States citizen suits <sup>(90)</sup> and Canadian environmental legislation <sup>(91)</sup>. In European law, consumer organisations have the right to seek injunctions against entrepreneurs who are in breach of a provision of consumer law <sup>(92)</sup>, and The Aarhus Convention also stipulates this right in relation to environmental protection <sup>(93)</sup>.

A similar arrangement should be established in respect of human rights or ethical principles in clinical trials violations. Organisations representing collective interests harmed by violations shall be given legal standing to enforce respective statutes. Any person who has a sufficient interest or maintains an impairment of right should have the right to bring a lawsuit. To this end, the interest of any non-governmental organisation promoting public interest endangered in the case shall be deemed sufficient.

## 3. Costs of litigation

'Rules on cost recovery play an important role as incentives or disincentives for bringing an action. In view of the fact that Community law as well as the European Convention on Human Rights demands effective access to courts for civil claims, consideration should be given to how cost rules can facilitate such access' <sup>(94)</sup>.

Unsuccessful claimants in human rights cases should pay costs only if they acted in a manifestly unreasonable manner by bringing the case. Further, the court should have the discretionary power to order, at the beginning of a trial, that the claimant not be exposed to any cost recovery, even when the action is unsuccessful.

## 4. Exemplary damages

The deterrent effect of civil litigation is relatively low compared to criminal prosecution and sanctions. U.S. and British courts can address this by awarding plaintiffs with punitive damages

<sup>88</sup> See Article 10 of Council Directive 2000/78/EC of 27 November 2000 establishing a general framework for equal treatment in employment and occupation. Also in Commission Green Paper on Damages, Option 10, p. 6.

<sup>89</sup> Code de procédure pénale, Article 2, Modifié par Ordonnance n°58-1296 du 23 décembre 1958 - art. 1 () JORF 24 décembre 1958 en vigueur le 2 mars 1959.

<sup>90</sup> Such as the U.S. CERCLA§ 9659, RCRA § 6972, EPCRA § 11046, Clean Water Act§ 1365, Clean Air Act § 7604, SDWA § 300j-8(a)(1), SMCRA § 1270, TSCA § 2619.

<sup>91</sup> The Canadian Environmental Protection Act, 1999, S.C. 1999 c. 33.

<sup>92</sup> Directive 98/27/EC of the European Parliament and of the Council of 19 May 1998 on injunctions for the protection of consumers' interests, OJ L 166, 11.6.1998, p. 51–55

<sup>93</sup> The UNECE Convention on Access to Information, Public Participation in Decision-making and Access to Justice in Environmental Matters, usually known as the Aarhus Convention, that was ratified by the EU and most of the Member States. It obliges its Parties to enable the affected public, expressly including NGOs, access to justice against a state's decisions in environmental matters (Article 9.2), and against private persons (Article 9.3).

<sup>94</sup> Commission Green Paper on damages, p. 9

(termed exemplary damages in the United Kingdom). They are not awarded in order to compensate the plaintiff, but in order to reform or deter the defendant and similar persons from pursuing a course of action such as that which damaged the plaintiff.

Plaintiffs in human rights cases should be able to claim punitive damages. Punitive damages could be either awarded to them, or to the state budget, or a special trust with the aim to mitigate negative impacts of globalisation on human rights, or be ordered to pay the victims of the violations who are not party of a proceeding.

As said there is no European legislation dealing with civil (nor criminal) liability for clinical trials. Therefore:

**The aforementioned proposals can be implemented in the EU law either as a brand new legislation in a form of a directive or regulation**

#### **4.5 Conclusions legal instruments**

The options available to victims of unethical clinical trials conducted outside the European Union are limited. They can sue pharmaceutical and clinical research companies who are domiciled in the European Union but not foreign companies unless there is no other appropriate forum available. The companies can be held liable only if they have been directly involved in managing or controlling the clinical trials in respect of issues that violate ethical standards. This might not necessarily be the regular arrangement. Pharmaceutical companies that take the form of transnational corporations consisting of many separate legal persons by principle do not share the legal obligations of the other members of the economic group.

These obstacles can be removed if the legislation allocates civil liability for violations of ethical standards to the company seeking market authorisation of the medicinal product, or to the parent company of the transnational corporation which sponsored the clinical trial, and extends jurisdiction of the courts of the Member State to such parent companies which are domiciled outside of the European Union.

Material obstacles that face victims of clinical trials and prevent them from access to justice represent a separate problem. These obstacles include lack of publicly available evidence, financial costs of litigation and a large array of cultural and logistical issues. They can be addressed by specific reforms of the process - shifting the burden of proof, relieving the risk of cost recovery by the other party of the litigation, and collective means of redress.

## 5 - INTERVIEWS WITH EUROPEAN MEDICINES AGENCIES

Chapter 5 presents an analysis of the mandate, the organisation and the functioning of the European regulatory authorities, more specifically of the European Medicines Agency (EMA) responsible for the centralised marketing authorisation procedure, and the national medicines agencies responsible for the national and decentralised or mutual recognition procedure. The information in this chapter is based on interviews and desk research, we decided to focus the analyses of the regulatory authorities on the marketing authorisation procedure, the GCP inspections, transparency, the role of the ethics committees, the status of the Declaration of Helsinki (DoH) at medicines agencies and the financial dependence on fees paid by the industry. SOMO had a number of interviews with representatives of the EMA and national medicines agencies (together called 'the interviewees' in this part) and SOMO participated in an expert meeting on this subject on December 4, 2008, in The Hague (NL) where the industry, Dutch competent authority and registration authority, and parliamentarians of the Dutch socialist party (PvdA) of the Dutch and European Parliament and several NGOs active on this issue were represented.

### 5.1 The EU marketing authorisation procedure.

About 10% of the medicines entering the EU market is authorised by the EMA which leaves about 90% of the medicines to be authorised through the mutual recognition and decentralised procedures by the national authorities. According to the table 'Number of centralised procedures in 2007', there were 90 procedures in 2007<sup>(95)</sup>. For 2008 the estimation is more than 100. The countries supplying the highest number of rapporteurs and co-rapporteurs are the United Kingdom, Germany, Sweden, Spain, and the Netherlands; these countries carry out a large proportion of the European regulatory work. For instance, the Netherlands was the rapporteur in 9 procedures in 2007 (that is 10% of the total) and co-rapporteur in 11 procedures<sup>(96)</sup>. Compared with the centralised procedure<sup>(97)</sup> 1,034 decentralised procedures were initiated in 2007 and 397 mutual recognition procedures. These numbers correlate more or less with the statement in the 2007 annual report of the EMA that the work of the Coordination Group for Mutual-Recognition and Decentralised Procedures–Human (CMD(h)) is essential for the effective authorisation and maintenance of more than 90% of medicines entering the EU market<sup>(98)</sup>. The countries which have the largest 'market shares' are Germany (carrying out 26% of the decentralised procedures), United Kingdom (21%), Denmark (21%), the Netherlands (14%) and Sweden (5%). The 'market shares' for the mutual recognition procedure are slightly different, divided among the same players with the leading position for the Netherlands (23%), Denmark (15%), Germany (13%), Sweden (11%) and the UK (9%). The reason why these countries are so much more popular than others is not known but interesting to establish.

It is clear that the regulatory authorities of only a few European countries are responsible for authorising the majority of the medicines entering the EU market, because these countries supply most of the rapporteurs and co-rapporteurs for the centralised procedure but are also responsible

<sup>95</sup> See 'Table 4: Number of centralised procedures in 2007', source: Annual Report 2007, Medicines Evaluation Board, Netherlands, p. 45.

<sup>96</sup> Annual Report 2007, Medicines Evaluation Board, Netherlands.

<sup>97</sup> As said, there were 90 centralised procedures in 2007, however it is not completely clear if these concern also *initiated* procedures in 2007, like the 2007 figures on the mutual recognition and decentralised procedures.

<sup>98</sup> Annual report EMA, 2007, p. 42.

for most of the mutual-recognition and decentralised procedures. Only five EU countries (Germany, the UK, Denmark, the Netherlands and Sweden) are responsible for 87% of the decentralised procedures and for 71% of the mutual-recognition procedure and four out of these five countries (the UK, Germany, Sweden, and the Netherlands) also deliver the highest number of rapporteurs and co-rapporteurs for the centralised procedure. Besides the question whether this is a desirable situation, it is important that the responsible authorities of these countries are involved in any possible follow-up of the recommendations in this report.

## 5.2 The GCP verification by the EMEA

First of all, the EMEA is not a competent authority for clinical trials, these are evaluated and authorised by the national authorities in the country where the trial takes place.

The number of clinical trials included per Marketing Authorisation Application (MAA) varies considerably. It can be 1 trial for a very simple generic product. For example, a trial in which a new generic product is tested against the European reference product that is normally the brand product. This type of study is increasingly done in India and Canada, the two leading countries for testing generics for the EU market. Similarly, MAAs for biosimilar products and orphan drugs undergo a very limited number of trials. However, for the full clinical trial development programme of a new product with a major indication and a big potential population, such as a cardiovascular, 50 to 100 trials with 3,000 or up to 20,000 patients may be involved. And the legislation requires that the dossiers contain all the clinical trial study reports in module 5, including the positive and negative trials and the discontinued trials<sup>99</sup>. Within such a dossier with so many trials the number of pivotal trials (the decisive trials for proving efficacy and safety) is often much lower than ten. Keeping in mind that the EMEA deals with about 100 applications per year, the number of trials to verify during the validation period is huge. Therefore not all trials can be verified. In practice, only the pivotal trials are verified on Good Clinical Practice in more detail. However, Regulation (EC) 726/2004 says that in particular the trials in *third countries* should be verified, it does not say in particular the pivotal trials: 'In particular, with respect to clinical trials conducted outside the Community on medicinal products destined to be authorised within the Community, at the time of the evaluation of the application for authorisation, it should be verified that these trials were conducted in accordance with the principles of good clinical practice and the ethical requirements equivalent to the provisions of the said Directive'.

Different modules of the technical dossier contain information about the ethics of trials:

- Module 1 contains the statement by the applicant that 'clinical trials carried out outside the European Union meet the ethical requirements of Directive 2001/20/EC' as required by article 8 (ib) of directive 2001/20/EC. That statement belongs to module 1 because it is a regional requirement; it is only required by EU legislation, for Japan and the US do not have this requirement.
- Module 2 contains a short statement of the expert on the compliance of the trials in the dossier with GCP. In case there is a significant deviation from GCP, the expert is required to make a comment on that.
- Module 5 contains all the clinical trial study reports, each trial has its own report and each report contains a section on ethics, as required by ICH guideline E3.

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<sup>99</sup> See for more explanation on the legislation also in chapter 2.2 of this report.

As said, the statement in module 1 concerns a statement by the applicant. If the applicant was not the sponsor of the trial, the applicant has to make sure to be informed well and assured that the trial was in accordance with GCP. It is important to note that such a statement by the applicant is a very simple document; it lists all the trials included in the MAA by protocol number, lists all the countries for each clinical trial and then gives the statement that the trials comply with the ethical requirements. This content of the statement is specified in the 'Note for the applicants'. Details such as the investigators involved are expected to be provided in the clinical study reports in module 5. The same applies to information concerning the approval of the ethics committee, the CROs involved, samples of the informed consent documents and the information on the procedure, the possible involvement of vulnerable trial subjects and how that is dealt with and an audit certificate, if the trial is audited. On the cover of the report there should be a statement on Good Clinical Practice for that particular trial as well as the signatures of the principal investigator and the sponsor. Furthermore, any protocol violations should be described in the report.

In the initial assessment, the verification of the ethical requirements by the EMEA involves the EMEA checking the presence of the statement by the applicant in module 1, the presence of the statement by the expert in module 2, and whether additional comments are made on ethics by the expert. Based on the expert statement it will be clear what the pivotal trials (the trials on which the major decision making is based) are and those trials will be checked in more detail by the inspection section. This section checks the details in the clinical study reports of the pivotal trials as summed up in the paragraph above. If information is not complete or unclear the inspection section will ask the company to supplement. If the dossier is accepted then the assessment procedure will start and the dossier will be sent to the rapporteur and co-rapporteur from two different EU countries and each of them will devote a section on the compliance with GCP and they can decide if a GCP inspection is needed.

It is important to note that only the pivotal trials are verified by the inspection section of the EMEA, which comes to a fraction of the total number of clinical trials that are part of MAAs in the centralised procedure. While Regulation (EC) 726/2004 states that in particular the trials in third countries should be verified, there does not seem to currently be a special GCP check on them in the initial EMEA assessment process.

### **5.3 The GCP verification by national medicines agencies**

According to one of the interviewees, sponsors of clinical trials should receive a charter provided by the EMEA on how to perform clinical trials in third countries ethically. This is actually in accordance with one of the planned actions included in EMEA's strategy paper: 'to clarify the practical application of ethical standards for clinical trials'. An example given by one of the interviewees is that the term 'best available treatment' is interpreted differently. The fact that in some countries the normal situation is that there is no available treatment, is used to conduct placebo-controlled trials without follow-on treatment. That would be unacceptable in Germany, for example.

Additionally, it was said that the technical requirements for the MAA dossier should include a template for the review of ethics for each clinical trial. The assessors need to be provided with a checklist of what ethical aspects need to be assessed and how, and what information should be provided by the applicant in the marketing authorisation dossier for each clinical trial. The current situation at the national agencies is that the interpretation of the ethical standards varies. Mainly,

the presence of the statement by the applicant is checked and such a statement is only a few lines. Also it was said that the clinical trial study reports do not provide much detail on ethics. The difficulty is that the verification of GCP at the national regulatory authorities takes place at the end of the process and by this time the pivotal trials are completed. Based only on the information in the technical dossier it is rather impossible to really check compliance of GCP. One example of reviewing the informed consent process was mentioned at the expert meeting in The Hague; it has occurred that informed consent papers were drawn up in Chinese making the process of informed consent impossible to reconstruct. Therefore the GCP verification should take place at an earlier stage. This is in fact also in line with one of the planned actions in EMEA's strategy paper: to find out how inspections can be done in an earlier stage, prior to the marketing authorisation process.

#### **5.4 Outcomes on GCP inspections**

There are two types of GCP inspections: the routine inspections and the triggered inspections. Routine inspections are initiated by the EMEA and the triggered inspections by the rapporteurs. For the routine inspections the EMEA chooses to take samples across the different companies, different therapeutic areas, different disease areas, different population types (paediatric, adults, elderly, psychiatric), and across geographic areas. The EMEA counts the number of patients recruited in different countries and makes sure the important countries are inspected.

GCP inspections in third countries are increasing. In 2008 (counted until November) 45 inspections were conducted, 32 routine and 13 triggered inspections. Of the 32 routine inspections, 15 were done in Europe and 17 in third countries (under which 3 in North America and 14 in the rest of the world) Of the 13 triggered inspections, 6 in North America, 5 in Europe and 2 in the rest of the world. In 2007, 38 GCP inspections were conducted. See also Table 1 'Total GCP Inspections per country from 1997 to 2008'.

Because of the huge number of trials in the MAAs yearly, it has already been stated that not all trials can be verified on GCP in detail and that is even more true for the inspections; not all trials can be inspected. And it is important to know that typically per trial two investigator sites will be inspected while a trial might contain hundreds of investigator sites, so current samples are tiny. However, the EMEA already anticipates increasing the number of inspections, especially in third countries, though the question remains what would constitute a reasonable sample. At the expert meeting in The Hague it was said that the US regulatory authority, the FDA, has made site inspection obligatory and has set up regional offices outside the US in non-traditional research areas. Further research is needed to check how the FDA has taken this issue on. In Europe, all inspections are coordinated by the EMEA and carried out by the national competent authorities on behalf of the EMEA and the CHMP in case of triggered inspections. Besides the 45 GCP inspections in 2008, other inspections are also carried out in Europe by the CHMP; this concerns routine checks of companies, sponsors of trials and CROs and within these broader inspections (not connected to a marketing authorisation procedure) GCP procedures and a number of clinical trials are also checked. However, clinical trials inspected in third countries are always part of an MAA, as those are the ones that fall within the scope of the EMEA. Interviewees expressed the view that GCP inspections in combination with the provision of training courses in third countries are key for improvements.

## 5.5 EMEA's strategy and work plan for the coming years.

As referred to in 1.3 and 5.3, the EMEA has recently drafted a three-year strategy paper on the acceptance of clinical trials in third countries for marketing authorisation applications (MAAs) <sup>(100)</sup>. In the coming period they want to work on 4 main questions:

- What are we doing now concerning Clinical Trials in third countries that are part of MAA? (How do we interpret the ethical standards?)
- What can we do differently?
- How can we further develop the assessment process?
- What can we do to improve transparency?

The objective is to reinforce the EMEA's contribution to assuring that trials carried out in third countries have been conducted in accordance with the required good-clinical-practice and ethical standards. The idea is to assess what the EMEA can do within the existing framework, not to make proposals for new legislation.

Ideas to work on in the coming years are:

- A more transparent verification process of GCP at the time of the evaluation of the MAA, be to be described in the EPAR;
- Inspections to be held at an earlier stage than during the marketing authorisation process;
- Clarification of the practical application of ethical standards to clinical trials;
- Consideration of the issues driving the recruitment of subjects in third countries;
- Identification of inspection triggers which target specific potential ethical concerns or areas where the ethical sensitivity is higher to help prioritise inspection;
- Review of which actions are available in response to non-compliance and new policy development;
- Ensure links to other initiatives by EU/Member States in this area, in consultation with the EC DG Enterprise and the Heads of Medicines Agencies.
- Contribution to capacity building with developing countries' authorities, in cooperation with Member States and EC initiatives, and with the WHO, and improved coordination of these initiatives.

Members of different EMEA Committees and working groups were involved in drawing up the strategy paper. National authorities are not involved <sup>(101)</sup> as the centralised procedure is the responsibility of the EMEA and the strategy paper solely concerns the centralised procedure. As the centralised procedure accounts for about 10% of the EU marketing authorisation procedure only, more efforts need to be taken to address the problems with the national responsible authorities and to take action with respect to the expressed need for templates and checklists. As the EMEA has a coordination task towards the decentralised and mutual recognition procedure it should take the lead in working towards a similar strategy paper and work plan for these procedures. Currently, experts from developing countries and NGOs who take a stand for the rights of trial subjects in developing countries are not consulted or involved, but this is definitely recommended.

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<sup>100</sup> EMEA, EMEA strategy paper: Acceptance of clinical trials conducted in third countries, for evaluation in marketing Authorisation applications, February 12, 2009, <<http://www.emea.europa.eu/Inspections/docs/22806708en.pdf>>

<sup>101</sup> Although the representatives from the CHMP scientific committee come from the national authorities.

It is also important here to highlight what actions are already being taken by the Commission and the EMEA. For example, the improvement of bilateral relations with third countries such as India, training programmes to increase expertise of EU and third country regulators, and the training of GCP inspectors within capacity building projects with the WHO, the Council of Europe and Unesco. These activities are very important and should continue; interviewees emphasised the importance of education and training in combination with inspections.

## 5.6 Outcomes on the role of the ethics committees in third countries

According to the interviewees, the quality of the legal frameworks in third countries varies considerably. In their opinion, resources should be spent on supporting third country regulatory systems. This is in line with the opinion of NGOs who say that EU Member States and the Commission should take more responsibility safeguarding the quality of ethics committees in developing countries. The expectation of GCP is that the competent authority will consult an ethics committee, that is properly set up according to GCP standards, to get an opinion on the ethics of the trial. Currently, the GCP inspectors do not inspect the ethics committees systematically and several studies indicate that the functioning of ethics committees in developing countries is problematic; conflicts of interest are a big problem for instance. It seems that the regulatory authorities in Europe take too many risks though their current confidence in the opinions of ethics committees in non-traditional research areas. In the view of one of the interviewees, it would be possible to check procedures and structures of ethics committees in third countries and the ethical standards used during a GCP inspection. This can be done without changing the legislation because the legislation already says that trials must be conducted against GCP standards and this is one way to do that. According to NGOs, more attention should be given to a declaration of conflict of interest signed by the ethics committees during a GCP inspection. Another suggestion made by one of the interviewees is to set up a double review process; one in the country where the sponsor is based and one in the country where the study is conducted, in case the quality of the ethics committees is not up to standard. This was actually one of the recommendations of a Round Table held in France on this issue in which one of the interviewees participated. Also recommended by the participants was that an independent Data Safety Monitoring Board should be set up with systems to ensure the effective reporting of Serious Adverse Events (SAE) and to specify the sponsor's obligations after the end of the study. This because simple declaration of SAE in a clinical trial conducted in a developing country is generally inadequate; reason for under-reporting is often that there is no institution for recording and processing. Further, there is the question of compensation for any harm experienced by a participating trial subject; the participants of this Round Table concluded that few companies insure clinical trials and the national insurances do not necessarily cover foreign participants<sup>(102)</sup>. According to the EMEA, the informed consent form, of which each trial subject receives a copy, provides contact details for compensation, however, in practice this information cannot be checked by third parties and it is the experience of local researchers in India that trial subjects are not able to show their copy of the informed consent form<sup>(103)</sup>.

<sup>102</sup> Muriel Vray, Francois Simon, Francois Bompard and the participants in Round Table N° 2, Giens XXII, Guidelines for clinical research in Developing Countries, *Therapie* 2007, Mai-Jun 62 (3), 223-227.

<sup>103</sup> In 2008, the Centre for Studies in Ethics and Rights in Mumbai, India conducted a research in close cooperation with SOMO en Wemos, see also the report of S. Sandhya Srinivasan, 2009.

## 5.7 Outcomes on transparency

Except for the paediatric clinical trials, there is no legal basis for including clinical trials conducted in third countries in the public clinical trials database on medicinal products under construction (EudraPharm), even though they are part of MAA. Recently, on 4 February 2009, the guideline listing the data fields to be made public in the EU clinical trials database was published and it turns out that the fields are very similar to those in the US database Clinicaltrial.gov. Only when a trial is being conducted completely outside of the EEA countries does the sponsor have to specify the 'regions' in which trial sites are planned. No data is required on ethical considerations like justification of placebo use, the justification of the use of vulnerable trial participants, and the arrangements for post trial treatment. Some of the interviewees are in favour of opening up the legal framework to include third country trials in the public European clinical trial registry and results database, in the same way as now for paediatric trials. One of the recommendations, made during the EMEA conference of 3 October 2007, is to open up the legal framework to include all clinical trials, not only those that are part of a marketing authorisation, and to include clinical trials for medical devices because the ethical requirements for medical devices are poorly developed compared to those for biomedical research.

A brief public statement from the involved ethics committee on their ethical review of the clinical trial is also a possibility proposed by one interviewee. There was also support for the idea to copy the ICJME initiative into EU legislation, meaning that trials can only be part of an application if the trial is registered beforehand in the public European clinical trial registry. At the same time it was observed that making this part of legislation would mean that inspectors are forced to check this, resulting in additional cost while it is unclear whether this cost is justified. Another issue is time pressure, people want to have new medicines on the market quickly and this is adding an extra time-consuming hurdle to the assessment procedure.

## 5.8 The status of the DoH according to European authorities

From the interviews it can be concluded that the DoH applies to biomedical research in general while the ICH GCP guidelines are developed for biomedical research for pharmaceutical products in marketing authorisation process, which is a narrower focus. In order to get a Clinical Trial of a pharmaceutical conducted successfully for marketing authorisation processes one needs the ICH guidelines because they provide the necessary details, while the DoH does not.

Because the World Medical Association (WMA) is not part of the legislative system it is not possible to specifically refer to the DoH in the legislation. The next update of the DoH can in theory be entirely different. Therefore, in reaction to the lobby by NGOs for a more clear reference to the DoH in EU legislation, the EMEA says it cannot be changed. Regarding the GCP inspections, answers of the interviewees differ: according to the EMEA, one of the reference documents for the GCP inspections is the DoH. However, according to interviewed representatives of national medicines authorities, inspectors are only using the ICH GCP. Moreover, it will not be possible for an inspector to refuse the outcomes of a clinical trial for not complying with the ethical standards of the Declaration of Helsinki, simply because the DoH is not part of the legislation (the reference to DoH is in the 'where as clauses', the background principles on which the legislation is based, but not in the articles). It is also not possible for a national registration authority, or the EMEA, to say: 'we won't accept something on our market unless it has met the standard of DoH', for that particular rule is not in the EU legislation and not in the detailed guidelines.

In addition to the NGO lobby for a clear reference to the most recent version DoH in EU legislation, there is at the same time a strong lobby for a clear reference in the legislation to the ICH guidelines. This is expressed several times by different actors in the EMEA conference report on the implementation of the EU legislation on clinical trials: 'Include a clear framework for the CPMP/ICH/135/95 GCP Guideline in the Directives and their implementing texts' <sup>(104)</sup>. The companies present at the expert meeting in The Hague made clear that the DoH will never be accepted by the US, and indeed the FDA has now officially abandoned the DoH. The biggest pharmaceutical companies are US companies; the majority of the medicines on the European market are marketed by US companies. This dominance makes it very difficult to implement the DoH in EU guidelines. There is also the risk when including 'social clauses' into marketing authorisation legislation that companies will bring it before the World Trade Organisation (WTO) as an unfair competition policy protecting the domestic market.

Actually what interviewees are saying here is that the Declaration of Helsinki is not part of EU legislation, and is not going to be, and therefore it is not used in practice.

## 5.9 The fee structure

For EMEA, the fees accounted for 67% of total revenue in 2007, other revenue concerns contributions of the EU and from Member States. 67% stands for € 108,570 million. The total revenue of the Dutch MEB is € 29,654 million, of which € 27,620 is third party revenue (93%) originating from fees from companies for delivered services like marketing authorisation procedures. Generating income from the marketing authorisation is important, this can be concluded from the fact that the Dutch MEB experienced a loss in 2007 because 'the income was € 2.4 million lower than originally estimated. This was mainly because 'fewer national, centralised and decentralised procedures were completed than had been anticipated' <sup>(105)</sup>. Clearly, for the Dutch MEB their financial situation is at stake when not enough marketing authorisation procedures are submitted by pharmaceutical companies. For the Dutch MEB the mutual recognition and decentralised procedure is much more important than the centralised procedure which is assigned through a more neutral system. However, within the scope of this research it is not possible to define what makes the one national authority more preferable over the other. There is no evidence to support the concept that fees alter the regulatory decisions of the EMEA or national authorities.

The fee regulation foresees in a specific fee per inspection regardless where the inspection takes place. Increasing inspections in third countries will substantially increase the level of resources needed. Maybe it will be needed to raise the fee. Companies are legally obliged to pay for the inspections, once entering the procedure

## 5.10 Conclusions regarding the functioning of the European regulatory authorities

- **Related to marketing authorisation procedures** The conduct of the European regulatory work is concentrated in five European countries; it should be further investigated whether

<sup>104</sup> European Commission-European Medicines Agency Conference on the Operation of the Clinical Trials Directive (Directive 2001/20/EC) and perspectives for the future, Conference held on 3 October 2007 at the EMEA, London, Report on the Conference, London, 30 November, 2007, Doc. ref.: EMEA/565466/2007.

<sup>105</sup> Annual Report 2007, Medicines Evaluation Board (CBG), Netherlands.

this is a desirable situation. The responsible authorities of at least these 5 countries should be involved in any possible follow-up of the recommendations in this report.

- **Related to GCP verification** There is now a strong focus on the verification of GCP of the pivotal trials, however, in line with Regulation (EC) 726/2004, there should be a stronger focus on the verification of GCP of trials in third countries.
- **Related to GCP verification** The EMEA is principally checking *presence* of GCP verification documents in the technical dossier and is checking only a fraction of the clinical trials study reports in more detail out of the total number of clinical trials which are part of MAAs.
- **Related to GCP verification** The statement by the applicant that 'clinical trials carried out outside the European Union meet the ethical requirements of Directive 2001/20/EC' is too simple a document; it does not provide enough information to enable the assessors to verify GCP as is their legal duty.
- **Related to GCP verification** Assessors at national responsible authorities need a template for reviewing the ethics of clinical trials, especially those in third countries. The assessors need to be provided with a checklist of what ethical aspects need to be assessed and how. This will also serve the objective of harmonising the practices at national responsible authorities.
- **Related to GCP verification** The difficulty is that the verification of GCP at the national responsible authorities takes place at the end of the process and based on the information in the technical dossier it is rather impossible to really check compliance of GCP. Therefore the GCP verification should take place in an earlier stage than during the marketing authorisation process.
- **Related to GCP inspections** The number of GCP inspections should be further increased.
- **Related to GCP inspections** It should be investigated if and how CHMP routine inspections as they take place now in Europe also can take place in third countries. Currently, these CHMP inspections only take place in Europe, but only one third of the pivotal clinical trials in MAAs take place in Europe.
- **Related to GCP inspections** It should be investigated if it is possible for the EMEA to set up regional offices in crucial third countries like India, Russia, Argentina and China.
- **Related to EMEA's strategy paper** EMEA's strategy paper is a very good start to tackling these issues. It is recommended that the EMEA will start to involve experts from developing countries and NGOs who take a stand for the rights of trial subjects in developing countries.
- **Related to EMEA's strategy paper** More efforts should be taken to address the issue at the national responsible authorities and to address the needs expressed by them for templates and checklists.
- **Related to EMEA's strategy paper** The training programmes to increase expertise of EU and third country regulators, and the training of GCP inspectors within capacity building projects with WHO, the Council of Europe and UNESCO should continue.
- **Related to ethics committees** EU Member States and the Commission should take more responsibility on safeguarding the quality of ethics committees in developing countries
- **Related to ethics committees** It can be investigated whether a double review process when the quality of the ethics committees is not up to standard offers better protection for trial subjects; one in the country where the sponsor is based and one in the country where the study is conducted.
- **Related to ethics committees** Checking procedures and structures and possible conflicts of interest of ethics committees in third countries and the ethical standards used should be done systematically during a GCP inspection.

- **Related to ethics committees** Next to the ethics committees an independent Data Safety Monitoring Board should be set up and systems to ensure the effective reporting of Serious Adverse Events (SAE) in developing countries.
- **Related to ethics committees** There should be a possibility for third parties to receive a blank informed consent form upon request, related to specific trials to be able to check the details and contact information for the compensation arrangement in case of harm. A blank informed consent form should be provided by the sponsor and/or the involved ethics committee upon request.
- **Related to transparency** The fact that clinical trials conducted in third countries are missing in the public clinical trials database on medicinal products under construction (EudraPharm), although they are part of MAA, is a serious deficit because this excludes two thirds of the clinical trials underlying the approval for medicines to enter the EU market.
- **Related to transparency** Opening up the public clinical trials database on medicinal products (EudraPharm, under construction) for clinical trials conducted in third countries will enforce the European regulatory framework as will including trials to test medical devices for the EU market and making registration compulsory so that trials can only be part of an application if the trial is registered beforehand. This will preferably be done in the public European clinical trial registry, but otherwise in one of the acknowledged databases of the WHO or ICJME initiative.
- **Related to the status of the DoH** According to the responsible authorities the Declaration of Helsinki is not part of EU legislation, and is not going to be, and therefore it is not used in practice.
- **Related to the fee structure** the responsible authorities are highly dependent on the fees paid by the industry. There is currently no evidence to support the concept that fees alter the regulatory decisions of the EMEA or national authorities.

## Part Three

### PRACTICAL RECOMMENDATIONS

## 6 – RECOMMENDATIONS AT THE LEVEL OF EU LEGISLATION

### 6.1 Role of European Commission and intergovernmental Organisations

A remark by one of the interviewees was an important eye opener: the whole debate about the post trial treatment is taking place in literature and on the internet but not in the regulatory framework. Although there is willingness on the part of the regulatory authorities to work on improvements to ensure that trials carried out in third countries are conducted in accordance with the required good clinical practice and ethical standards, to effect any real change it is necessary to put some crucial discussions on the agenda of the regulatory authorities and the companies, and this is a role of the European Commission and intergovernmental organisations. Many very practical recommendations are made during the research, and they will be listed below, however, to put them into practice will be difficult if there no agreement is reached about some very important issues.

These issues are the same issues that make the Declaration of Helsinki a strong standard for developing countries and that are missing in the ICH GCP guidelines. The contrasts in opinions are very strong with regards to the issues of placebo-controlled trials, the sponsors' obligations in the developing country once the study is finished (post trial treatment), and the precondition that the investigated medicine must be beneficiary to the population. First it is necessary for the discussion about these issues to take place inside the regulatory framework, with the companies, civil society organisations, experts from developing countries and the experts within intergovernmental organisations like the WHO. It must become clear what the authorities prepared are to ask for exactly, what companies are prepared to do (after all, they almost all endorse the Declaration of Helsinki in their policies), what are governments of developing countries prepared to enforce, taking into account they see clinical research as an attractive source of income, and what are the possibilities in the international arena, with the WTO having anti-competition policies and with the FDA having abandoned the Declaration of Helsinki.

Without having the discussion on these issues with these actors first, it will not be possible to 'clarify the practical application of ethical standards for clinical trials', or to 'provide the assessors with a checklist of what ethical aspects need to be verified and how', or 'to make the Declaration of Helsinki operational in guidelines'. Without having this discussion first, NGOs will keep arguing that certain clinical trials are unethical while the legislation allows companies to say they comply with Good Clinical Practice.

Therefore the role of the European Commission is to make sure that this discussion will take place, otherwise the EMEA cannot fulfil its role properly.

The European Commission and EU Member States should continue their supporting capacity building with regard to clinical trials in developing countries. They should continue to provide the resources needed to ensure that the regulatory bodies and ethical review committees in developing countries are able to function and that health workers are trained to carry out clinical

trials to required standards and make sure that the different initiatives are coordinated. What currently does not receive enough attention in the capacity building efforts is the adequate reporting of Serious Adverse Events (SAEs) in developing countries, this should be included in the programmes.

Additionally, more research is required to define the scope of the problem. By monitoring the clinical dumping in developing countries, to assess which investigational products bring more risks, and to assess what the high risk countries and the main problems are.

## **6.2 Ways to hold pharmaceutical companies to their commitments**

Interesting in this respect was the remark of one of the companies that it is increasingly important to test new medicines against the 'golden standard' (the best available treatment) otherwise insurance companies will not refund the treatment and that is currently the strongest incentive for pharmaceutical companies not to test their medicine against a placebo. Therefore, a commercial incentive is a good way to make placebo tests unnecessary. It should be a requirement for marketing authorisation procedure to prove that the investigative treatment is tested against the best available treatment.

Apply sanctions more actively. The current legislation offers a very strong sanction: the refusal of applications in which unethical trials are included or the withdrawal of an authorisation in case the particulars supporting the application (like the statement of the applicant that the clinical trials carried out outside the European Union meet the ethical requirements of Directive 2001/20/EC) turn out to be incorrect. But to date there is no record of these sanctions ever being applied.

Furthermore, appropriate penalties should be imposed for submitting misleading documents and statements by sponsors, investigators or applicants, as well as for not submitting them. A successful method that has been used in cases of environmental pollution by multinational companies in developing countries is to make natural persons personally liable for the accuracy of the reported information. In this case, natural persons representing the sponsor, the investigator or the applicant who submits the information, as well as any other responsible corporate officer who controls the submission of the information, should be personally liable for the accuracy of the reported information. If the reported information is misleading or inaccurate, this person should be subject to financial sanctions or other 'effective, proportionate and dissuasive penalties'. This would serve as an incentive to report accurate information.

Furthermore, it is important to ask companies to take full responsibility for their supply chain; to take full responsibility for the outsourced trials to CROs and for all the trials that are part of the marketing application although they were not the sponsor of these trials.

The companies themselves must be punishable by criminal sanction if they fail to prevent violations where are able to do so. This could be accomplished by the requirement to exercise reasonable care that such violations do not occur.

To make public when companies are guilty of clinical dumping.

### 6.3 Recommendations to enforce the European legislation and responsible regulatory authorities.

The following table is made to give an overview of all recommendations in the report that are focused on ways to enhance the effectiveness of European regulatory authorities in protecting trial subjects in developing countries against unethical practices. Core instruments provided by the European Community legislation are the marketing authorisation process, Good Clinical Practice (GCP) Inspections, clinical trial database and penalties.

For each of these instruments a table is made with the recommendations

<b>The marketing authorisation procedure</b>	
Recommendations within the current regulatory framework	Investigation of the desirability (and the risks) of the current concentration of the execution of the European regulatory work in only five countries.
	The debate about some controversial ethical principles in the Declaration of Helsinki needs to be held inside the regulatory framework so as to develop consensus guidance on these specific ethical issues.
	The Declaration of Helsinki needs to be made operational in assessment guidelines for the review of the ethics of clinical trials, especially those in third countries, for regulatory authorities evaluating the marketing authorisation applications, thus forcing them to look into the ethical issues more thoroughly. This way only checking the presence of the statement by the applicant is no longer possible. The assessors need to be provided with a checklist of which ethical aspects need to be assessed and how. The application would only be taken into account if presented evidence is sufficient to prove that the ethical requirements are indeed met.
	More coordinating efforts by the EMEA are required to harmonise the application of ethical standards by the responsible authorities.
	The good clinical practice verification should take place in an earlier stage than during the marketing authorisation phase. (One possibility is investigating the role of groups such as the Data Monitoring Committees (DMC), to see if they can play a role in monitoring of GCP and reporting of non-compliance with GCP at the time a trial is running, however, special precautions should be taken to ascertain the independency of these 'other groups').
	There should be a stronger focus on the verification of GCP of trials in third countries (EC 726/2004, Art. 16)
	The verification process of GCP at the time of the evaluation of the MAA should become more transparent and should be described in the EPAR.***
Recommendations to change the current regulatory framework	Directive 2001/83/EC could be amended in favour of legal certainty and protection of clinical trial participants explicitly stating that the marketing authorisation application should be refused in case of providing <i>misleading</i> statements by the applicant.
	Accept only Clinical Trials approved by ethics committees with full disclosure of declaration of conflicts of interest. (Directive 2001/83/EC)

\*\*\* This is already included in the EMEA Strategy Paper: Acceptance of clinical trials conducted in third countries, for evaluation in Marketing Authorisation Applications, 12 February 2009 (see also footnote 14).

<b>The Good Clinical Practice Inspections</b>	
Recommendations within the current regulatory framework	<p>Check procedures and structures (and declaration of conflicts of interest) of ethics committees in third countries and the ethical standards used systematically in GCP inspections.</p> <p>The number of GCP inspections should be increased.</p> <p>The GCP inspections should be held at an earlier stage than during the marketing authorisation process.***</p> <p>GCP Inspection should include post trial aspects, for example checking whether patients have been informed about the results of the trials they have participated in and checking the post trial treatment, the SAE reporting system, and the compensation arrangement in the informed consent form.</p> <p>It should be investigated if it is possible for the EMEA to set up regional offices in crucial third countries like India, Russia, Argentina and China.</p> <p>It should be investigated if and how CHMP routine inspections which now only take place in Europe can also take place in third countries.</p>
Recommendations to change the current regulatory framework	<p>To make it possible for anyone to initiate GCP inspections through the Commission. Such person should only have to produce reasonable evidence of a risk that good clinical practice principles have been violated during the clinical trial outside the Community.</p> <p><b>Regulation 2001/20/EC Article 15 (4) and Reg. 726/2004 Article 19 (3)</b></p>

\*\*\* This is already included in the EMEA Strategy Paper: Acceptance of clinical trials conducted in third countries, for evaluation in Marketing Authorisation Applications, 12 February 2009 (see also footnote 14).

<b>The clinical trials database</b>	
Recommendations within the current regulatory framework	<p>The public clinical trial database EudraPharm should contain information about ethical considerations, for example, a brief public statement from the involved ethics committee on their ethical review, including ethical considerations such as the justification of placebo use, the justification of the use of vulnerable trial participants and explanation of the benefits for the population, and the arrangements for post trial treatment.</p> <p>It is needed to adapt the list of data fields<sup>(106)</sup>.</p>

<sup>106</sup> List of fields contained in the 'eudract' clinical trials database to be made public, in accordance with article 57(2) of regulation (ec) no 726/2004 and its implementing guideline 2008/c168/021, Brussels, 04.02.2009  
[http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-10/2009\\_02\\_04\\_guideline.pdf](http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-10/2009_02_04_guideline.pdf)

Recommendations to change the current regulatory framework	To provide a legal basis for including clinical trials conducted outside the Community relating to medicinal products intended for use in the Community in the public clinical trial registry and results database EudraPharm for clinical trials (which is currently under construction). <b>Reg. 726/2004 Article 57 (l) subject for change</b>
	To make registration compulsory in such a way that trials can only be part of an EU application if the trial is registered at the time the recruiting took place in, preferably, the public European clinical trial registry but otherwise in one of the acknowledged databases of the WHO and ICJME initiative. <b>Reg. 726/2004 Article 57 (l) and 2001/83/EC art. 26 subject for change</b>
	To provide a legal basis to include the clinical trials to test medical devices for the EU market. <b>Reg. 726/2004 Article 57 (l) subject for change</b>
	Penalise the failure to submit documents and statements by sponsors, investigators or applicants, as well as the submission of misleading or inaccurate documents and statements by sponsors, investigators or applicants. Natural persons representing the sponsor, the investigator or the applicant who submit the information should be personally liable for the accuracy of the information reported to the database. <b>The Commission Regulation (EC) No 658/2007 and Directive 2001/83/EC, Article 26 (3)</b>

<b>Penalties</b>	
Recommendations within the current regulatory framework	No recommendations
Recommendations to change the current regulatory framework	The Commission Regulation (EC) No 658/2007 should explicitly state that the interests of the Community are involved: <ul style="list-style-type: none"> <li>- when a breach of good clinical practice principles occurs while conducting clinical trials in developing countries. This requirement results from the fact that the Community's international reputation is affected by the way it approaches the problems concerning infringements on human rights during the clinical trials conducted outside its territory.</li> <li>- in case of inadequate reporting of SAEs in third countries.</li> </ul> <b>The Commission Regulation (EC) No 658/2007 subject of change</b>
	The statement " <i>the applicant or the holder of a marketing authorisation shall be responsible for the accuracy of the documents and the data submitted.</i> " should be amended to the effect that Member States must take all appropriate measures to ensure that the applicant who submits misleading documents and data is

	subject to “effective, proportionate and dissuasive penalties”.
	<b>Directive 2001/83/EC, Article 26 (3) subject of change</b>
	Personal liability for those submitting information for the marketing authorisation procedure representing the applicant, including the experts responsible for the summaries.
	<b>Regulation 726/2004 and Directive 2001/83/EC Article 26 (3), subject of change</b>

#### 6.4 The role of the European Parliament to enforce the European legislation and regulatory authorities

Related to the above tables with concrete recommendations to enforce the current legislation and recommendations for amendments the European Parliament can play a specific role to start the practical execution of the suggested recommendations.

In its responsibility to protect the rights of trials subjects in developing countries and to protect the health of EU citizens the European Parliament should:

1. Use the right to initiate investigations;
2. Pressure for the monitoring of the EMEA on certain issues;
3. Use the co-decision procedure to take the initiative to draw up a new directive to make the recommended amendments to the current legislation or put pressure on the European Commission to take this initiative;
4. To raise awareness about the ethical standards of the Declaration of Helsinki that are crucial for protecting trial subject in developing countries and that are currently not implemented.

Elaboration:

##### 1. European Parliament should use the right to initiate investigation.

In the four tables above a number of recommendations include further investigation. The European Parliament should have one of the Committees (likely the Committee on Development or the Committee on Environment, Public Health and Food Safety <sup>(107)</sup>) the right to initiate further investigation on the following issues:

- Related to the marketing procedure, it is recommended that it should be investigated what the risks are of the fact that the current execution of the European regulatory work is concentrated in only five countries;
- Related to the marketing procedure, it should be investigated what the risks are of the fact that the regulatory authorities are highly dependent on the fees paid by the industry;
- Related to the Good Clinical Practice Inspections, it should be investigated if it is possible to set up regional EMEA offices in crucial third countries.
- Related to the Good Clinical Practice Inspections, it should be investigated if CHMP routine inspections also can take place in third countries.

<sup>107</sup> The Committee Environment, Public Health and Food Safety of the sixth legislature has 68 Members, drawn from political groups, the Committee has (amongst other) oversight and political responsibility for the activities of the European Medicines Agency (EMA). [http://www.europarl.europa.eu/compar/envi/default\\_en.htm](http://www.europarl.europa.eu/compar/envi/default_en.htm)

## **2. The European Parliament should pressure the Committee on Environment, Public Health and Food Safety to monitor the EMEA on certain issues.**

Various recommendations are already mentioned in the strategy paper of the EMEA for 2009 complete with a three year planning. It is important to closely monitor how the EMEA is taking on the good intentions in this plan (see also note 14) and to add actions to this plan. As the Committee on Environment, Public Health and Food Safety has oversight and political responsibility for the activities of the European Medicines Agency (EMA), the European Parliament should pressure this Committee to appoint a rapporteur to:

- Check what actions the EMA undertakes to clarify the practical application of ethical standards to clinical trials;
- Make sure EMA is putting efforts in harmonising the application of ethical standards by the responsible authorities;
- Check what actions the EMA undertakes to have the good clinical practice verification taking place in an earlier stage than during the marketing authorisation phase.
- Make sure EMA gets a stronger focus on the verification of GCP of trials in third countries;
- Check what actions the EMA undertakes to be more transparent about the verification process of GCP;
- Make sure that EMA systematically include the ethics committees in GCP inspections;
- Make sure that EMA increases the number of GCP inspections in third countries.
- Make sure EMA is putting efforts in including ethical considerations in the public clinical trial database EudraPharm.

## **3. The European Parliament should use its powers to initiate amendments to the current legislation.**

- The highest priority has the change of law to make it possible for anyone to initiate GCP inspections through the Commission.
- The second in priority is to provide a legal basis for including clinical trials conducted in third countries in the public clinical trial registry and results database EudraPharm for clinical trial.
- The third in priority is to make registration compulsory in such a way that trials can only be part of an EU application if the trial is registered at the time the recruiting took place in a public database.

And the EP should use its powers to initiate **new** legislation. New legislation is needed to regulate civil liability of companies who market pharmaceutical products and new legislation is needed to remove material obstacles of access to justice for victims of clinical trials.

## **4. The EP should raise awareness.**

The EP should raise awareness about the standards that are crucial for trial subjects in developing countries: the precondition of the beneficiary element and the affordability of the investigational medicinal products for the population, the right to arrangements for post trial treatment, and the obligation to test the investigational medicine against the best current proven intervention instead of testing against placebos. The EP has a role to make sure that these issues are discussed between the various stakeholders; otherwise the EMA cannot fulfil its role properly.

## **7 - RECOMMENDATIONS AT THE LEVEL OF INTERNATIONAL LAW**

There are no options in the field of criminal law unless victims can be proven to have been coerced to take part in the clinical trials.

Currently, a lawsuit can be filed if the sponsor of the clinical trial is domiciled in the EC. In some member states a lawsuit can be filed if the sponsor is present or has assets in that state. In other member states a lawsuit can be filed if there is no other appropriate forum that would ensure fair trial to both parties. The recommendation is for new legislation to be developed to regulate civil liability of companies who market pharmaceutical products. The new situation should be that parent companies in enterprises that market medicine products shall be strictly liable in the sphere of private law for damage caused to the participants of the clinical trials carried out on behalf of said products. And that persons who seek the market authorisation shall be jointly liable with the parent companies or pharmaceutical enterprises.

Furthermore, new legislation is proposed which should specify that the rules on civil liability must be applied by the courts of the Member States irrespective of where the damage caused by infringement of the law occurs. Alternatively, the Rome II Regulation should be amended to enable a choice of applicable law to be made by plaintiffs seeking compensations for damage they have suffered in the course of a clinical trial.

There are serious material obstacles to access to justice; victims bear burden of proof but don't have the means to access evidence held by the pharmaceutical enterprises; physical, financial, logistical and cultural barriers prevent victims from litigation and last but not least the costs of the proceedings. Therefore, it is recommended that:

1. Court should be able to order disclosure of the evidence
2. Burden of proof should be shifted in victim's favour.
3. Organisations representing victims should be given legal standing to file lawsuits on their behalf.
4. Unsuccessful claimants should not be obliged to bear the costs of the proceedings unless acting in manifestly unreasonable manner.
5. Victims should be able to claim punitive damages.

**Table 1: Analysis of legal instruments available to third country citizens**

	<b>Options available to victims of unethical trials in third countries</b>	<b>The obstacles</b>	<b>The recommendation</b>	<b>Change in legislation needed? Yes/no</b>
<b>Criminal liability</b>	Not available, unless victims were coerced to take part in the clinical trials.	-	-	-
<b>Civil liability</b>	<p>1. Lawsuit can be filed if the sponsor of the CT is domiciled in the EC</p> <p>2. In some member states lawsuit can be filed if the sponsor is present or has assets in that state</p> <p>3. In other member states lawsuit can be filed if there is no other appropriate forum that would ensure fair trial to both parties.</p>	<p>1. Sponsors might not be domiciled as legal persons in the EC. Even if they are part of large pharmaceutical enterprises, principles of separate legal personality and limited liability insulate other members of the enterprise from sponsor's obligations.</p> <p>2. Victims can claim liability of other members of the pharmaceutical enterprise (which may fall in the jurisdiction of courts of the Member States) only if they can prove that these other members have orchestrated the violations.</p>	<p><b>1.</b> Parent companies in enterprises who market medicine products shall be strictly liable in the sphere of private law for damage caused to the participants of the clinical trials carried out on behalf of these products.</p> <p><b>2.</b> Persons who seek the market authorisation shall be jointly liable with the former.</p>	Yes, brand new legislation regulating civil liability of companies who market pharmaceutical products.
<b>Conflict of laws</b>	Law applicable to the aforementioned lawsuits is the law of a country where victims suffered harm.	The choice of third country law would rule out applicability of the aforementioned recommendations.	<p><b>1.</b> The proposed legislation should specify that the rules on civil liability must be applied by the courts of the Member States irrespective of where the damage caused by infringement of the law occurs.</p> <p>or</p> <p><b>2.</b> Rome II Regulation should be amended as to enable a choice of</p>	Yes, to change Rome II Regulation

			applicable law to be made by plaintiffs seeking compensations for damage they have suffered in a course of clinical trials.	
<b>Material obstacles to access to justice</b>	-"-	<ol style="list-style-type: none"> <li>1. Victims bear burden of proof but are don't have means to access to evidence held by the pharmaceutical enterprises</li> <li>2. Physical, financial, logistical and cultural barriers preventing victims from litigation</li> <li>3. Costs of the proceedings</li> </ol>	<ol style="list-style-type: none"> <li>1. Court should be able to order disclosure of the evidence.</li> <li>2. Burden of proof should be shifted in victim's favour.</li> <li>3. Organisations representing victims should be given legal standing to file lawsuits on their behalf.</li> <li>4. Unsuccessful claimants should not be obliged to bear the costs of the proceedings unless acting in manifestly. unreasonable manner.</li> <li>5. Victims should be able to claim punitive damages.</li> </ol>	Yes, new legislation

**Table 2: Information on GCP inspections related to the centralised procedure**

**Total GCP Inspections per country from 1997 to 2008**

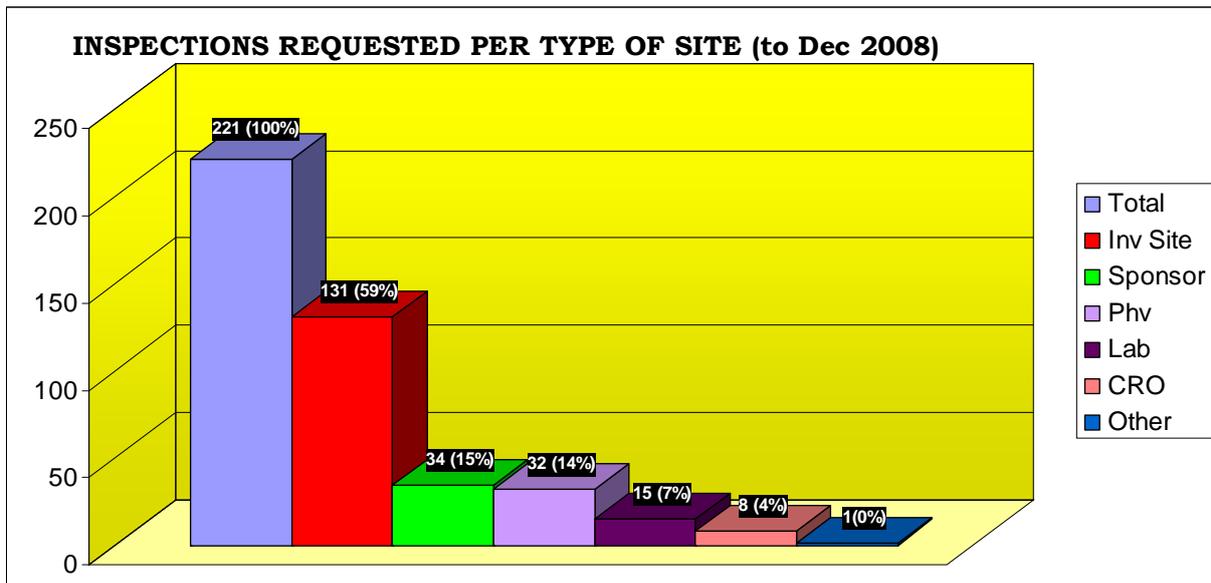
<b>Country</b>	<b>Total</b>
Argentina	1
Austria	4
Belgium	3
Brazil	1
Bulgaria	1
Canada	10
Chile	1
China	4
Colombia	1
Costa Rica	1
Croatia	1
Czech Republic	3
Denmark	3
Estonia	1
Finland	1
France	18
Germany	20
Ghana	1
Hungary	2
India	9
Italy	3
Lithuania	2
Malaysia	1
Mexico	1
Morocco	1
Netherlands	6
Peru	1
Philippines	2
Poland	13
Portugal	1
Romania	4
Russia	8
Serbia	1
South Africa	2
Spain	5
Sweden	2
Switzerland	4
Thailand	1
Turkey	1
Ukraine	2
UK	5
USA	37
<b>Total</b>	<b>189</b>

**Total GCP Inspections per region from 1997 to 2008**

Region	Total
EU/EEA/EFTA	101
North America	47
Rest of the World	41
<b>Total</b>	<b>189</b>

Source: EMEA, 2009

**Table 3: GCP inspections per type of site (to December 2008)**



**Note:** Please note that this table include also PhV inspections (32)

Source: EMEA, 2009

## Table 4: Number of procedures initiated per Reference Member in 2007

### Number of procedures initiated per Reference Member State (RMS) in 2007

#### Mutual recognition procedure

#### Decentralised procedure in 2007

No. Country	Total initiated	Market share in %	No. Country	Total initiated	Market share in %
1 Netherlands	93	23	1 Germany	273	26
2 Denmark	61	15	2 United Kingdom	221	21
3 Germany	51	13	3 Denmark	219	21
4 Sweden	45	11	4 Netherlands	140	14
5 United Kingdom	37	9	5 Sweden	49	5
6 Finland	27	7	6 Austria	26	3
7 France	17	4	7 Finland	21	2
8 Ireland	16	4	8 Hungary	17	2
9 Czech Republic	12	3	9 Czech Republic	15	1
10 Portugal	11	3	10 France	14	1
11 Hungary	8	2	11 Poland	11	1
12 Norway	7	2	12 Norway	8	1
13 Austria	5	1	13 Estonia	6	1
14 Estonia	3	1	14 Belgium	6	1
15 Slovakia	2	1	15 Italy	5	<1
16 Belgium	1	<1	16 Portugal	2	<1
17 Italy	1	<1	17 Spain	1	<1
18 Poland	0	0	18 Ireland	0	0
19 Spain	0	0	19 Slovakia	0	0
<b>Total</b>	<b>397</b>	<b>99</b>	<b>Total</b>	<b>1034</b>	<b>99</b>

Source: annual report MEB/CBG 2007

### Number of centralised procedures in 2007 (source: EMEA)

Year	EU	NL rapporteur	NL co-rapporteur	Total NL
2007	90	9	11	20
2006	78	9	6	15
2005	41	7	5	12
2004	51	5	7	12

Source: annual report MEB/CBG 2007

**Table 5: Financial statement of the MEB/CBG, 2007**

## Income statement for 2007

Amounts in € 1,000

Description	(1) Estimate	(2) Actual	(3)=(2)-(1) Difference between actual and estimate
<b>Income</b>			
Revenue, parent department	225	225	0
Revenue, other departments	300	597	297
Third-party revenue	30,335	27,820	-2,715
Interest income	80	251	171
Extraordinary income	0	961	961
Operating subsidy	0	0	0
<b>Total benefits</b>	<b>30,940</b>	<b>29,654</b>	<b>-1,286</b>
<b>Expenses</b>			
Operating expenses	30,228	27,781	-2,445
– staff costs	14,253	14,372	119
– tangible costs	15,973	13,409	-2,564
Board	380	486	126
Depreciation charges	354	958	604
– depreciation	354	487	133
– amortisation		471	471
Extraordinary expenses	0	1,128	1,128
BD expenses	0	0	0
<b>Total expenses</b>	<b>30,940</b>	<b>30,353</b>	<b>-587</b>
<b>Balance of Income and expenses</b>	<b>0</b>	<b>-699</b>	<b>-699</b>

Source: Annual Report 2007 MEB/CBG

**Table 6: Income statement of EMEA, 2007**

The summarised comparative budget statements for 2006 to 2008 are as follows:

	2006		2007 <sup>1</sup>		2008 <sup>2</sup>	
	€ '000	%				
<b>Revenue</b>						
Fees	92,580	66.76	108,570	66.56	126,318	72.89
General EU contribution	22,000	15.87	19,813	12.15	16,816	9.70
EU contribution for SME policy			3,895	2.39	3,702	2.14
EU contribution for Paediatrics policy	n/a	0.00	2,022	1.24	2,710	1.56
EU contribution for IT Telematics strategy	8,000	5.77	13,914	8.53	8,772	5.06
Special EU contribution for orphan medicinal products	7,400	5.34	6,000	3.68	6,000	3.46
Contribution from EEA	650	0.47	904	0.55	765	0.44
Community programmes	760	0.55	706	0.43	600	0.35
Other	7,286	5.25	7,289	4.47	7,624	4.40
<b>TOTAL REVENUE</b>	<b>138,676</b>	<b>100.00</b>	<b>163,113</b>	<b>100.00</b>	<b>173,307</b>	<b>100.00</b>

Source: Annual report EMEA, 2007

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