Ethics for Drug Testing in Low and Middle Income Countries

Considerations for European Market Authorisation

Irene Schipper & Francis Weyzig

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In this report SOMO links clinical trials carried out on people in low and middle income countries to medicines that are currently available on the European market. The number of clinical trials off-shored to countries like China, India, Russia and Argentina has experienced enormous growth in the last five years. However, trial subjects in these countries are more vulnerable and their rights are less secured than in high income countries. Conditions such as poverty, illiteracy, poor health systems and inadequate research ethics committees result in international ethical standards not being met.

Current EU legislation requires that results from unethical clinical trials that have not been conducted in accordance with the Declaration of Helsinki not be accepted for marketing authorisation. With three case studies on recently approved drugs in the EU (Abilify, Olmetec, and Seroquel), SOMO demonstrates that this principle is being violated. European authorities devote little to no attention to the ethical aspects of the clinical trials submitted, and they accept unethical trials as well as trials of poor quality.

Transparency about clinical trials in low and middle income countries is insufficient, both with regard to the amount of trials covered in public databases and with regard to the amount of information on ethical considerations. In addition, national medicine authorities fail to promptly publish public assessment reports on medicines approved for the EU market as is legally required.

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Colophon

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Executive summary

Clinical trials are increasingly conducted in low and middle-income countries because of lower costs and faster enrolment. Since 2004, the EU has explicitly required that all clinical trials be in accordance with global standards of ethical conduct, whether they are conducted in the EU or elsewhere, if they are to be taken into account for marketing authorisation. Global standards of ethical conduct are described in the Declaration of Helsinki of the World Medical Association (WMA). Previous reports show that although clinical trial ethics are not always properly regulated or enforced in low and middle-income countries, the European Medicines Agency (EMEA) and national medicines agencies of EU member states pay little attention to the ethics of clinical trials conducted in those countries.

This study analyses the ethical aspects of phase III clinical trials conducted in low and middle-income countries for drugs approved in the European Union. The research focuses on phase III trials because these play a pivotal role in the marketing authorisation process and are more recent than phase I and II trials for the same drugs. The study first identified branded medicines currently available on the European market and that have been tested in low and middle-income countries. After this, the information about ethical aspects of the trials for these drugs that is publicly available was analysed. Finally, the ethical aspects of phase III trials and the implications for the marketing authorisation process were analysed in more detail for three specific drugs.

A complete overview of all phase III trials conducted in low and middle-income countries for the largest selling drugs available on the European market could not be constructed. Publicly available databases are incomplete and have a relatively weak coverage of trials in low and middle-income countries. Therefore the research approach was reversed and relevant drugs were identified from overviews of trials conducted in a selection of low and middle-income countries. Seven relevant drugs were identified, most of which are psychotherapeutic agents.

The information about clinical trials that is publicly available is also limited in nature. No database has separate data fields for ethical aspects. In a few cases information about post-trial access provisions was included in trial descriptions. No explanation on the inclusion of vulnerable patient groups, mention of special protection measures, justification of placebo use, or assessment of benefits to the population could be found in any of the trial descriptions, even though the nature of some trials raised serious questions about these issues. Most European Public Assessment Reports (EPARs) or National Public Assessment Reports (NPARs), if available, do not contain information about ethical conduct other than a statement of the applicant that Good

Clinical Practice (CGP) was observed. Original trial protocols, which should contain more information on ethical considerations, are not publicly available.
More generally, the findings confirm that attention to clinical trial ethics in assessments for EU marketing authorisation is extremely limited. This not only applies to trials conducted in low and middle-income countries but also to trials conducted in the EU itself.

Three more detailed case study analyses were performed for the drugs Abilify, Olmetec, and Seroquel. Phase III trials for these drugs were conducted in various countries in Latin America, Central and Eastern Europe, Asia and sometimes Africa.

Abilify (aripiprazole) is a drug for schizophrenia that was approved by the EMEA in 2004. In the case of Abilify, the trials that were pivotal in the EPAR can be considered unethical because of the use of placebos, which involve serious risks for schizophrenia patients, while effective alternative treatments already exist. The trials also had a questionable design and were poorly conducted from a scientific perspective. The EMEA nonetheless accepted the results of the trials and granted marketing authorisation on the basis of these results. This case study shows that European authorities paid little attention to the ethical aspects of clinical trials even though Regulation No 726/2004 had just come into force, requiring all clinical trials, inside and outside the EU, to be conducted in accordance with ethical principles. The study also illustrates that trials of poor quality are not always rejected by the authorities.

Olmetec (olmesartan medoxomil) is a drug for hypertension that was approved for the EU by the German drug authorities in March 2003. No public information is available from the German drug authorities or the company that developed Olmetec.
Information from other sources raises questions about the ethics of phase III Olmetec trials conducted in low and middle-income countries. The trials were placebo-controlled and included children from 1 to 16 years old in developing countries, who constitute a vulnerable patient group for which the benefit of the hypertension drug trials is not obvious. Although a sound justification might exist, no such justification was provided by the sponsor of the trials.

Seroquel (quetiapine fumarate) is a drug for schizophrenia that was approved in the EU in 1999. A once-daily extended release formula, Seroquel XR, was approved in August 2007 by the Medicines Evaluation Board (MEB) of the Netherlands. Two placebo-controlled trials that were submitted to obtain marketing authorisation for Seroquel XR started in November 2004 and March 2005. Denying existing treatment to acutely ill and stable schizophrenia patients is unethical according to the Declaration of Helsinki, and no justification was given for placebo use. The stable schizophrenia patients receiving placebo clearly experienced harm from their participation in the trial as they had an estimated 68% risk of a psychiatric relapse in six months versus 14% for patients receiving Seroquel XR. 8.3% of the patients

receiving placebo had to be hospitalised due to worsening of schizophrenia and one 25 year-old patient committed suicide after 173 days of placebo treatment. What is especially striking in this case is that these trials are set up only to investigate the differences between formulations of the same antipsychotic which never justifies the use of placebo. Nonetheless, the results of the trials were accepted by the Dutch medicines agency as a valid basis to grant marketing authorisation in 2007.

Two overall conclusions can be drawn from this research.
1) European authorities not only grant EU market authorisation based on unethical clinical trials, they actually induce the offshoring of unethical trials to countries outside Western Europe, by requiring trials that are rejected by the ethics committees in Western Europe, resulting in the fact that these trials mainly end up in low and middle-income countries like Central and Eastern Europe, Latin America and Asia (India and China). The research of SOMO shows that this is indeed the case with placebo-controlled studies involving stable patients and acutely ill patients diagnosed with schizophrenia and acute mania; these studies almost exclusively take place outside Western Europe .

2) The degree of transparency about clinical trials in low and middle-income countries is low, both with regard to the number of trials covered in public databases and with regard to the amount of information on ethical considerations for each trial. Voluntary initiatives of the pharmaceutical industry to increase transparency about clinical trials have clearly been insufficient in this respect. Information from national medicines agencies in EU member states is limited too, even though current EU legislation requires that all assessment reports be published without delay.

1. Introduction

Medicines are increasingly being tested in low and middle-income countries in Asia, Latin America, and Eastern Europe. More and more this also applies to medicines that are approved in the European Union (EU). Since 2004, the EU has explicitly required that all clinical trials be in accordance with global standards of ethical conduct, whether they have been conducted in the EU or elsewhere, if they are to be taken into account for marketing authorisation.

In low and middle-income countries, clinical trial ethics are not always properly regulated or enforced. Several studies show that in these countries ethical review committees are inadequately equipped to assess whether research protocols meet the ethical requirements.[1] The European authorities reviewing the applications for marketing authorisation of medicines therefore cannot simply rely on these local regulatory systems or on statements made by the applicants themselves that clinical trials have been conducted in an ethical manner.

Nevertheless, a research report published in 2007 by the non-governmental organisation Wemos showed that the European Medicines Agency (EMEA) and the national medicines agencies responsible for issuing the market authorisation devote little attention to the ethics of clinical trials conducted in low and middle-income countries.[2] The main findings of the research were the following:

- In most cases EU authorities do not verify whether the form and membership of local ethical review committees comply with the guidelines for good clinical practice;
- There is little attention to the relevance of the trials for the research population;
- There is little concern for the protection of vulnerable study populations;
- Ethical shortcomings are not automatically considered grounds for rejection of the trial;
- Registration authorities' procedures are insufficiently transparent.

Against this background, the aims of SOMO (Centre for Research on Multinational Corporations) for this study are to find out which medicines currently available on the European market have been tested in low and middle-income countries and whether these tests have been conducted in an ethical manner. In particular, this study aims to answer the following questions:

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1 Wemos, Final report of the expert meeting 'Clinical trials and protection of trial subjects in low and middle-income countries' (Amsterdam: Wemos, December 2007).

2 'Do European registration authorities ascertain whether clinical trials in developing countries have been conducted in an ethical manner?: a study by the Wemos Foundation, Amsterdam', June 2007. http://www.wemos.nl/Documents/summary_english.pdf

- Which of the largest-selling prescription drugs approved for the EU market have been tested in low and middle-income countries?
- What information is publicly available about the phase III trials of these drugs?
- What ethical considerations can be found in the research protocols of clinical trials conducted in low and middle-income countries?
- Can unethical practices be identified for trials of specific drugs?
- Are there differences in design between trials taking place in the EU and in low and middle-income countries?

A draft version of this research report was presented at an expert meeting at the European Parliament on 6 November 2007. This final report takes into account the input from the expert meeting.

The structure of the report is as follows. Chapter Two provides background information on the offshoring and outsourcing of clinical trials and ethical standards. It briefly discusses the Declaration of Helsinki, which is the global standard for clinical trial ethics, and relevant EU Directives and Regulations. Chapter Three presents a selection of drugs in the EU market and assesses the information available about the phase III trials of these drugs. This chapter also describes the methodology used for case studies of the drugs Abilify, Olmetec and Seroquel. Chapters Four, Five and Six present the findings from the case studies of these three drugs, including discussions on trial designs and potentially unethical practices. Chapter Seven briefly reports the outcomes of the expert meeting held on 6 November 2007, and Chapter Eight presents the overall conclusions of the report.

2. Facts on offshoring clinical trials and ethical standards

2.1. Why offshoring of clinical trials?

The explosion of the amount of clinical trials conducted in low and middle-income countries has several reasons:

- In general, more and more clinical trials are conducted each year.[3]
- According to the industry, companies are developing an increasing number of medicines for diseases that have a higher prevalence in developing countries and must be tested in the countries where the disease exists. [4]
- Pharmaceutical companies are conducting a larger proportion of clinical trials in low and middle-income countries for the development of drugs for global or developed country diseases. This development may be called offshoring. There are several specific reasons for the increase in offshoring:
  - **Fast subject recruitment**.[5] Globally, more than 80% of clinical trials fail to enrol on time, and this recruitment problem is extremely costly for drug companies. The pool of trial subjects in high-income countries is shrinking while the low-income countries offer large patient populations containing patients with a wide range of diseases, including diseases more prevalent in high-income countries. Many people in low and middle-income brackets are eager to participate, as it may be their only option for access to medication and treatments, and sometimes is a way to earn some money.[6]
  - **Treatment naive trial subjects**. This refers to the availability of an extensive population which has never been part of a trial and hardly exposed to medicines before, which is very attractive for the industry.
  - **Cost savings**. The amount of cost saving differs per country, and a range of estimates can be found in literature. One study indicates that

[3] Website PhRMA visited 19 October 2007. The Pharmaceutical Research and Manufacturers of America (PhRMA) represents the leading pharmaceutical research and biotechnology companies in the US. http://www.phrma.org/about_phrma

[4] Website PhRMA visited 19 October 2007. http://www.phrma.org/about_phrma

[5] Kirsty Barnes, 'Pharma giants risk reputation through clinical trial cost-cutting', in-Pharma technologist.com, 6 June 2006. <http://www.in-pharmatechnologist.com/news/printNewsBis.asp?id=68150> (October 2007).

[6] 'SOMO briefing paper: examples of unethical trials', December 2006, http://www.somo.nl/html/paginas/pdf/Examples_of_unethical_trials_dec_2006_NL.pdf

companies achieve 40-60% cost savings by offshoring clinical trials to India.[7]

- **Faster approval of research protocols**. Less stringent regulation and/or weak enforcement can result in faster approval of research protocols, which saves valuable time for pharmaceutical companies.

2.2. How many clinical trials are offshored?

The question how many trials are conducted each year in these countries is hard to answer. It turns out to be very difficult for the industry as well as scientists to estimate the number of clinical trials being run worldwide. Some trials are not registered with any agency in any country. Some drug companies do not communicate their clinical trials until they have ended, for instance, and in some cases trials may not be reported at all if the results are disappointing. Furthermore, some types of clinical research do not require registration, such as preclinical and post-marketing studies and studies for new uses for existing drugs. Many trials leading to rejected drug applications are also not registered.[8]

Thomson CenterWatch, which keeps a drugs trial database, estimated the number of trials worldwide on 50,000 in 2003.[9] And this is a conservative figure, because CenterWatch uses the US Food and Drug Administration (FDA) estimates of the number of trials initiated annually on the basis of US submissions, the number of drugs currently in development, and the average length of trials.[10] Their starting point is therefore the US industry and the US market, which is dominant but does not cover the entire sector. Taking account of the fact that the number of trials is growing each year and that the number of 50,000 is conservative, the current total would be least 60,000 per year.

It has been estimated that nearly 40% of all clinical trials were conducted in low and middle-income countries in 2005.[11] For large pharmaceutical companies, the

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7 Economic Times of 26 January 2007 “India No. 2 destination for clinical trial outsourcing” <http://economictimes.indiatimes.com/articleshow/msid-1462872,prtpage-1.cms> (October 2007).

8 Adriana Petryna, ‘Clinical Trials offshored: on private sector science and public health’, Biosocieties, 2007, p. 2.

9 Julie Schmit, “Costs, regulations move more drug tests outside USA: other nations want drugs tested on their populations’”, USA TODAY, 16 May 2005, <http://www.usatoday.com/news/health/2005-05-16-drug-trials-usat_x.htm> (October 2007).

10 Adriana Petryna, ‘Clinical Trials offshored: on private sector science and public health’, Biosocieties, 2007, 2, p.22, see footnote 1.

11 Clinical Trials Advisor, Vol. 10, No. 18, 22 September 2005 India to Create New Agency to Strengthen Clinical Trials Standards.

proportion may be well over 50%.[12] Some figures are available from individual companies.[13]

- GlaxoSmithKline (GSK) conducted 29% of its clinical trials were outside the US and Western Europe in 2004, and in 2006 this would have been about 50%.
- Wyeth Pharmaceuticals had 50% of its clinical trials outside the US in 2004, and this would have been 70% in 2006.
- Merck conducted 50% of its clinical trials outside the US in 2004.

It can be safely concluded that about 30 to 40% of all clinical trials are offshored to low and middle-income countries and that this figure is even higher for large pharmaceutical companies. This produces an estimate of roughly 18,000 to 24,000 clinical trials per year in low and middle-income countries.

2.3. To which countries?

Most offshoring of clinical trials takes place in a few large countries. A 2006 study by consulting firm AT Kearney found that China tops the list of the most preferred destinations for offshoring, with India in second place and Russia a close third. The study looked at factors such as patient availability, cost efficiency, relevant expertise, regulatory conditions and national infrastructure availability.[14] According to US government publications from 2006, 8.9% of clinical trials registered with US health authorities are conducted in low and middle-income countries in Asia, 7.4% in Latin America, 7.1% in Central and Eastern Europe and 1.6% in Africa. Together, this is approximately a quarter of the total.

Almost two-thirds of all clinical trials worldwide include at least one research centre in the US.[15] Clinical trials identified in this research, for the development of medicines that were approved for the European market, were conducted in the low and middle-income countries shown in table 1. Most of these were multi-centre studies, often conducted simultaneously at locations in the US or Western European countries as well. A majority of the trials identified in this research were conducted in the US alone.

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[12] Drug companies walking test-tubes, by Sonia Shah, NACLA Report on the Americas, March April 2006, Vol 39, No. 5.

[13] Julie Schmit, "Costs, regulations move more drug tests outside USA: other nations want drugs tested on their populations'", USA TODAY, 16 May 2005, <http://www.usatoday.com/news/health/2005-05-16-drug-trials-usat_x.htm> (Oct 2007).

[14] 'India No. 2 destination for clinical trial outsourcing ', The Economic Times, 26 January 2007, <http://economictimes.indiatimes.com/articleshow/msid-1462872,prtpage-1.cms> (October 2007).

[15] Clinical trials are now increasingly outsourced to developing countries such as India, website Offshoring times, <http://www.offshoringtimes.com/Pages/2006/BPO_news926.html> (October 2007 .

Table 1: Identified low and middle-income countries for this research

Region	Countries
Latin America	Argentina, Brazil, Chile, Colombia, Ecuador, Mexico, Peru, Uruguay, and Venezuela.
Africa	Egypt, Kenya, South Africa, Uganda, and Zambia
Central and Eastern Europe	Bulgaria, Croatia, Estonia, Latvia, Lithuania, Poland, Romania, Russian Federation, Serbia Montenegro, and Ukraine.
Asia	China, India, Indonesia, Korea, Malaysia, Philippines, Thailand, and Vietnam

2.4. Why can offshoring be problematic?

Several studies, books and articles report about controversies related to clinical trials in low and middle-income countries.[16] These identify several problems, often related to the fact that trial subjects in these countries are more vulnerable and their rights are less secured than in high-income countries. Poverty, illiteracy and the unequal relationship between doctor and patient may hamper the informed consent procedure. In some cases, patients have not been not aware that they are participating in a clinical trial or have been manipulated to participate. Besides that, in poor areas people may not have access to appropriate treatment after a trial comes to an end or once the new drug is approved.

Another important problem is that medical professionals with relatively low salaries are very willing to increase their income and prestige by working for the industry which bears risks for the liability and independence of the research and it is often at the expense of the capacity for regular health care. Furthermore, the Research Ethics Committees (RECs), responsible for the approval of the research protocols of clinical trials, may be understaffed, poorly funded, and lacking sufficient training on ethics to properly evaluate the quality and the relevance of clinical trials. A recent study conducted by the Latin American Network on Ethics and Medicines (*Red Latina Americana de Ética y Medicamentos*, RELEM), for example, shows that none of the RECs investigated monitor the implementation of the approved trials that are conducted in Latin America for foreign companies.[17]
Regulatory agencies in low and middle-income countries have not been strengthened to cope with the upsurge in clinical trials. Most countries do have the minimum regulatory requirements although enforcement is often extremely weak. Some

[16] For references, see "SOMO briefing paper on unethical trials, # 1. Examples of unethical trials," February 2008. http://www.somo.nl/html/paginas/pdf/Examples_of_unethical_trials_feb_2008_AND.pdf

[17] Wemos, Final report of the expert meeting 'Clinical trials and protection of trial subjects in low and middle-income countries' (Amsterdam: Wemos, December 2007).

countries, such as Peru and Costa Rica, have also recently relaxed their laws on clinical trials. The newly appointed ministers of health in these two countries have strong links to the pharmaceutical industry and one of the first actions of the Peruvian minister was to modify the regulations on clinical trials that were approved just a few months before his appointment to weaken the protection of research subjects.[18] India also relaxed its legislation on clinical trials in January 2005.[19]

The testing of drugs is never free of risk. Sometimes new drugs need to be withdrawn in the final stage of clinical development by the pharmaceutical companies because of problems encountered in clinical trials.[20] In addition, drugs already on the market may be withdrawn later because of safety risks. It is therefore a relevant question as to what types of drugs are tested in low and middle-income countries. Do the benefits for the participants and the communities where the drugs are tested outweigh the risks?

2.5. Outsourcing of clinical trials

Another important trend to mention alongside offshoring is the outsourcing of the process of clinical research to Contract Research Organisations (CROs). CROs are crucial players in the globalisation of clinical trials. They describe their own activities as follows:

'*Most CROs are involved in locating research sites, recruiting patients and in some cases, drawing up the study design and performing analyses. Sometimes they work directly with primary health care facilities, hospitals of consortia of therapeutic specialists. Some have even their own centralised ethical review boards'.*[21]

This description indicates some conflicts of interests. A strict separation of investigators recruiting the participants from treating physicians is recommended. And CROs having their own ethical review boards would mean that the industry is reviewing itself. It has been estimated that in 2002 pharmaceutical companies used CROs for more than 60% of their clinical research projects.[22] The CRO industry itself states that roughly 40% of all staff involved in clinical drug research is provided by

[18] The old regulation concerns DS N° 017-2006-SA of July 29, 2006. The new one is DS Nº 006-2007-SA , 8 June 2007.

[19] From the presentation of Amar Jesani, Indian journal of Medical Ethics, Centre for Studies in Ethics and Rights, Mumbai, India, and the presentation of RELEM, held on the expert meeting of 6 November 2007 in Brussels. See: 'Final Report of the expert meeting 'Clinical Trials and protection of trial subjects in low and middle-income countries', December 2007, by WEMOS.

[20] Torcetrapib by Pfizer in December 2006, and BMS terminated a new diabetics drug and AstraZeneca halted a drug for stroke patients Subodh Varma, 'India a hotbed for clinical trials', Times of India, 18 march 2007. <http://timesofindia.indiatimes.com/articleshow/1776215.cms> (October 2007).

[21] Adriana Petryna, 'Clinical Trials offshored: on private sector science and public health', Biosocieties, 2007, 2.

[22] M. Mathieu, Parexel's Pharmaceutical R&D Statistical Sourcebook 2002.

CROs.[23] The outsourcing of clinical trials complicates oversight and responsibility regarding ethical issues in drug research.

2.6. Research protocols and ethical standards in clinical trials

The analysis of risks to and benefits for the populations where the trial is carried out should be addressed in the trial protocol. The IFPMA clinical trial portal explains: *'A protocol is a study plan specific to each clinical trial. The plan is carefully designed to safeguard the health of the participants as well as answer specific research questions. A protocol describes what types of people may participate in the trial; the schedule of tests, procedures, medications, and dosages; and the length of the study.'*[24]

The Declaration of Helsinki (DoH) of the World Medical Association (WMA) sets global ethical standards that each clinical trial protocol should comply with.[25] European regulations specify that the trials providing the underlying data for marketing applications of new drugs need to comply with the Declaration of Helsinki. The World Health Organization (WHO) Guidelines for Good Clinical Practice (GCP) for trials on pharmaceutical products also endorses the DoH as the generally accepted basis for clinical trial ethics. The main paragraphs of interest for this study in the DoH are listed below. First, the DoH requires an explicit statement on ethical standards to be included in the trial protocol.

Paragraph 14 of the Declaration of Helsinki:
'The research protocol should always contain a statement of the ethical considerations involved and should indicate that there is compliance with the principles enunciated in this Declaration.'

A basic norm is that the research should benefit the populations where the trial is conducted.

Paragraph 19 of the Declaration of Helsinki:
'Medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research.'

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[23] Adriana Petryna, 'Clinical Trials offshored: on private sector science and public health', Biosocieties, 2007, 2.

[24] IFPMA website, <http://www.ifpma.org/clinicaltrials.html> (October 2007).

[25] For a more comprehensive overview of both technical and ethical guidelines, see "Official guidelines on clinical trials," *m*CRT website, <http://www.controlled-trials.com/links/guidelines> (October 2007).

Another aspect that should be addressed is the right to continued treatment once a trial is over, also known as post-trial access. This is most relevant for patients who cannot afford the drug at commercial prices after it has obtained marketing approval.

Paragraph 30 of the Declaration of Helsinki:
'At the conclusion of the study, every patient entered into the study should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study.'

Clarification in endnote (2004):
'(…) Post-trial access arrangements or other care must be described in the study protocol so the ethical review committee may consider such arrangements during its review.'

This research also focuses on the widely used method to compare a new drug against placebo to prove the safety and efficacy of the drug. The Declaration of Helsinki is very clear about the use of placebos in paragraph 29.

Paragraph 29 of the Declaration of Helsinki:
'The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists. '

Clarification in endnote (2002):
'The WMA hereby reaffirms its position that extreme care must be taken in making use of a placebo-controlled trial and that in general this methodology should only be used in the absence of existing proven therapy. However, a placebo-controlled trial may be ethically acceptable, even if proven therapy is available, under the following circumstances:
- Where for compelling and scientifically sound methodological reasons its use is necessary to determine the efficacy or safety of a prophylactic, diagnostic or therapeutic method; or
- Where a prophylactic, diagnostic or therapeutic method is being investigated for a minor condition and the patients who receive placebo will not be subject to any additional risk of serious or irreversible harm. (…)'

Thus, the spirit of this paragraph is always to avoid placebo-controlled trials unless there are some very good justifications for it. However, the pharmaceutical industry appears to have no intention to reduce the use of placebos, including in cases where safe and effective alternatives are readily available, and this position is supported by regulatory authorities. This results not only in depriving clinical trial participants of adequate treatment, but also in the approval of new drugs that are no better or even inferior than already existing treatments.

In practice, the regulatory authorities of Europe, Japan and the United States and experts from the pharmaceutical industry refer to the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) for the most relevant guideline on the ethics of placebo use. The 2001 ICH guideline 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'*. [26] This is considerably weaker than the DoH. In fact, it leaves all options open and gives research efficiency precedence over ethical considerations.
Another guideline pharmaceutical companies refer to is the 'Note for Guidance on the Clinical Investigation of Medicinal Products in the Treatment of Schizophrenia' published by the EMEA in 1998, in which regulatory requirements for placebo-controlled studies are set out.[27] About the use of placebo it says that "*in principle placebo-controlled trials will be required to show efficacy of a new product, but it is recognised that suitable alternative designs may be developed. In the latter case it is recommended to discuss this approach in the expert report and/or with the competent authorities.*" So the door is not closed but left ajar. However not for trials intended to demonstrate efficacy in patients with predominant and persistent negative symptoms, therefore the EMEA does require a placebo-controlled trial design.
Both the ICH guideline and the EMEA guidance acknowledge the ethical problem of placebo use, especially when changes are irreversible. Companies ask attention for the fact that in academic literature,[28] *'there is an extensive debate on the use of placebos in schizophrenia research'* and that there is *'no consensus on the topic'*.[29] AstraZeneca also underlines this in its response to this report.[30] According to AstraZeneca, in most Western European countries the ethical committees no longer approve placebo use in trials to test a treatment for schizophrenia. In the Netherlands the CCMO does not approve these trial designs.[31]

With regard to placebo testing, Annex I to EU Directive 2001/83/EC specifies:

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[26] 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 (EMEA). Section 2.1.3 Ethical issues.
http://www.emea.europa.eu/pdfs/human/ich/036496en.pdf

[27] EMEA, Committee for Proprietary Medicinal Products (CPMP), 'Note for Guidance on the Clinical Investigation of Medicinal Products in the Treatment of Schizophrenia', 1998.
http://www.emea.europa.eu/pdfs/human/ewp/055995en.pdf

[28] Organon refers to: Leber P. The use of placebo-control groups in the assessment of psychiatric drugs: an historical context. Biol Psychiatry 2000; 47: 699-706; Khan A, et al. Symptom Reduction and Suicide Risk Among Patients Treated With Placebo in Antipsychotic Clinical Trials: An Analysis of the Food and Drug Administration Database. Am J Psychiatry 2001; 158: 1449-1454; Fleishacker WW, et al. Placebo or active control trials of antipsychotic drugs? Arch Gen Psychiatry 2003; 60: 458-464.

[29] H. J. Out, Organon International, Reaction Organon on "Akzo Nobel: Overview of controversial business practices in 2006", SOMO draft report by Irene Schipper and Francis Weyzig, 2 Apr 2007.

[30] Telephone call with Mr. Roeland van der Heide, AstraZeneca Netherlands, Friday 15 February, 2008.

[31] Telephone call with Mr. Roeland van der Heide, AstraZeneca Netherlands, Friday 15 February, 2008.

'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.'

The EU therefore requires that new medicines are normally tested in controlled trials, but not necessarily in placebo-controlled trials. The Directive states that the appropriate trial design will depend on ethical considerations and explicitly mentions that testing against an existing medicine may sometimes be preferred. But it is obvious that in the DoH the placebo use must be justified, and for the EU i.e. the EMEA not using a placebo-controlled test must be justified. It is the other way around.

A last ethical aspect included in this research is testing drugs on subjects who are in a vulnerable position. Poor trial participants are often in a vulnerable position because participating in a trial may be their only option for access to medication and care. Other examples are patients with severe mental disorders such as dementia or schizophrenia. These patient groups cannot always easily decide for themselves to participate or give informed consent.

Paragraph 8 of the Declaration of Helsinki:
'(…) Some research populations are vulnerable and need special protection. (…) Special attention is also required for those who cannot give or refuse consent for themselves, for those who may be subject to giving consent under duress, for those who will not benefit personally from the research and for those for whom the research is combined with care.'

It is evident that monitoring of adherence to ethical principles by external actors, such as academics or civil society organisations, requires the original protocol to be publicly available.

EU legislation currently requires that all clinical trials are conducted in accordance with the DoH. The following EU legislation is relevant in this regard:

- Directive 2001/20/EC of 4 April 2001, which sets standards for the conduct of clinical trials in the EU itself;
- Directive 2001/83/EC of 6 November 2001, amended by Directive 2003/63/EC of 25 June 2003 and Directive 2004/27/EC of 31 March 2004, which regulates marketing authorisation of medicinal products;
- Regulation (EC) No 726/2004 of 31 March 2004, which defines the centralised procedure for marketing authorisation.

The latest version of Directive 2001/83/EC requires in article 8(3)(ib) that the following information is submitted with an application for marketing authorisation:

'A statement to the effect that clinical trials carried out outside the European Union meet the ethical requirements of Directive 2001/20/EC.'

Regulation (EC) No 726/2004 sets standards for the centralised procedure for marketing authorisation and contains the same requirement. Annex I to Directive 2001/83/EC further specifies:

'(…) 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.'

Thus, the Directive explicitly requires that clinical trials conducted anywhere in the world must have been carried out in accordance with the same ethical standards that apply to trials in the EU, including the DoH, if they are to be taken into account for applications for marketing authorisation in the EU.

A more detailed overview of EU legislation on clinical trials is provided in Annex 1.

3. Data sources and methodology

3.1. Selection of drugs

In order to investigate the ethical aspects of phase III clinical trials for drugs approved in the European market, and in particular for such trials conducted in low and middle-income countries, a selection of drugs was made. The selection is shown in the table below.

Table 2: Selection of largest selling branded drugs approved in the EU from 2000 onwards.

Generic name	Brand name	Approval date	Drug class
etanercept	Enbrel	03-02-2000	Antiarthritic drugs
celecoxib	Celebrex	29-03-2000	Antiarthritic drugs
risedronine acid	Actonel	09-06-2000	Diabetics drugs
rosiglitazone	Avandia	11-07-2000	Diabetics drugs
trastuzumab	Herceptin	28-08-2000	Cancer drugs
pioglitazone	Actos	13-10-2000	Diabetics drugs
esomeprazol	Nexium	07-12-2000	Gastrointestinal drugs
Salemeterol xinofoate	Seretide/Advair	21-12-2000	Respiratory drugs
budesonide + formoterol	Symbicort	22-12-2000	Respiratory drugs
pneumococcal saccharide conjugated vaccine	Prevenar	02-02-2001	Vaccines
zoledronic acid	Zometa	20-03-2001	Musculo-skeletal system
darbepoetin alfa	Aranesp	08-06-2001	Blood modifiers
glatimamer acetate	Copaxone	07-08-2001	Multiple sclerosis
imatinib mesilate	Glivec	07-11-2001	Cancer drugs
gemcitabine hydrochloride	Gemzar	12-11-2001	Cancer drugs
alendronate sodium	Fosamax	21-12-2001	Diabetics drugs
tiotropium	Spiriva	02-04-2002	Respiratory drugs
escitalopram oxylate	Cipralex	07-05-2002	Psychotherapeutic agents
oseltamivir phosphate	Tamiflu	22-06-2002	Anti-infective agents
pegfilgrastim	Neulasta	22-08-2002	Blood modifiers
bicalutamide	Casodex	09-09-2002	Cancer drugs
rosuvastatin	Crestor	07-03-2003	Cholesterol drugs
olmesarten medoxomil	**Olmetec**	**30-03-2003**	**Cardiovascular drugs**
adalimumab	Humira	08-09-2003	Antiarthritic drugs
aripiprazole	Abilify	04-06-2004	Psychotherapeutic agents
cetuximab	Erbitux	29-06-2004	Cancer drugs
pregabalin	Lyrica	06-07-2004	Antiarthritic drugs

ezetimibe + simvastatin	Vytorin	24-09-2004	Cholesterol drugs
duloxetine hydrochloride	Cymbalta	17-12-2004	Psychotherapeutic agents
bevacizumab	Avastin	12-01-2005	Cancer drugs
emtricitabine + tenofovir disoproxil	Truvada	21-02-2005	Anti-infective agents

Source: Med Ad News, July 2007, 200 Best-selling prescription medicines – Therapeutic categories (global sales for 2006); for approval dates, see below. The drugs in bold are case studies in this report.

The selection is limited to the branded drugs with the largest sales (within the largest selling drug classes) approved in Europe from 2000 onwards. The focus is on more recent trials because the offshoring of clinical trials has greatly increased in recent years. In addition, the Declaration of Helsinki, which is used as a normative benchmark for this research, was revised in 2000 with a few clarifications added in 2002 and 2004, and EU regulations on marketing authorisation were revised in 2003 and 2004, as described in the previous chapter. The research focuses on phase III trials because these play a pivotal role in the marketing authorisation process and they are of a more recent date than phase I and II trials for the same drugs.
Some data was also sought on the following drugs because they belong to the top selling drugs worldwide, although they were approved before 2000.

Table 3: Selection of largest selling branded drugs approved before 2000.

Generic name	Brand name	Approval date	Drug class
simvastatin	Zocor	1988	Cholesterol drugs
amlodipine	Norvasc	1990	Cardiovascular drugs
risperidone	Risperdal	1993	Psychotherapeutic agents
olanzapine	Zyprexa	27-09-1996	Psychotherapeutic agents
atorvastatin	Lipitor	21-04-1997	Cholesterol drugs
pantoprozole	Protonix	1998	Gastrointestinal drugs
clopidogrel hydrogen sulphate	Plavix	15-07-1998	Blood modifiers
quetiapine	**Seroquel**	**30-11-1999**	**Psychotherapeutic agents**

Source: Med Ad News, July 2007, 200 Best-selling prescription medicines – Therapeutic categories (global sales for 2006); for approval dates, see below.

In the case of some of these drugs, additional phase III trials have been carried out for new formulations or new patient groups after the original marketing approval. For example, risperidone was originally approved for schizophrenia in adults in 1993, but was later approved for bipolar disorder as well and recently also for schizophrenia in children. Although these are not listed in the tables above, the research also covered these new indications.

3.2. Data sources and limitations

The data used for this research is mainly from public registers. The main sources for information about the approval data of drugs were the EMEA website, the European Product Index website, and the websites of a few national drug authorities. These sources are listed below.[32]

- **EMEA** website: http://www.emea.europa.eu/htms/human/epar/l.htm. Approval data for drugs approved through the centralised procedure is available from the European Public Assessment Reports (EPARs) of the EMEA.
- The **European Product Index**: http://mri.medagencies.org/mrindex/index.html. This website provides approval information on medicines approved by individual member states of the European Union according to the mutual recognition procedure.
- ***Geneesmiddeleninformatiebank*** [Drug database] of the Dutch Medicines Evaluation Board (MEB/CBG): http://www.cbg-meb.nl/nl/prodinfo/gibhumaan.htm. A database with product information on drugs available on the Dutch market.
- The **Public Assessment Reports of the UK** The Medicines and Healthcare products Regulatory Agency (MHRA): http://www.mhra.gov.uk/home/idcplg?IdcService=SS_GET_PAGE&nodeId=910. In accordance with Directive 2004/27/EC, the MHRA makes the assessment reports available for all new licenses granted after 30 October 2005, albeit with commercially or personally confidential information removed.
- The **Electronic Orange Book**: http://www.fda.gov/cder/ob/default.htm. This contains information on drugs approved in the US by the FDA.

Information on clinical trials, including the countries where they were conducted and ethical aspects, was mainly obtained from clinical trials databases. These sources are listed below.

- **EMEA** website: http://www.emea.europa.eu/htms/human/epar/l.htm (see also above). Note that information about the location of the clinical trials is not always mentioned in EPARs, and even then usually only the region is mentioned, such as 'clinical trials for this drug are carried out in the US and Europe'. Specific countries other than the US are not identified as standard .
- The ***meta*Register of Controlled Tials** (*m*RCT): http://www.controlled-trials.com/mrct/search.html. This is an international database of ongoing randomised controlled trials in all areas of healthcare, built by combining registers held by public, charitable and commercial sponsors of trials. The *m*RCT also contains some completed trials. It is an initiative of ISRCTN,

[32] For a more comprehensive overview of clinical trial registers, see *m*RCT website, "Trial registers," <http://www.controlled-trials.com/links> (October 2007).

administered by Current Controlled Trials Ltd. and published by Biomed. The total number of records is 36,574. It seems that the majority of information is derived from the Clinicaltrials.gov database, as the overlap is very large. In the near future the Netherlands Trial Register will be included in the *m*RCT.

- The **ClinicalTrials.gov** register: http://clinicaltrials.gov/ct/screen/SimpleSearch. This database has been developed by the US National Institutes of Health (NIH), through its National Library of Medicine (NLM), in collaboration with the US Food and Drug Administration (FDA). ClinicalTrials.gov was launched in February 2000 and currently (October 2007)[33] contains more than 41,000 clinical studies sponsored by the NIH, other federal agencies, and private companies. Studies listed in the database are conducted in over 140 countries.
- The **ClinicalStudyResults.org** website is developed by the pharmaceutical industry as an online clearinghouse to provide greater access to the results of its clinical studies. In line with PhRMA's 2002 Principles on Conduct of Clinical Trials and Communication of Clinical Trial Results, the industry wants to increase the transparency of its clinical trial results. It is meant as a one-stop shop to find information about marketed drug products.
- **IFPMA** clinical trials portal: http://www.ifpma.org/clinicaltrials.html. This portal establishes links to IFPMA member company websites as well as other commercial and government-sponsored websites containing information on clinical trials provided by pharmaceutical companies. It enables the user to find results of clinical trials conducted on medicinal products that have been approved for marketing and redirects to the other databases.

It is worth mentioning in this context that the **EudraCT** database of all clinical trials commencing in the European Community from 1 May 2004 onwards, in accordance with Directive 2001/20/EC, is not publicly available.

It is only possible to search in the *meta*Register of Controlled Trials (*m*RCT), by locations using a country name as a free text search term. This is a very time consuming procedure. In ClinicalStudyResults.org, it is not possible to search the database on clinical trial locations, not even using a free search term such as a country name. The clinical study reports (called 'Synopsis') do mention the countries where the study centres are located, but reviewing the reports this way is again a very time consuming process.

[33] ClinicalTrials.gov was upgraded on 10 February 2008 and has 50,918 trials with locations in 153 countries.

Table 4: Number of phase III trials in various countries as registered in Clinicaltrials.gov.

Country	Total	Ongoing/Completed	Recruiting
United States	4,837	3,076	1,761
Germany	1,256	737	519
United Kingdom	955	601	354
The Netherlands	692	431	261
Sweden	430	248	182
Russian Federation	400	212	188
Brazil	365	198	167
Mexico	360	203	157
Argentina	347	196	151
India	290	126	164
China	220	103	117
Peru	134	79	55
Philippines	119	63	56
Kenya	16	7	9
Zambia	7	4	3

Source: Based on data from the Clinicaltrials.gov database, 10 October 2007.

Due to these important limitations, the ClinicalTrials.gov trials register turned out to be the most feasible way to search on trial locations. However, this database appears to be far from complete. The table above illustrates the coverage of trials in different countries in the ClinicalTrials.gov database.

The ClinicalTrials.gov database only contains 126 records of ongoing and completed trials conducted in India and 103 in China. Most of these are multi-centre trials taking place in various countries at the same time, including the US. According to a recent study, India is currently home to five to ten percent of all clinical trials worldwide.[34] Using the estimate of 60,000 trials per year globally, this means at least 3,000 trials take place each year in India and probably a large part of these are phase III trials. It is therefore likely that ClinicalTrials.gov only covers a fraction of the actual number of trials carried out in India and China in recent years.

3.3. Methodology

After making a selection of medicines, two research procedures were attempted. First, , the databases with information on clinical trials were searched for a selected medicine by phase III trials in low and middle-income countries. This approach turned out to be too inefficient. Furthermore, the results would not be so useful because the coverage of trials in low and middle-income countries in public registers is far from

[34] 'India No. 2 destination for clinical trial outsourcing ', The Economic Times, 26 January 2007, <http://economictimes.indiatimes.com/articleshow/msid-1462872,prtpage-1.cms> (October 2007).

complete. This study originally aimed to produce a reliable overview of the largest selling drugs in the European market tested in low and middle-income countries and of relevant characteristics of the trials in those countries. However, due to the limitations of the clinical trial databases as described above, this was not possible and results cannot be generalised.

In the second procedure, for a specific country of interest, all trials in the ClinicalTrials.gov database that include this country as a study location were retrieved. These results were then scanned for trials of the selected medicines. This second approach turned out to be more efficient and more useful. In order to search the selected databases on trials carried out in low and middle-income countries, it was necessary to select a few countries and use these as free text search terms. The following countries were selected: India, Russian Federation, Mexico, Argentina, Peru, the Philippines, Kenya, and Zambia.

For the following selection of drugs, trials in low and middle-income countries could be identified following this approach:

- Abilify (aripriprazole) of Bristol Myers Squibb (BMS).
- Seroquel (quetiapine fumarate) of AstraZeneca
- Zyprexa (olanzipine) of Eli Lilly
- Crestor (rosuvastatin) sponsored by AstraZeneca
- Olmetec (olmesartan) sponsored by Pfizer/Daiichi Sankyo
- Seretide (salmeterol) of AstraZeneca
- Risperdal (risperidone) of Johnson & Johnson

Clearly, most of the trials that were identified for low and middle-income countries involve the testing of psychotherapeutic agents. An article about a study on schizophrenia trials in China confirms this: the research identified a total number of 3,275 records of which 982 randomised controlled trials were relevant to schizophrenia. This is almost 30%[35]. The question as to why so many trials being offshored to countries outside Western Europe involve psychotherapeutic agents is answered by AstraZeneca: placebo-controlled trials for schizophrenia are no longer being approved by most of the Western European Research Ethics Committees (RECs).[36]

The drugs Abilify (aripiprazole), Seroquel (quetiapine fumarate) and Olmetec (olmesarten medoxomil) were chosen to study in more detail. The next chapters present case studies on these drugs. These case studies examine the availability of the research protocol, the number of registered trials, and to what extent these trials are conducted in low and middle-income countries. After that, the ethical aspects of

[35] Chakrabarti A, Adams CE, Rathbone J, Wright J, Xia J, Wong W, Von Reibnitz P, Koenig C, Baier S, Pfeiffer C, Blatter J, M. Mantz M, Kloeckner K. Schizophrenia trials in China: a survey, Acta Psychiatrica Scandinavica, Volume 116, Number 1, July 2007 , pp. 6-9(4)

[36] Telephone call with Mr. Roeland van der Heide, AstraZeneca Netherlands, Friday 15 February, 2008.

these trials are analysed with using the Declaration of Helsinki as benchmark. In principle, the case studies seek to answer questions such as:

- What are the ethical considerations in this trial?
- How is informed consent guaranteed?
- How is post-trial access dealt with?
- Is there an explanation on the participation of vulnerable patients?
- How is the use of placebos justified?
- What is the benefit for the population where the research is carried out?

To obtain the information on ethical aspects, we chose to use the public clinical trial databases as mentioned in paragraph 3.2 and company websites and not to include medical journals as a source of trial information.

4. Case study Abilify

4.1. Background information on the drug

Abilify (aripiprazole) is an antipsychotic belonging to the class of atypical antipsychotic drugs. It is approved for the treatment of Schizophrenia. It was first approved on 17 July 2002 in Mexico for schizophrenia in adults. Subsequently, the drug was approved by the FDA on 15 November 2002 and by the EMEA on 4 June 2004. Comparator drugs are: Zyprexa (olanzipine), Risperdal (risperidone), and Seroquel (quetiapine fumarate).

4.2. Database records with Abilify trials

Clinical trial data on Abilify was collected from the sources below. It turned out that the clinical trial descriptions on the company website of BMS and the Clinicaltrials.gov database provided all available information. The other websites mostly reproduce this information.

Table 5: Publicly available information on Abilify trials.

Source	Description
EMEA website[37]	The European Public Assessment Report (EPAR) on Abilify, 13 phase III trials mentioned.
FDA website[38]	Summary information on trials from approval letters, medical review, chemistry review, statistical review, clinical pharmacology bio pharmaceutics review, and administrative document(s) & correspondence.
Company website: BMS Clinical Trial Registry[39]	Clinical trials for psychiatric disorders, contains 38 trials on Abilify, some of them overlap with the Clinical trial results database of BMS.
Company website: BMS Clinical Trial Results [40]	The information contained in this section provides Clinical Trial Results for interventional trials that were conducted on marketed products for which Bristol-Myers Squibb has disclosure responsibility. 30 trials on Abilify.

[37] EMEA website, http://www.emea.europa.eu/humandocs/PDFs/EPAR/abilify/089304en6.pdf (October 2007).

[38] FDA website, http://www.fda.gov/cder/foi/nda/2002/21-436_Abilify.htm, (October 2007).

[39] BMS Clinical Trial Registry, http://ctr.bms.com/ctd/InitTrialAction.do?linkname=Psychiatric%20Disorders&type=pharma&sortby=default, (October 2007).

[40] BMS Clinical Trial Results, http://ctr.bms.com/ctd/ClinicalResultAction.do?productid=14&fullname=Otsuka%20Pharmaceutical%20Co.,%20Ltd.&sortby=default, (October 2007).

Company website: Abilify product site[41]	No information on or reference to clinical trials.
Clinicaltrials.gov	This US register contains 39 records of Phase III trials on Abilify, 10 recruiting and 27 completed/ongoing.
Cochrane library[42]	One review of aripiprazole studies, referring to different trials and original research articles in medical journals. It is difficult to match the trials included in the review with the records from trial registers, though.
Otsuka America Pharmaceutical website, co-sponsor[43]	No information on trials. This website is leading directly to the 'Full Product Information' including Boxed Warnings for Abilify.
*meta*Register of Controlled Tials	All 15 trials on Abilify link to the ClinicalTrials.Gov website.
ClinicalStudyResults.org	Nine hits on Abilify, all referring to trial results which are available on the BMS company website.

Sources: See footnotes and previous chapter.

4.3. Low and middle-income countries

Table 6 lists 13 Abilify trials conducted in low and middle-income countries. All of these were multi-centre studies and had at least one research location in the US or another high-income country.

It should however be recognised that the majority of identified Abilify trials were carried out in the US. Of the 39 phase III trials in the ClinicalTrials.gov register, six had at least one research centre in low and middle-income countries, whereas 33 took place in the US alone. The BMS trials database contains a different selection of Abilify trials. Out of the 27 records in this database, seven trials were only in the US and Western Europe, five were also in low and middle-income countries, and 15 did not clearly identify the countries where the trials were performed. An analysis of the trial descriptions did not show any indications for differences between the research design regarding trials in low and middle-income countries and in the US or Western Europe only.

[41] Abilify product site, http://www.abilify.com, (October 2007).
[42] Cochrane library, website, http://www.mrw.interscience.wiley.com/cochrane/clsysrev/articles/CD004578/frame.html, (October 2007).
[43] Otsuka America Pharmaceutical website, http://www.otsuka.com/oapi, (October 2007).

Table 6: 13 Abilify trials conducted in low and middle-income countries.

Trial identifiers	Source	Countries
NCT00097266 138-162	CT & BMS	US (17 centres), Bulgaria (7), Croatia (4), Mexico (11), Peru (3), Russia Federation (17), and South Africa (4).
NCT00095524 138-122	CT & BMS	US, Brazil and UK
NCT00239356 138-112	CT & BMS	Canada, Croatia, Czech Republic, France, Hungary, Netherlands, Poland, Romania, Russia, South Africa and UK
NCT00257972 CN138-134	CT & BMS	US, Bulgaria, Czech Republic, Estonia, France, Germany, Hungary, Italy, Netherlands, Poland, Russia, South Africa (8), Spain, Switzerland, UK
NCT00046384 CN138-077	CT & BMS	US and Argentina
CN138-008LT	BMS	Canada and Croatia
CN138-10	BMS	Argentina, Mexico and the US
CN138-002LT 26-52 wks	BMS	Argentina (4), Brazil (1), Canada (2) and the US (13)
CN138-002ST up to 26 wks	EPAR & BMS	Same locations as CN138-002LT 26-52 wks
CN138-003	BMS	119 study centres in Australia, Austria, Belgium, Croatia, Czech Republic, Estonia, Finland, France, Germany, Hungary, Israel, Italy, Netherlands, Poland, Portugal, Romania, Russia, South Africa, Spain, Sweden, Switzerland, and the United Kingdom.
CN138-047 (extension study) 26-52	BMS	The US (8 centres), Czech Republic (2), Poland (3), Russia (11) and Ukraine (4)
CN138-047ST up to 26 weeks	EPAR	Same locations as CN138-047 (extension study) 26-52
31-98-217/304	EPAR	US, Australia, New Zealand and South Africa and the other in Russia, Estonia, Poland, Bulgaria, France and Hungary.

Sources: CT = ClinicalTrials.gov, BMS = BMS company website, EPAR = EPAR from EMEA website.

4.4. Information availability on ethical considerations

SOMO reviewed the available information on the 13 Abilify trials in low and middle-income countries. The EPAR of the EMEA and the Medical Review of the FDA both summarise the trial designs of the clinical trials that were pivotal to the marketing application. The *m*CRT, ClinicalStudyResults.org, ClinicalTrials.gov and BMS company databases in general include the following standard data fields:

- title of the study
- status: completed, ongoing or recruiting
- sponsors
- clinical trial identifier
- purpose of the study
- study type and design (very brief, such as 'placebo-controlled' or 'active controlled')
- primary and secondary outcomes
- start date
- enrolment (no. of patients, not always)
- inclusion criteria, such as age, gender, specification of the patients
- location (only in ClinicalTrial.gov)

It is important to note that there is *no* register or website that provides the original trial protocol. On the basis of the limited data fields in these databases, and without access to the full protocols, it is not possible to answer the research questions listed at the end of the previous chapter, because no information was available for *any* of the Abilify trials information on ethical considerations in general, explanations on vulnerable patient groups, benefits for the population where the research was carried out, or the justification of placebo use. In a few cases, though, information on post trial access to treatment was available.[44] This is summarised in table 7, which also presents a few basic trial characteristics.

Table 7: Publicly available information on Abilify trials

Trial identifiers	Source	No. of patients	Year	Placebo used	Placebo justification	Info about informed consent	Info about post-trial access
NCT00097266 138-162	CT & BMS	615	2004	Yes	No	No	No
NCT00095524 138-122	CT & BMS	300	2004	No	-	No	No
NCT00239356 138-112	CT & BMS	400	2003	No	-	No	No
NCT00257972	CT & BMS	400	2004	Yes	No	No	No

[44] In response to this case study, BMS offered to provide SOMO with information regarding how the Aripiprazole team has provided for the continuing treatment of patients, sometimes for many years, in countries that aripiprazole is available. Response of BMS, by email dated 15 February 2008, sent by Ronald Marcus, MD, Executive Director, Bristol-Myers Squibb.

CN138-134							
NCT00046384 CN138-077	CT & BMS	..	..	No	-	No	No
CN138-008LT	BMS	..	2002	No	-	No	No
CN138-10	BMS	578	2003	Yes	No	No	No
CN138-003	BMS	..	..	Yes	No	No	No
CN138-047 (extension study) 26-52	BMS	..	..	Yes	No	Yes[1]	Yes[2]
CN138-002LT 26-52 wks	BMS	..	..	No	-	No	No
CN138-002ST up to 26 wks	BMS & EPAR	..	..	No	-	No	No
CN138-047ST up to 26 weeks	EPAR	..	..	No	-	No	Yes[3]
31-98-217/304	EPAR	..	..	No	-	No	No

Sources: CT = ClinicalTrials.gov, BMS = BMS company website, EPAR = EPAR from EMEA website. Notes:

[1] *"One hundred forty-seven (69%) patients completed the study, 81/110 (74%) in the olanzapine group and 66/104 (63%) in the aripiprazole group. The primary reason for discontinuation was patient withdrawal of consent (18% overall)."* Report on the extension phase in the section of 'Number of patients', <http://ctr.bms.com/pdf//CN138047.pdf>

[2] *"Duration of Treatment: Fifty-two weeks of open label treatment. Five patients at US sites continued treatment beyond Week 52 as per Amendment 4."* Report on the extension phase, <http://ctr.bms.com/pdf//CN138047.pdf>.

[3] The Addendum of Clinical Trial study report CN138002, which concerns the extension phase beyond 52 weeks, mentions that in Canada, Brazil and Argentina the patients could remain in extended treatment until aripiprazole is commercially available for marketing.

It is not clear why so little information is available about the procedure of informed consent in the trial registers and the assessments reports of the authorities like the FDA and the EMEA. Perhaps it is considered a standard procedure that does not need any specification. However, several examples of unethical trials in literature show that illegally obtained informed consent forms are an existing problem. As the approval authorities do not mention the issue in their evaluations, it is not possible to assess how informed consent is handled and whether it is properly monitored.

4.5. Trials reviewed in the EPAR

An overview of the phase III trials reviewed in the EPAR is provided in the table below. Note that the EMEA had serious criticism on several of the trials and some were simply invalidated due to non-compliance with GCP.

Table 8: Nine pivotal studies reviewed in the EPAR.

Trial identifiers	In LICs and MICs[a]	Duration	Design	Remarks
31-97-201	No (US only)	Short term	Short term 4-weeks, placebo-controlled and active controlled with haloperidol 10 mg. against aripiprazole 15 and 30 mg.	In this trial about 100 acutely relapsed schizophrenic patients were randomised to a placebo group. Total no. of drop outs 40%
31-97-202	No (US only)	Short term	Short term 4-weeks, to compare 20 mg and 30 mg aripiprazole against placebo and against risperidone 6 mg	400 patients who were in an acute relapse were enrolled and 78 schizophrenia patients out of that group were randomised to the placebo group. 40% of in total 289 schizophrenia patients dropped out.
CN138-001	No (US and Canada)	Short term	A multi-centre, randomised, double-blind, placebo-controlled study of three fixed doses of aripiprazole in the treatment of patients with acute schizophrenia	Also in this trial about 100 acutely relapsed schizophrenic patients were randomised to a placebo group. Total no. of drop outs was 66%.
31-98-217 and 31-98-304-01	Yes	Long term	two double-blind, active-controlled, long-term studies, 52 weeks, assessed maintenance of efficacy versus haloperidol	These two trials have the same design and are considered as 1 trial. The GCP/CHMP inspection discovered serious shortcomings but ultimately accepted the study for registration.
CN138-047	Yes	Long term	26-week, double-	Serious criticism on the

			blind, placebo-controlled study providing information on long-term maintenance treatment	trial in the EPAR. The study was accepted by FDA for maintenance claim.
CN138-002	Yes	Long term	26-week double-blind, active-controlled trial to compare safety and tolerability of aripiprazole and olanzapine as evidenced by weight gain during treatment	-
31-98-202	No data available	Long term	No data available	Invalidated due to non-compliance with GCP.
31-98-213	No data available	Long term	Open label design	Excluded for approval process because of its open label design.
31-97-301	(no info)	Long term	(no info)	Excluded for approval process due to lack of quality. This trial was terminated early due to unsatisfactory dissolution tests of over encapsulated (blinded) tablets of haloperidol.

Source: EPAR Abilify. Note: [a] LICs and MICs = lower income countries and middle-income countries.

The three short term trials were earlier submitted to the FDA for US approval and can be found in the Medical review of the FDA. In these trials, about 300 schizophrenia patients in a state of acute relapse were assigned to placebo and therefore denied the best proven diagnostic and therapeutic treatment. According to the Declaration of Helsinki, this is unethical. Also regarding the ICH guideline as well as the EMEA guidance (see page 17 of this report) placebo use is unethical when changes are irreversible. In cases of relapses in schizophrenic patients (which is provoked in the placebo trials) some professionals from the practice state that every relapse causes irreversible harm, see also the comment in the box below.

A Comment on testing new schizophrenia drugs against placebos

Rimke, a nurse on a psychiatric ward treating patients with acute psychiatric psychoses, reacts surprised hearing about the placebo tests with schizophrenic patients: she can't imagine that this is really happening because every relapse can cause permanent damage. According to Rimke this involves medical damage in the first place, meaning brain damage: "I often see that patients do not return at their old level after a psychiatric relapse". In the second place it involves social damage and Rimke explains that the social damage is often ever more destructing: "A relapse has a big impact on the often small social life of Schizophrenics and each psychosis can disturb their social relations even further." From her 8 years experience as a nurse she says: "The more rapidly you intervene with a treatment, the better the prognosis for the development of the disease." So giving acute schizophrenia patients a placebo was something inconceivable for her.

Source: Interview by telephone with Rimke van der Geest, October 2007.

Of the six long term studies, three were excluded by the EMEA, and the design of the three other studies was criticised by the EMEA. To begin with, in the latter three studies the issue of finding the best recommended dose was not addressed properly and different doses were used in the trials. Concerns were also raised regarding the differences in the definitions of failure to maintain response. Further, it was noted that the definition included 'worsening of schizophrenia' as an Adverse Event; there were doubts as to how this was counted in the actual analyses. Another concern: there was no time frame for the occurrence of a defined response in order to allow meaningfulness to the primary end-point (time to failure maintenance or response). And only stable patients were enrolled in the CN138-047 study, which makes the study less relevant for the general schizophrenic population.[45] These are serious shortcomings in the trial design which affects the outcomes in terms of the efficacy. Two studies validated for the marketing approval process will be discussed in greater detail below.

CN138-047

The first is study CN138-047, called 'a multi-centre, randomised, double-blind, placebo-controlled, 26 week study of a fixed dose of aripiprazole (15 mg) in the treatment of *stabilized patients with chronic schizophrenia*'. The primary objective of this study was to compare the time to relapse from randomised patients receiving 15 mg of aripiprazole versus placebo over a minimum of 26 weeks in the treatment of stabilised patients with chronic schizophrenia. 54% of the aripiprazole group and 71% of the placebo group had to discontinue the treatment due to lack of efficacy or adverse events, including the worsening of schizophrenia. Of those patients not dropping out of the study, 63% of aripiprazole group had no relapse versus 39% of

[45] EPAR Abilify, p. 22.

the placebo group.[46] Aripiprazole was therefore associated with a 50% reduction in the risk for relapse compared with placebo, but after excluding those patients who experiences worsening schizophrenia. These figures also imply that out of the 149 stabilised schizophrenia patients in the placebo group, only 17 patients (39% of 29%) did not experience worsening of schizophrenia, relapse, or other problems.

31-98-217 / 31-98-304-01

The second is study 31-98-217/31-98-304-01. One protocol was conducted in the US and the other in Europe, Australia, New Zealand and South Africa. The study lasted between two and 52 weeks and used haloperidol 10 mg as an active comparator drug. The primary efficacy variable was *'the time to failure to maintain response'* in patients. There was no statistical difference between aripiprazole and haloperidol.

The EPAR states the following: *'The non-USA protocol was conducted in a large number of centres 80% of which were located in Europe (Western and Eastern). In fact most of the Western European centres (the exception was France) failed to enrol a significant number of patients and the European contribution came mostly from Russia, Poland, Bulgaria and Hungary. The CPMP [Committee for Proprietary Medicinal Products, a scientific body of the EMEA] requested a GCP inspection, as this study concerns a vulnerable psychiatric population and as much of the data comes from countries where GCP inspections for Centralised Procedure applications had not yet been carried out. A number of inspections were carried out at clinical investigator sites, firstly in Estonia and Bulgaria.'*[47]

The first EMEA inspection found critical problems that threatened the validity of the data, such as dosing, amendments and monitoring:

- The adjustments of the doses during the trial were poorly documented at one of the inspected sites, the failures related to the poor design of the tear-off labels of the study and made it impossible to administer the true doses retrospectively.
- The EMEA notes: *"The definition of the response was amended three times during the trial always to loosen its criteria. The last time was just one month for the end of the study. One of the amendments proposed the introduction of 'worsening of schizophrenia' as an adverse event."*[48]
- The monitoring of the trial by the sponsor was inadequate: it failed to detect and to solve the problems in particular related to the dose administered.

A re-inspection by the CPMP confirmed the problems and defined some additional problems about the training of the investigators and standardisation of the assessment tool (using so-called PANSS scores) including the use of the local language in this regard. Although the answers of BMS did not fully resolve the

[46] EPAR Abilify.
[47] EPAR Abilify.
[48] EPAR Abilify, p. 23.

concerns, the EMEA nonetheless accepted the results of the study *"to support long-term efficacy, when considered in conjunction with other clinical trials."*[49]

4.6. Case study analysis

The information available on the ethical aspects of phase III Abilify trials is very limited. Two references were found on post-trial access arrangements for trial participants and a brief reference was found to informed consent. Additional information could not be found in the EPARs, in the clinical trial registers or in the clinical trial results database of BMS. In response to this, BMS says that is not true that no attention was paid to ethics, and refers to the protocol; however this information is not available for external actors such as SOMO researchers.[50] Furthermore, no methodological justifications were given for testing against placebo in this research.[51] As aripiprazole is not the first drug for schizophrenia on the market, and as schizophrenia is not a minor condition, and as patients receiving placebo can be subject to additional risk of serious or irreversible harm, these trials can be regarded as unethical taking the Declaration of Helsinki as benchmark.

One of the six long-term studies (31-98-202) was later invalidated due to non-compliance with GCP. However, as this is the only information available about this study, it remains unknown why this trial was deemed noncompliant, which is something worth knowing. Not only in the context of helping others avoid making the same mistakes but also this way the fundamental ethical obligations to the research participants are ignored. The potential risks of their voluntary participation, which exist in any type of trial, are justified primarily by the presumed social good resulting from the creation of publicly accessible knowledge, which is totally lacking now.

The trial with number 31-98-217 / 31-98-304-01 is problematic not only from an ethical but also from a scientific perspective: the trial design had serious shortcomings in terms of proving efficacy, the trial conduct showed serious shortcomings, the trial was monitored inadequately by the sponsor, and investigators tried to manipulated the outcomes by leaving 'worsening of schizophrenia' out of the study results. The acceptance of such study results for the marketing authorisation raises serious questions.

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[49] EPAR Abilify, p. 23.

[50] Response of BMS to the case study Abilify, by email dated 15 February 2008, sent by Ronald Marcus, MD, Executive Director, Bristol-Myers Squibb.

[51] BMS responds to this that the regulatory process requires placebo-controlled studies to prove that medications such as anti-psychotics are effective in patients (page 8 of the EMEA guidance). The design of the 047 study came from a careful review of the EMEA guidance (Section 6.4.2 page 10) and was accepted by FDA for a maintenance claim in the US. Source: email dated 15 February 2008, sent by Ronald Marcus, MD, Executive Director, Bristol-Myers Squibb.

It is clear that trial 31-98-217 / 31-98-304-01 failed to recruit patients in Western Europe (except for France) so the patients came mostly from Russia, Poland, Bulgaria, and Hungary. This is in line with what are known as ‘rescue trials’: when the recruiting fails in USA or Western Europe and a trial is about to fail completely the trial is ‘rescued’ in countries of Eastern Europe where apparently enough patients are available. This alarmed the EMEA, because some of the countries concerned had not yet been given GCP inspections for Centralised Procedure applications. Serious problems were identified, but apparently the focus of the investigations was on the validation of the study results only; the ethics of the placebo use were not evaluated during the inspections. The inspection did mention the vulnerable position of the patient group before starting the inspection, but eventually did not attach any conclusions to this. In both trials health problems were provoked, such as the worsening of schizophrenia and psychiatric relapses which can cause irreversible harm.

It should however be noted that there was no difference here between the trials in the US and those in low and middle-income countries, and that most of the trials identified in this case study were conducted in the US alone.

This case study on Abilify highlights the fact that European authorities devote little attention to the ethical aspects of the clinical trials, resulting in unethically tested medicines being approved for the EU market. However, another cause for concern in this case study is that the overall quality of the submitted trials was really poor: of the six long-term trials submitted to the EMEA, two were excluded because of lack of quality, one was invalidated because of non-compliance with GCP and two others are seriously criticised by the inspection but were nonetheless accepted by the EMEA to support long-term efficacy.

5. Case study Olmetec

5.1. Background information on the drug

There are two Olmetec products:

- Film coated tablets of 10, 20 or 40 mg. Olmetec with active ingredient olmesartan medoxomil
- Olmetec Plus, the active ingredient is the same but this is an 'additional strength/form' and is known as hydrochlorothiazide.

Olmesartan medoxomil and the olmesartan medoxomil/hydrochlorothiazide combination are both indicated for the treatment of hypertension and are currently available in many countries, including the United States.[52] Olmesartan medoxomil is in a class of anti-hypertensive drugs called angiotensin II receptor blockers (ARBs). The second component of the combination product, hydrochlorothiazide, is in a class of drugs called thiazide diuretics. Comparator drugs: valsartan, losartan, and candesartan[53]

- For Olmetec, the applicant initiated the "Mutual Recognition Procedure" (MRP) to obtain market authorisation for EU Member States. In Europe the MA (marketing authorisation) holder is Sankyo Pharma GmbH, Munchen, Germany. The RMS (Reference Member State) is Germany, it was approved by the German approval authority The Federal Institute for Drugs and Medical Devices (Bundesinstitut für Arzneimittel und Medizinprodukte, BfArM)[54] on March 30, 2003.
- Olmesartan medoxomil was earlier approved by the FDA for the US market on 4/5/2002 under the brand name Benicar.

Olmetec alias Benicar is developed by Daiichi Sankyo but is also marketed by Pfizer in several countries. And in April 2005, Sankyo granted Schering-Plough exclusive rights to market olmesartan in Bolivia, Peru, Chile, Argentina, Paraguay and Uruguay. In addition, Schering-Plough and Sankyo will co-market the product in Mexico,

[52] The ClinicalStudyResults.org database somehow states that olmesartan is not approved in the United States. However, olmesartan medoxomil alone was approved May 2002 and olmesartan medoxomil plus hydrochlorothiazide was approved by the FDA in May 2003.

[53] The Medical Review of the FDA states on page 19: "There is a pretty good argument that olmesartan medoxomil is not demonstrably different from other members of its class, so it should share the same claim for use in mild-to-moderate hypertension, as long as any of them do'. Based on this statement it is fair to say that olmesartan is a 'me-too'."

[54] Website Bundesinstitut für Arzneimittel und Medizinprodukte, BfArM http://www.bfarm.de/

Venezuela, Panama, Costa Rica, Honduras, El Salvador, Guatemala, Nicaragua and the Dominican Republic.[55]

5.2. Database records with Olmetec trials

Table 9: Free available information on Olmetec trials on the internet .

Websites	Description	URL
The EMEA website	Not relevant (no central procedure)	
The BfArM website	No info available	
The FDA website	Approval letters, medical review, chemistry review, statistical review, clinical pharmacology biopharmaceutics review, and administrative document(s) & correspondence.	[56]
The Company Website	No clinical trial Registry or clinical trial results on the website of Daiichi Sankyo	
The Company Website	For clinical trial registry Pfizer refers to www.ClinicalTrials.gov and for the clinical trial results Pfizer refers to ClinicalStudyResults.org	
Clinicaltrials.Gov website	This US register contains 20 records of Phase III trials on olmesartan, recruiting (8) and completed/ongoing (12).	[57]
The Cochrane library	Three records, not available for free to the general public.	[58]
*meta*Register of Controlled trials	All 28 trials on olmesartan link to the ClinicalTrials.Gov website (some doublers).	[59]
ClinicalStudyResults.org	Two hits on olmesartan, and the statement that 'olmesartan is not approved in the United States' (?)	[60]
CenterWatch	No info	[61]

It is important to note that the National Public Assessment Report (NPAR) on Olmetec is not available. The German approval authority BfArM has no obligation to publish the national public assessment report (NPAR) on Olmetec. According to

[55] News release Schering-Plough, 8 April 2005, 'Schering-Plough and Sankyo Enter License Agreement for Olmesartan in Select Latin American Territories', http://www.schering-plough.com/schering_plough/news/release.jsp?releaseID=740164

[56] FDA website, http://www.fda.gov/cder/approval/index.htm

[57] Clinicaltrials.Gov website, http://clinicaltrials.gov/ct/screen/SimpleSearch.

[58] The Cochrane library, http://www.mrw.interscience.wiley.com/cochrane/cochrane_search_fs.html?mode=startsearch&products=all&unitstatus=none&opt1=OR&Query2=&zones2=article-title&opt2=AND&Query3=&zones3=author&opt3=AND&Query4=&zones4=abstract&opt4=AND&Query5=&zones5=tables&FromYear=&ToYear=&Query1=aripiprazole&zones1=%28article-title%2Cabstract%2Ckeywords%29&submit_go.x=21&submit_go.y=1

[59] Website *meta*Register of Controlled trials, http://www.controlled-trials.com/mrct/search.html.

[60] \website ClinicalStudyResults.org, http://www.clinicalstudyresults.org

[61] Website Centerwatch, http://www.centerwatch.com

article 34 (1a) of the German law for medicinal products (Arzneimittelgesetz/AMG) no NPAR has to be provided for marketing authorisation applications that were submitted before 6 September 2006. The NPARs after this date will be published 'on the AMIS open part reporting system'.[62] This means that no clinical trial information is available on all medicines approved by the BfArM before September 2006, which is a serious lack of transparency. The date of September 2006 is not in accordance with EU Directive 2004/27/EC, amending Directive 2001/83/EC. Article 21(4) of the amended Directive requires that all NPARs are made public by the national authorities and the deadline for implementation of the Directive at the national level was 30 October 2005.

There is also a lack of information on clinical trial results for olmesartan on company websites. For its clinical trial results, Pfizer refers to the website ClinicalStudyResults.org, however only two references can be found on olmesartan, one concerns a link to Clinicaltrials.Gov website and one leads to Clinical Study Synopsys A0021001, a trial conducted in the Philippines. This is very little company information on study results, especially when compared to the website of BMS, where 38 trial results on Abilify can be found.

Daiichi Sankyo is the sponsor of most trials, but this company is not disclosing trial results on olmesartan at all. In the case of olmesartan, the voluntary initiative of the industry is clearly not working ('Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases'[63] which says that "*The results of all clinical trials, other than exploratory trials, conducted on a drug that is approved for marketing and is commercially available in at least one country should be publicly disclosed on a free, publicly accessible, clinical trial results database, regardless of outcome*."

For this case study on Olmetec, only the medical review of the FDA gives information on trial results and the completed trials in the Clinicaltrials.gov.

5.3. Olmetec trials in low and middle-income countries

Table 10: In which low and middle-income countries is olmesarten tested?

Trial identification	Source, status and location	Title, sponsor, design and Location of the trials
NCT00151775	CT.gov	Assessment of efficacy and safety of olmesartan medoxomil in children and adolescent patients with high blood pressure
	Recruiting	Daiichi Sankyo, placebo-controlled, post trial access one

[62] E-mail correspondence of 31 October 2007, with Dr. Birka Lehmann, Director and Professor, Head of Licencing Division 3, Bundesinstitut für Arzneimittel und Medizinprodukte.

[63] http://clinicaltrials.ifpma.org/wps/PA_1_1_12E/Final_Joint%20PositionPortal_3.pdf

		year, children ages 1-16
	location	US, Argentina, Brazil, Chile, Colombia, India, Kenya, Peru, South Africa, Uganda, and Zambia (recruiting)
NCT00139698	CT.gov	Olmesartan alone or in combination with hydrochlorothiazide in subjects with mild to moderate essential hypertension (OSCAR)
	completed	Pfizer, Open label, treatment mild to moderate hypertension.
	location	Colombia (5 Pfizer centres), Ecuador (2), Hong Kong, Indonesia (4), Malaysia (2), Philippines (2), Singapore (2), Taiwan (4), Thailand (5), Turkey (5).
NCT00141453	CT.gov	Olmesartan Reducing Incidence of End Stage Renal Disease in Diabetic Nephropathy Trial
	ongoing	Daiichi Sankyo, placebo-controlled.
	location	China and Japan
NCT00362960	CT.gov	Olmesartan medoxomil and diabetic nephropathy
	completed	Daiichi Sankyo, active control is Losartan,
	location	Czech Republic (3), Estonia (1), Germany (3), Netherlands (1), Poland (10), Slovakia (7) and Spain (2),
NCT00430508	CT.gov	Use of the combination of olmesartan and hydrochlorothiazide in essential hypertension
	upcoming	Daiichi Sankyo Europe,
	location	Recruitment will probably will take place in Germany, Bulgaria, France Spain, Ukraine, Czech Republic, and Poland.
NCT00382213	CT.gov	A randomised, double-blind study to compare the effects of olmesartan medoxomil versus placebo in patients with established atherosclerosis
	completed	Daiichi Sankyo, placebo-controlled, patients will be randomised to receive either olmesartan medoxomil or placebo for one year.
	location	Location unknown.
A0021001	Clinicalstudy.org	A multi-centre, open-label, dose-titrating, 8-week study evaluating the efficacy, tolerability and safety of olmesartan medoxomil 20 mg and 40 mg in Filipino subjects with mild to moderate hypertension
	completed	Pfizer, open label, September 2004 till 13 January 2005.
	location	7 centres in the Philippines.
SE-866-10-01 1 year	Medical review FDA for approval	A multi-centre, double-blind long term safety, efficacy, and tolerability study of the oral angiotensin II-antagonis CS-866 in patients with mild to moderate essential hypertension (prolongation of study SE-866-10)
	completed	Sankyo Pharma,
	location	Germany and Poland
SE-866-10-01	Medical review	A multi-centre, double-blind long term safety, efficacy, and

2 year	FDA for approval	tolerability study of the oral angiotensin II-antagonis CS-866 in patients with mild to moderate essential hypertension (prolongation of study SE-866-10-01
	completed	Sankyo Pharma, placebo-controlled, long term study of 52 weeks, trials subjects received 5, or 10, or 20 mg of olmesartan or olmesartan +HCTZ or a placebo alone.
	location	42 sites in Germany and Poland with a total of 462 patients.
866-09	Medical Review FDA	Randomised, double-blind, placebo-controlled, mono-therapy, safety and efficacy studies with patients with essential hypertension
	location	EU: Germany, Czech Republic and Poland
866-17	Medical review FDA	Randomised, double-blind, placebo-controlled safety and efficacy studies with patients with essential hypertension.
	location	EU: 12 sites in Germany and Czech Republic.

Table 11: Clinical trials submitted for FDA approval

Study	Placebo use	Region	No. of patients receiving olmesartan (at start)	No. of patients receiving placebo	Duration
866-204	Yes	US	286	48	8 weeks
866-305 plus extension	Yes	US	435	91	In total 1 year
866-306 plus extension	Yes	US	341	116	8 weeks plus 4 months open label extension
866-06	Yes	EU*	50	26	6 weeks
866-09	Yes	EU: Germany, Czech Republic and Poland	682	110	12 weeks
866-10 plus long term extension	Yes	EU: Germany and Poland	526	93	12 weeks, plus 40 weeks
866-11	Yes	EU*	221	71	12 weeks
866-17	Yes	EU, Germany and Czech Republic	164	164	12 weeks
866-18	Yes	EU*	165	161	12 weeks
866-19	Yes	EU*	160	156	12 weeks
866-20	Yes	EU*	148	143	12 weeks

EU is the only indication for these trials, but as the other trials in this series are conducted both in Germany and Eastern European countries it is likely that these are also conducted in Eastern Europe.

The studies in table 11 were Pivotal for the FDA approval, although they were not conducted in developing countries. They all involved randomised, double-blind, placebo-controlled, monotherapy, safety and efficacy studies with patients with essential hypertension.

5.4. Information availability on ethical considerations

The available records on trials conducted in low and middle incoming countries are used to answer the following questions:

- What are the ethical considerations in these trials?
- How is the informed consent guaranteed?

- How is post-trial access handled?
- Is there an explanation for the use of vulnerable patients?
- How can the use of a placebo be justified?
- What is the benefit for the population and does it outweigh the risks?

Table 12: Olmesartan tested in trial in low and middle-income countries and the available information on ethical considerations.

Trial Identification	Source	Info on ethical considerations	Info on informed consent	Info on post trial access	Vulnerable patients/ explanation	Placebo use/ justification	Info about benefit for population	No. patients/ Year trial start
NCT00151775	Ct.gov	No	No	Yes, up to 1 year	Yes/No (children 1-16)	Yes/no[1]	No	240, 2005
NCT00139698	Ct.gov	No	No	No	No	No/no	No	410 2005
NCT00141453	Ct.gov	No	No	No	No	Yes/no[1]	No	400 2003
NCT00362960	Ct.gov	No	No	No	No	No/no	No	300 2003
NCT00430508	Ct.gov	No	No	No	No	No/no	No	-
NCT00382213	Ct.gov	No	No	No	No	Yes/no[1]	No	210 2000
A0021001	Clinicalstudy.org	No	No	No	No	No/no	No	67 2004
866-09	FDA	No	No	No	No	Yes/no	No	992
866-17	FDA	No	No	No	No	Yes/No	No	368

[1] Trial is placebo-controlled, but no justification given for placebo use.

In table 12 it is clear that an ethical issue is only covered in one trial description; namely that the children participating in trial NCT00151775 'can continue to take olmesartan medoxomil for up to one year in the study'.

Furthermore, no justification is given in any of the trial reports for placebo use, while five of the nine trials are placebo-controlled. Additionally, none of the reports mention informed consent procedures, whether vulnerable patients are included or what the benefit for the population is.

5.5. Olmetec trials reviewed on ethical aspects

The placebo use in the trials

Olmesartan appeared to be effective to treat mild to moderate hypertension, and on that ground it was approved by the FDA. It was not tested with the intention of proving that it is better than already existing treatments. The pivotal trials for the FDA are all mono-therapy, placebo-controlled trials meaning that in these trials it is not tested against comparative drugs, despite the fact that the Declaration of Helsinki specifically states that the effectiveness of a new method should be tested against those of the best current methods, unless there is a very good reason for not doing so. In the case of the olmesartan trials, no justification was given for the use of placebos. In some long term trials, patients with essential hypertension are treated with placebos for up to one year. As several effective treatments already exist, such as valsartan, losartan, and candesartan, these patients are being deliberately denied a standard treatment required by their condition. This leads to the question of whether all these participants really know that there is a 37%[64] chance that they will not receive get appropriate treatment? To avoid unnecessary risks for participating patients in clinical trials, the approval authorities should require that the efficacy of a drug must be proven by testing it against an active treatment with a relevant comparator drug.

There is no difference detected in placebo use in trials related to the location of the trial: placebo trials are common practice both in high-income countries and in low and middle-income countries.

Children as vulnerable group

In Clinical trial NCT00151775 to check the efficacy and safety of olmesartan medoxomil in children and adolescents, the vulnerability of this group of patients should have been addressed carefully.

- When trials include vulnerable patients, such as very young children as in this case (ages 1-16), the sponsor of the trial should specify the reason for involving vulnerable research subjects with a condition that renders them unable to give informed consent. And this reason must outweigh the risk of off-shoring trials with vulnerable patient groups to countries where the conditions for conducting trials are not ideal. This includes the countries where this trial was conducted: the US, Argentina, Brazil, Chile, Colombia, India, Kenya, Peru, South Africa, Uganda, and Zambia.
- The informed consent issue is very sensitive in this case as there is a relative big chance that the trial subjects may be poor, and their reason for joining lies in the fact that this is their only hope for treatment (or they may be motivated by the financial incentive). The children cannot provide consent for

[64] See table with the pivotal studies for the FDA approval on page.

themselves and there is a chance that the trial subjects and/or their parents are illiterate or may not speak the language of the investigator. The question remains unanswered whether there was a careful process to fully inform the parents or guardians of the children in this trial about the fact that this was a placebo-controlled trial? That there was already a licensed drug available which could have been used as comparator drug?

Post trial access
Clinical trial NCT001517755 contains a reference to post-trial treatment, in this trial the trial subjects are offered continual treatment for up to one year. The question here is also: will the drug be affordable for the trial subjects after this year? See also the paragraph on the patent case.

What are the benefits for the population?
A relevant ethical question in the case of trials in developing countries, such as the NCT00151775 trial, is whether the risks of the trial outweigh the benefits for the population. Is it relevant to test a drug to treat hypertension on very young children, such as one-year-olds, in a developing country? Is hypertension a condition that occurs in children in developing countries just as much as it does in developed countries? Is there a need for this drug in developing countries? Hypertension is a condition most often associated with adults, and among children it is very closely related to their current weight. Asia and Sub-Saharan Africa have the lowest rates of obesity in the world.[65] In other words, what is the justification for testing a treatment for hypertension on 1 to 16 years olds in developing countries?

Although the trial design is questionable; there may be a very good justification for it, but the fact is that there is no explanation given. To avoid speculations and misunderstandings, it is very important that these ethical considerations are made by the sponsor and are publicly available, so that stakeholders can discuss such a trial design in a well-informed manner.

5.6. Patent case olmesartan

In December 2006, some articles were published about Pfizer, who were threatening Orient Euro Pharma (OEP) Philippines, a subsidiary of EOP Taiwan, with legal action to prevent the commercialisation of the generic version of Olmetec.

OEP Philippines recently (2006) launched a generic version of olmesartan Medoxomil, known as olmezar. Olmetec, the version of olmesartan mexodomil combined with hydrochlorothiazide, is marketed by Pfizer in the Philippines. There is

[65] Reynaldo Martorell, Health and Nutrition Emerging and Reemerging Issues in Developing Countries), Brief 7 of 11, February 2001 http://www.ifpri.org/2020/focus/focus05/focus05_07.htm

currently no patent for olmesartan medoxomil on its own in the Philippines, Sankyo does have a patent application pending.

Pfizer prices (under brandname Olmetec):
20mg strength PHP 47.20 per tablet (0.75 Euro as per November 2007)

OEP Prices (under brandname Olmezar):
20mg strength PHP 18.53 per tablet (0.29 Euro as per November 2007)

Pfizer claims that:

- They have five years of data exclusivity since Olmetec was launched in the Philippines (January 2005) under article 39.3 of the TRIPS Agreement and the Intellectual Property Code of the Philippines (Republic Act No. 8293).
- OEP relied on Pfizer's undisclosed test data to register its generic version. However, some specialists who studied this issue came to the following conclusion: *In conclusion, there is no regime of test data/marketing exclusivity in the Philippines. The obligation of Article 39.3 of the TRIPS agreement was implemented into the Philippines with a pure test data protection regime that is in compliance with the TRIPS Agreement. Therefore Pfizer claims that they have 5 years of data exclusivity since Olmetec was launched in the Philippines is a misinterpretation of the current legal regime as mandated by the TRIPS Agreement and implemented in the Philippines and in most of the countries of the world.*[66]

It is not only academics, civil society associations and generics companies who are defending the proposition that the Philippines do not have to grant 'data/marketing exclusivity' on pharmaceutical test data when implementing its obligations under article 39.3 of the TRIPS Agreements, the TRIPS negotiating history also supports this.[67] In other words, Pfizer is misusing the TRIPS agreement to prevent a Philippine company from bringing a generic version on the Philippines market, thereby providing access to more affordable medicines.

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[66] " Pfizer threatens another Philippine generic company with litigation to stop legal competition: Pfizer is striking the Philippines generics industry again", Second view, 19 December 2006, http://secondview.blogspot.com/2006/12/pfizer-threatens-another-philippine.html

[67] the WHO's Commission on Intellectual Property Rights, Innovation and Public Health (CIPIH) 2006 report is clear about this:
"*Article 39.3, unlike the case of patents, does not require the provision of specific forms of rights. But it does oblige Members to protect undisclosed test or other data against unfair commercial use. It does not create property rights, nor a right to prevent others from relying on the data for the marketing approval of the same product by a third party, or from using the data except where unfair (dishonest) commercial practices are involved*.'

The prices charged by Pfizer for Olmetec are quite unaffordable. Olmetec has to be taken daily to be effective, and the most common dose is 20 mg. If you bear in mind that the minimum wage of a Filipino worker is currently 4.50 euros per day,[68] it is plain to see that a daily dose of 20 mg, costing 0.75 euros, is far too expensive for Filipinos. In addition to the issue of the relevancy (see paragraph on benefit for the population as above) this raises the issue of affordability/availability to the population. Pfizer conducted a clinical trial at seven sites in the Philippines (protocol A0021001) between September 2004 and January 2005. The available information about this trial does not include a reference to post-trial access for the trial participants.

The issue of testing drugs in countries where the majority of the population will not have access to these medicines should be addressed as one of the ethical considerations in the original trial protocol of this trial by Pfizer.

5.7. Case study analysis

There is no information made available on the clinical trials which were pivotal for the approval for European countries by the German approval authority through the publication of an NPAR. The reason for this is lies in the fact that this obligation only accounts for drugs approved by the German authorities after September 2006.

The Medical review report of the FDA, drawn up in the context of the approval of olmesartan medoxomil in 2002, does contain information about the pivotal clinical trials. However, information about the locations of the trials is very limited: the region 'Europe' is often not specified further, for example.

The information provided on company websites is non-existent. Daiichi Sankyo, the company that developed Olmetec, is not providing any data on clinical trials whatsoever and Pfizer, the co-sponsor, refers to two other websites containing two and 20 records on olmesartan respectively: it is important to note that the pivotal trials for the FDA approval are not among them.
The aim of this study is to assess the extent to which the ethical considerations relevant to the clinical trials that are off-shored to low cost countries, are addressed in the protocols. However, the original protocols are not available, and studying the abstracts of the protocols, mainly available though the Clinicaltrial.Gov website, no information whatsoever can be found regarding the ethical considerations. The same applies to the assessment reports of the FDA concerning Olmetec:

- Nothing about the informed consent procedures, not even in the trial with 1 to 16 year old trial subjects;
- Only in one trial (out of nine) was post-trial access secured up to 1 year.

[68] By Carlos Conde Published: 3 January 2007, International herald tribune, ‘Philippine business groups denounce minimum wage increase Higher minimum pay would be 'disastrous'', http://www.iht.com/articles/2007/01/03/business/PESO.php

- Although vulnerable patients are included, no explanation is given.
- Although 37% of the patients in the pivotal studies for the FDA approval received a placebo instead of an active treatment, the use of placebos is not justified
- In some trials the benefits to the population remain unclear and questionable, so no judgement can be made as to whether they outweigh the risks.

Although no information has been made available by the German approval authority about the pivotal trials for the European market authorisation, information from other sources at the very least raises questions about the ethics of clinical trials conducted in developing countries. And this raises the question of whether Olmetec was approved based on these trials? It is a serious shortcoming that monitoring of adherence to ethical principles by external actors, such as academics or civil society organisations, is impossible in the context of Olmetec.

6. Case study Seroquel

6.1. Background information on the drug

Seroquel (quetiapine fumarate)[69] is an antipsychotic belonging to the class of atypical antipsychotic drugs. It was first approved by the U.S. Food and Drug Administration (FDA) in 1997 for the treatment of schizophrenia in adults, and since 2003 it has also been approved for mania associated with bipolar disorder. It was developed by Zeneca, now AstraZeneca.[70] In October 2006, the FDA approved Seroquel for the treatment of patients with depressive episodes associated with bipolar disorder.

Seroquel works by targeting the specific areas of the brain (pre-frontal cortex, striatum, limbic system and anterior pituitary) that are affected by the illness, and helps to regulate the actions of the neurotransmitters – dopamine and serotonin – which play an important role in brain functioning.[71] Comparator drugs are: Zyprexa (olanzipine), Risperdal (risperidone), and Abilify (aripiprazole).

In May 2007, Seroquel XR, once-daily Extended-Release tablets, was approved for the *acute* treatment of schizophrenia in adult patients in the US. In November 2007, the FDA approved Seroquel XR for maintenance treatment of schizophrenia in adult patients. Beyond schizophrenia, there are ongoing clinical studies of Seroquel XR covering bipolar disorder, major depressive disorder and generalised anxiety disorder (GAD).

In August 2007, the Netherlands regulatory authority MEB (Medicines Evaluation Board) approved Seroquel XR for the treatment of schizophrenia in adult patients and granted market authorisation via the Mutual Recognition Procedure across Europe.

World Health Organisation (WHO) statistics indicate that schizophrenia affects about 24 million people worldwide, but the National Institute of Mental Health (NIMH) estimates the real figure to be more than double this: 1.1% of the population over the age of 18, which would mean 51 million people worldwide.[72] It subjects people to social isolation, poor quality of life and increased mortality (the possibility of a suicide

[69] Also called Seroquel (R) or Seroquel IR, which is the original formulation. Seroquel XR is sometimes referred to as Seroquel "SR" or "Sustained Release".

[70] AstraZeneca was formed on 6 April 1999 as a result of the merger of Astra AB of Sweden and Zeneca Group PLC of the UK. The corporate office is located in London, UK.

[71] Product description by AstraZeneca on the website: http://www.astrazeneca.com/productbrowse/4_77.aspx

[72] According to estimates made by the Dutch Trimbos Institute there are between 60,000 and 80,000 patients in the Netherlands. http://www.astrazeneca.nl/organisatie/persberichten/bericht_14.asp?strMenuPath=%2Fmenu

attempt is inherent in schizophrenia, and close supervision of high-risk patients should accompany drug therapy). It is a severe mental disorder, characterised by profound disruptions in thinking, affecting language, perception (hallucinations and delusions), and the sense of self. It is estimated that Seroquel has been used to treat more than 19 million patients worldwide since its launch in 1997. Seroquel is the number one prescribed atypical antipsychotic in the United States and global sales for Seroquel reached US$3.4 billion in 2006.[73]

6.2. Database records with Seroquel trials

Data on Seroquel trials was collected from the sources mentioned in the table below. It turned out that the clinical trial descriptions in the Clinicaltrials.gov database provide the best information on trial *locations* and provides the *largest number* of clinical trials including Phase I, II, III and IV trials (164 Seroquel trials, of which 54 phase III trials were sponsored by AstraZeneca). It has even redesigned its database since October 2007 and now shows the trial locations on a highly informative map.

In this case, the second-best source is the ClinicalStudyResults.org database, because although it contains slightly fewer trials (15) than the clinical trial database of the Company itself (20), the clinical trial reports provide much more information, such as trial locations. However, sometimes only the region is mentioned, i.e. 'Europe' without specifying the countries, or there is not even any indication given as to whether it involves countries in Western, Central or Eastern Europe. The reports also do not mention whether the trials described are pivotal trials for market authorisation.

In this case, the Dutch regulatory authority Medicines Evaluation Board (MEB) *does not comply* with Directive 2004/27/EC (amending Directive 2001/83/EC on human medicines article 21 (3) and (4) in March 2004) which implies that National Public Assessment Reports (NPARs) have to be made public by the national authorities. Dutch legislation that implemented this directive states that the MEB is obliged to make NPARs publicly available for market authorisation approvals submitted after 30 May 2005. In response to the question as to why the NPAR of Seroquel XR (approved in 2007) is not available the MEB answered that 'it is unfortunately not available yet, but will be available in the short term: probably in January or February 2008'.[74]

The Medical Review of the FDA for Seroquel approval in 1997 lists all the clinical trials and describes four studies in more detail, because they were considered

[73] AstraZeneca's Once-Daily SEROQUEL XR(TM) Extended-Release Tablets Approved in Netherlands for the Acute and Long Term Treatment of Schizophrenia, 29 August 2007 http://www.presseecho.de/wirtschaft/NA3731040035.htm (February 2008)

[74] E-mail Els Verbeek, College ter Beoordeling van Geneesmiddelen Medicines Evaluation Board, received 17 December 2007.

capable by design of providing meaningful data for the efficacy of quetiapine acutely ill schizophrenic patients: studies 0006, 0008, 0012 and 0013. The submission includes data from 14 trials. The FDA not only lists all the trials, it also lists all the investigators by name, the name of the research centre, address and the number of the trials carried out. These trials are almost exclusively conducted in high-income countries in Western Europe and North America. In this respect, the FDA is much more transparent than the EMEA or the national authorities in Europe.

However, no clinical trials could be identified for the approval of the one-a-day extended release tablets: Seroquel XR. The FDA website only provides label information on Seroquel XR approved in May 2007.[75] The label mentions that ' six-week placebo-controlled clinical trials for the treatment of schizophrenia' are the basis for the approval and that 951 patients received Seroquel XR and 319 a placebo. But no trial identification codes are mentioned and no further information is given about the trials, which is a serious shortcoming. As a result, none of the regulating authorities responsible for the approval of Seroquel XR, the FDA and the Dutch MEB, provide information about the underlying clinical trials.

Table 13: Publicly available information on the internet on Seroquel trials.

Source	Description
EMEA website/European Public Assessment Report (EPAR)	Not relevant (no central procedure for Seroquel)
The website of the Netherlands regulatory authority MEB (Medicines Evaluation Board[76])/NPAR	Relevant because the MEB is the authority responsible for the Mutual Recognition Procedure on Seroquel R in 2001 and Seroquel XR in August 2007. They are legally obliged to publish the National Public Assessment Report (NPAR) on Seroquel XR.
The European Product Index	No information on or reference to clinical trials.
FDA website[77]	Summary information on trials from Approval letters, Medical review, Chemistry review, Statistical review and Administrative Documents. The Medical review on Seroquel is based on 14 trials all conducted before 30 June 1996. There is no Medical Review available for Seroquel XR.
Company website: AstraZeneca clinical trials database[78]	This database contains 20 completed Clinical Trial Report Summaries, no locations are mentioned, 13 trials are placebo-controlled studies. It also mentions six identification numbers (no

[75] The FDA website only makes label information available on Seroquel XR approved in May 2007, see http://www.fda.gov/cder/foi/label/2007/022047lbl.pdf . It mentions that '6-Week Placebo-Controlled Clinical Trials for the Treatment of Schizophrenia' are the basis for the approval and that 951 patients received Seroquel XR and 319 a placebo. But no trial identification codes are mentioned which is a serious ommission

[76] In Dutch the 'College ter Beoordeling van Geneesmiddelen (CBG)', the National Public Assessment Reports (NPARs) should be published in the Geneesmiddelen Informatiebank. http://www.cbg-meb.nl/CBG/nl/people/geneesmiddeleninformatiebank/default.htm

[77] < http://www.fda.gov/cder/foi/nda/97/20639_seroquel_toc.htm (February 2008).

	titles or further information) of trials the results of which are awaiting further analysis. About half of the trials can also be found at Clinicaltrials.gov.
Company website: AstraZeneca product site[79]	No information on or reference to clinical trials.
Company website: Clinical trials site for U.S. residents only[80]	No information on trial results or recruiting for Seroquel.
Clinicaltrials.gov[81]	The clinical trial database Clinicaltrial.gov contains 54 phase III trials[82] with Seroquel as testing drug and AstraZeneca as sponsor. 37 of these studies are placebo-controlled. Eight of the 54 studies in this database are still recruiting. The trial descriptions in this database do mention countries as trial locations
Cochrane library[83]	Three reviews of quetiapine studies, referring to different trials and original research articles in medical journals. It is difficult to match the trials included in the review with the records from trial registers, however.
*meta*Register of Controlled Tials	Ten trial descriptions on quetiapine, partly overlapping with other sources.
ClinicalStudyResults.org	15 hits on Seroquel, these overlap with the trial results in the AstraZeneca clinical trials database, however the Clinical Study Reports in this database are more extensive and include locations (although sometimes not specified beyond 'Europe'. One hit on quetiapine to treat behavioral disorders in patients with Alzheimer's dementia, the sponsor of this study is Astellas Pharma Inc. No locations are mentioned. What is mentioned however, is that a total of 58 centres are included in this study .[84]

Sources: See footnotes and previous chapter.

6.3. Seroquel trials in low and middle-income countries

Table 14 lists all the clinical trials that could be identified in the different databases and websites in which Seroquel was tested in phase III trials sponsored by AstraZeneca. Without deleting the overlap, adding up all the trials results in a total of

[78] < http://www.astrazenecaclinicaltrials.com/article/511070.aspx> (2 February 2008)
[79] < http://www.seroquel.info> (2 February 2008)
[80] <http://www.az-trials.com> (2 February 2008)
[81] <http://clinicaltrials.gov/ct2/results?term=seroquel&spons=AstraZeneca&phase=2&pg=2 (2 February 2008)
[82] Including the phase I, II and IV trials this database contains 164 trials with Seroquel.
[83] <http://www.mrw.interscience.wiley.com/cochrane>
[84] <http://www.clinicalstudyresults.org/documents/company-study_1337_0.pdf> (3 February 2008)

113 trials. With deleting an estimated overlap, about 70 different trials can be identified (the 14 trials for the first approval by the FDA are not included in this figure). Most trials are conducted after 2000.[85] Of these 70 trials, 20 are multi centre trials partly or completely conducted low cost and middle-income countries.

The table below lists 20 Seroquel phase III trials conducted in research sites in low and middle-income countries, often simultaneously with research sites in the US or Western Europe Countries.

Table 14: Seroquel Phase III trials in low and middle-income countries.

Trial identifiers	Source	Countries (no. of sites)	Title
NCT00228462	CT	Bulgaria (3), Poland (2).	Relapse prevention, RoW: study to evaluate prevention of relapse in patients in stable chronic **schizophrenia** receiving either Seroquel or Placebo.
NCT00227395	CT	US (18 states), India (1), Malaysia (2), Philippines (4), Poland (2), Russia (2), Serbia & Montenegro (2), South Africa (1) and Ukraine (3).	Quetiapine fumarate (SEROQUEL) in the treatment of adolescent patients with **schizophrenia** and bipolar I disorder. *(open label, active treatment, no placebo)*
NCT00090324	CT	US (24), Germany (1), India (4), Philippines (4), Poland (2), Russia (2), Serbia & Montenegro (2), South Africa (1), Ukraine (3).	Quetiapine fumarate (SEROQUEL) compared to placebo in the treatment of adolescent patients with **schizophrenia**
NCT00206128	CT	US (18), Australia (1), Bulgaria (3), Canada (9), Estonia (3), Finland (3), Germany (7), Hungary (6), Italy (7), Latvia (3), Lithuania (1), Spain (6).	Immediate release (IR) to sustained release (SR) switching study: study of switching from IR Seroquel to SR Seroquel in outpatients with **schizophrenia**. *(no placebo)*
NCT00351910	CT	Australia (7), Belgium (7), Canada (5), Czech republic (9), Finland (4), France (10), Germany (4), Norway (7), Poland	A multi-centre, double-blind, randomised, parallel-group, placebo-controlled phase III study of the efficacy and safety of quetiapine fumarate sustained release

[85] It is difficult to remove the overlapping trials because different identification numbers are used for some trials. For example, the trial numbers in the Clinicaltrials.gov database differ from the codes used by AstraZeneca, but you can often find the other code in the text. This is very time consuming so we took some samples and estimated the overlap. The number of 70 to 75 trials does not take into account the 14 trials mentioned in the FDA review, because they were conducted before June 1996, and off-shoring clinical trials was not common practice before 1997.

		(6), Romania (2), South Africa (3), Sweden (8).	(Seroquel SRTM) in combination with an antidepressant in the treatment of patients with major depressive disorder with inadequate response to an antidepressant treatment. (*no schizophrenia and in combination with anti depressant)*
NCT00278941	CT	US (144), (Bulgaria (1), Canada (10), Puerto Rico (1), Romania (3), Russia 2), Slovakia (4), UK (3)	A multi-centre, double-blind, randomised-withdrawal, parallel-group, placebo-controlled phase III study of the efficacy and safety of quetiapine fumarate sustained release (SEROQUEL SR™) as monotherapy in the maintenance treatment of patients with major depressive disorder. *(no schizophrenia)*
NCT00206141	CT	Canada (9), Croatia (4), Estonia (3), Germany (2), Indonesia (3), Korea Rep. (2), Latvia (2), Lithuania (3), Malaysia (3), Norway (5), Philippines (4), Poland (8), Russia (12), Serbia & Montenegro (5), Taiwan (2), Ukraine (8).	Multi-centre, double-blind, randomised, parallel-group, placebo-controlled, phase III study of the efficacy & safety of quetiapine fumarate & Lithium as monotherapy in adult patients with bipolar depression for eight weeks & Quetiapine in continuation (Abbreviated). (*no schizophrenia)*
NCT00206115 but also known as 'study 132' or D1444C00132	CT CSR.org	Bulgaria (4), Greece (4), India (4), Indonesia (3), Philippines 5), Romania (3), Russia (2), South Africa (7).	A six-week, multi-centre, double-Blind, double-dummy, randomised comparison of the efficacy & safety of sustained-release formulation quetiapine fumarate (SEROQUEL) & placebo in the treatment of acutely Ill patients with **schizophrenia**
NCT00119652	CT	US (30), Australia (6), Chile (2), Colombia (1), Costa Rica (1), Greece (3), Mexico (2), Peru, (2), Romania (4), South Africa (4), Turkey (3).	Multi-centre, double-Blind, randomised, parallel group, placebo-controlled, phase III study of the efficacy & safety of quetiapine fumarate & paroxetine as monotherapy in adult patients with bipolar depression for eight weeks & quetiapine in continuation (Abbreviated) (*no Schizophrenia)*
NCT00322595	CT	Argentina (7), Bulgaria (6), Canada (15), Czech republic (10), Denmark (3), Finland (4), France	An international, multi-centre, randomised, double-blind, parallel-group, placebo-controlled, active-controlled study of the efficacy &

		(9), Germany (7), Mexico (3), Norway (3), Romania (3), Slowakia (6), South Africa (4), Spain (5), Sweden (5).	safety of sustained-release quetiapine fumarate (Seroquel SR™) in the treatment of generalised anxiety disorder (SILVER) *(no schizophrenia)*
NCT00600756	CT	Belgium, Brazil, Bulgaria, Denmark, Finland, Germany Italy, Mexico, Portugal, Romania, Russia, Spain, Switzerland, Turkey.	A one-year randomised, prospective, parallel, open comparison of subjective well-being in schizophrenic out-patients treated with quetiapine XR (SEROQUEL XR™) or oral risperidone at flexible dose in a naturalistic setting. *Open label, comparator*
NCT00107731	CT	US (45), Belgium (7), Bulgaria (4), Czech Republic (8), Finland(5), France (9), Germany (8), Hungary (6), Italy (15), Norway (7), Poland (17), Russia (3), South Africa (5), Spain (13), Sweden (7), Turkey (4), UK (7).	A multi-centre, randomised, parallel-group, double-blind, phase III comparison of the efficacy & safety of quetiapine fumarate to placebo When used as adjunct to mood stabilisers (lithium or valproate) in the maintenance treatment of bipolar I disorder in adult patients (Abbreviated) (*no schizophrenia)*
NCT00389064	CT	US (17), Czech Republic (5), Estonia (3), Poland (9), Russia (10), Ukraine (8),	A multi-centre, double-blind, randomised, parallel-group, placebo-controlled phase III study of the efficacy and safety of quetiapine fumarate sustained release (Seroquel SR) in the treatment of elderly patients with generalised anxiety disorder
NCT00388973	CT	US (14), Argentina (6), Estonia (3), Finland (7), Russia (8), Ukraine (8),	A multi-centre, double-blind, randomised, parallel-group, placebo-controlled phase III study of the efficacy & safety of quetiapine fumarate sustained release (Seroquel SR) in the treatment of elderly patients with major depressive disorder
NCT00314184	CT	US (30), Argentina (6), Bulgaria (3), Colombia (4), India (10), Lithuania (3), Malaysia (2), Mexico (3), Peru 1), Philippines (5), Romania (12), Russia (3), Taiwan (4), Thailand (1), Ukraine (8).	Multi-centre, randomised, parallel-group, double-blind, placebo-controlled phase III study of the efficacy & safety of quetiapine fumarate and lithium as monotherapy for up to 104 weeks maintenance treatment of bipolar I disorder in adult patients
NCT00314210	CT	US (57), Australia (5),	A multi-centre, double-blind,

		Canada (9), Finland (7), Germany (9), Hungary (6), Indonesia (2), Korea (1), Philippines (5), Russia (3), UK (11).	randomised-withdrawal, parallel-group, placebo-controlled Phase III study of the efficacy and safety of quetiapine SR as monotherapy in the maintenance treatment of patients with GAD following an open-label stabilisation period (*no schizophrenia)*
D1444C0004 But also referred to as 'study 004'.	CSR.org	26 centres in Europe (not further specified) and India.	A one-year, international, multi-centre, randomised, double-blind, parallel-group, placebo-controlled phase III study to evaluate prevention of relapse in patients in stable condition with **chronic schizophrenia** receiving either sustained-release quetiapine fumarate (SEROQUEL) or placebo
5077IL/0105	CSR.org AZ	38 clinical sites in Bulgaria (6), China (2), Croatia (2), Greece (4), India (6), Romania (5), Russia (10), and Turkey (3).	An international, multi-centre, double-blind, randomised, placebo-controlled study of the safety & efficacy of Seroquel™ (quetiapine fumarate) and lithium as monotherapy in the treatment of **acute mania**
5077IL/0104	CSR.org AZ	49 clinical sites in Argentina (12), Chile (3), China(2), Croatia (3), Estonia (3), Indonesia (4), Latvia (3), Lithuania (5), Philippines (4), Poland (6), and Taiwan (4).	An international, multi-centre, double-blind, randomised, placebo-controlled study of the safety & efficacy of seroquel™ (quetiapine fumarate) and haloperidol as monotherapy in the treatment of **acute mania**
5077IL/0100	CSR.org AZ	44 clinical centres in Belgium (4), Bulgaria (1),Canada (10), Germany (6), India (1), Romania (2), South Africa (8), Spain (7) and the United Kingdom (5).	An international, multi-centre, double-blind, randomised, placebo-controlled study of the safety & efficacy of Seroquel™ (quetiapine fumarate) as add-on therapy with lithium or divalproex in the treatment of **acute mania**

Sources: CT = ClinicalTrials.gov, CSR.org = ClinicalStudyResults.org, AZ = Clinical Trial Database of AstraZeneca
Bold = severe mental disorders for which placebo-controlled trials are unethical.
Italic= addition by SOMO

From the table above it becomes clear that almost all clinical trials are multi centre trials with research sites in high-income countries as well as in low and middle-income countries. A high number of research sites in the US, in particular, are

included. The research protocol in a multi-centre trial is identical, so no differences are expected between countries. It is not known how the number of trial participants are divided among the countries, only the number of research sites are known. In response to this case study, AstraZeneca has added to this information that almost half of the patients enrolled were indeed located in the USA and Canada; just over a quarter were in Eastern Europe; and the remaining quarter were distributed in approximately equal numbers across Western Europe, the Far East, South Africa, India and South America.[86]

An analysis of the trial descriptions does show a remarkable point, however: the placebo trials including schizophrenia patients, in particular, take place in low and middle-income countries. Placebo trials in high-income countries covered major depressive disorder, bipolar depression, generalised anxiety disorder, and bipolar I disorder. These are also severe mental disorders but this distinction justifies the question why placebo trials with schizophrenia patients are predominantly conducted in low and middle-income countries and the other disorders are not. This question also applies to 'acute mania', as these trials are carried out only in low and middle-income countries. A spokesman for AstraZeneca explained in response to this that almost all Western European Research Ethics Committees (RECs) no longer approve this kind of trials because of the ethical concerns and AstraZeneca is therefore compelled to look for locations outside Western Europe, as such placebo-controlled studies are still required by the EMEA and the FDA for market authorisation.[87]

Another remarkable point is that the two trials with elderly patients do not include high-income countries (except for the US). This can be related to the fact that Seroquel has a Black Box warning for elderly people, as is the case with other atypical antipsychotic drugs: *'Increased mortality in elderly patients with dementia-related psychosis. Elderly patients with dementia-related psychosis treated with atypical antipsychotic drugs are at an increased risk of death compared to placebo.* (…)etc.'[88] The trials with elderly patients clearly have a higher risk profile. This justifies the observation that trials with this higher risk profile are predominantly located in low and middle-income countries. Astrazeneca's response to this is that in the studies with elderly patients, those with dementia were specifically excluded in every country where the research took place.[89]

A press release of AstraZeneca of 18 May 2007, says that based on the data from study '132' and study '004' and data from other trials, regulatory filings for the

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[86] Dr Martin Brecher MD DMSc, Executive Director, Medical Science, AstraZeneca . In an email dated 13 February 2008.

[87] Spokesman AstraZenece Roeland van der Heide, by telephone 15 February 2008.

[88] Website FDA, http://www.fda.gov/cder/drug/InfoSheets/HCP/quetiapineHCP.htm and http://www.fda.gov/cder/drug/advisory/antipsychotics.htm (4 February 2008).

[89] Dr Martin Brecher MD DMSc, Executive Director, Medical Science, AstraZeneca . In an email dated 13 February 2008.

treatment of schizophrenia with Seroquel XR formulation were submitted to the authorities in the US, EU and other markets in 2006.[90] These two studies can therefore be therefore considered as pivotal for market authorisation. Study 132 is also known as 'D1444C00132'[91] or NCT00206115, and study 004, is in full 'D1444C0004'.[92] These studies will be discussed further on in this chapter.

6.4. Information availability on ethical considerations.

Up to now, we have looked at availability of database records on Seroquel trials (about 70) and the locations of these trials (20 in low and middle-income countries). Now we will be analysing the ethical aspects of these trials, focussing on the following questions:

- Does the trial information contain a statement of the ethical considerations?
- How is informed consent guaranteed?
- How is post-trial access dealt with?
- Is there special attention given to or protection for the participating vulnerable patients?
- How is the use of placebos justified?
- What is the benefit for the population where the research is carried out?

Without making a table as was the case in the other two case studies, the questions can be answered quite shortly: it turns out that no considerations can be found of the ethical considerations as listed above in the database records or clinical study reports on phase III Seroquel trials.

The Clinical Study reports found at the website ClinicalStudyResults.org provide the most extensive information in this case study of Seroquel. But once again, the Clinical Study reports do not contain the original trial protocols; these are not available for the public.

The title page of each study report contains the statement "This study was performed in compliance with Good Clinical Practice'. But it should be kept in mind that this document is a submission document and that this statement is therefore made by the sponsor of the trial itself and not by the authorities.

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[90] Press release AstraZeneca, May 18, 2007, 'SEROQUEL® Sustained Release Schizophrenia Data presented at ECP Congress in Madrid', http://www.astrazeneca.com/pressrelease/5310.aspx (4 February 2008)

[91] Website FDA, http://www.clinicalstudyresults.org/documents/company-study_2637_0.pdf (4 February 2008)

[92] Website clinicalstudyresults.org, http://www.clinicalstudyresults.org/documents/company-study_3348_0.pdf (4 February 2008)

Looking for example at the Clinical Study Report of study 132[93], no ethical considerations can be assumed from the report. This is worrying because the trial subjects are a vulnerable patient group; suffering from schizophrenia in an acutely ill state. These patients are additionally vulnerable, because the rights of trials subjects are less secure in poorer countries[94], in this case the Philippines, India, and Indonesia, which are developing countries. But rights are also less secure in Middle and Eastern European countries like Romania and Bulgaria, where this trial also took place. Vulnerable patient groups need special protection (§ 8, Declaration of Helsinki (DoH)). Unfortunately the report on study 132 is exemplary for all other reports or data base records on Seroquel trials: no attention is paid to the vulnerable position of schizophrenia patients, especially those in poor countries.

None of the database records or reports explain how the informed consent procedure is designed. It must be difficult to obtain informed consent from acutely ill patients suffering from schizophrenia and explain to them they have a 20% chance of receiving a placebo, as was the case in this trial. Other aspects which also hamper a correct informed consent procedure in developing countries include poverty, illiteracy and the unequal dominance position between doctor and patient . Some references were found in the context of informed consent: sometimes it is mentioned that patients withdrew their consent during the trial. So procedures must be in place but they are kept undisclosed. Also none of the reports or database records address post-trial access: the right of continued treatment once a trial is over. It is unclear whether the schizophrenia patients are assured of access to the best proven method as identified by the study (see § 30 of the DoH).

On average, the trial subjects in the identified placebo-controlled trials have a 20 to 30 percent chance of receiving a placebo. 75% of the identified trials by SOMO in this case study are placebo-controlled trials. In the case of schizophrenia patients, in particular, there has been a long debate in the medical journals about placebo use in trials and the irreversible harm that can be done by withholding active treatment from patients: in schizophrenia, clinicians believe that each relapse contributes to long term deterioration and therefore that patients exposed to either placebo or an inactive new treatment may be put at a disadvantage in the long run if the trial leads to an additional relapse. However, some say that the risks of placebo use are limited to the period during which subjects are participating in the protocol and do not include long-term disability or progression of the underlying pathology. But there is agreement that the use of placebos in schizophrenia research presents various risks. Several authors

[93] Website clinicalstudyresults.org, http://www.clinicalstudyresults.org/documents/company-study_2637_0.pdf (4 February 2008)

[94] See for example the publications: Keya Acharya, 'HEALTH-INDIA: Prime Destination for Unethical Clinical Trials', http://www.ipsnews.net/news.asp?idnews=40472 or: SOMO Briefing paper on ethics in clinical trials, part 1, Examples of unethical trials, December 2006, http://www.somo.nl/html/paginas/pdf/Examples_of_unethical_trials_dec_2006_NL.pdf

underline the proposition that placebo use must be justified: 'investigators should be routinely required by regulatory agencies, institutional review boards, and funding agencies to justify in writing the use of placebos in any study that uses them. This explanation should be part of all proposals, protocols, and published papers. (…)The change needed most is the enforcement of ethical guidelines at regulatory agencies, such as the FDA, which review research that may never be published. The FDA should conduct an ethical review of every study submitted to it. Any study proposing to use placebos in place of effective treatments without making a persuasive ethical justification should be disapproved. Studies involving unethical use of placebos should be ignored in the drug-approval process.'[95] Note that this quote is dated 1994 and that since then apparently nothing has changed. In none of the trial descriptions for Seroquel could a justification for placebo be found.

Schizophrenia occurs in all societies, regardless of region, colour or culture etcetera, so testing for better treatments benefits populations around the world.

In response to this case study, Astrazeneca provided SOMO with a reference to an article in a scientific journal in which a number of ethical aspects of study 004 are addressed, such as a precaution to protect the vulnerable patients group and information about the informed consent procedure. Even more interesting than this, however, is that this article ends with an evaluation of the ethics of this trial:
An important consideration for future relapse trials is that although the use of a placebo arm is important to demonstrate efficacy or lack of efficacy for any treatment, its use in schizophrenia clinical trials is being questioned owing to the severe nature of the condition and the considerable negative impact of relapse on illness severity and future treatment. However, it is notable that the regulatory authorities in the countries in which this study was conducted required the use of a placebo in this study to determine the absolute efficacy of quetiapine XR in reducing the risk of relapse. (…)For future studies, it may, therefore, be appropriate to investigate the differences between formulations of the same antipsychotic or versus an active comparator. [96] The investigators responsible for the trials therefore also questioned the appropriateness of the placebo use, because it is in fact unnecessary.

6.5. The ethical aspects of the identified pivotal trials

This section will be analysing in greater detail the ethical aspects of two pivotal trials submitted for market authorisation by AstraZeneca in 2006. Based on these trials

[95] 'The Continuing Unethical Use of Placebo-controls', The New England Journal of Medicine, Volume 331:394-398, 11 August 1994, number 6. Kenneth J. Rothman, Karin B. Michels.

[96] Prevention of Schizophrenia Relapse with Extended Release Quetiapine Fumarate Dosed Once Daily: A Randomized, Placebo-Controlled Trial in Clinically Stable Patients. Peuskens J et al. Psychiatry (Edgemont) 2007 4(11):34-50. It can be viewed online using the following link: http://www.psychiatrymmc.com/prevention-of-schizophrenia-relapse-with-extended-release-quetiapine-fumarate-dosed-once-daily-a-randomized-placebo-controlled-trial-in-clinically-stable-patients/#more-176

(and other data) the Dutch Medical Evaluation Board approved Seroquel XR (extended release) and granted market authorisation via the Mutual Recognition Procedure for various European countries. The question is, was the approval based on ethical trials or not?

Table 15: Two pivotal studies submitted for approval

Trial identifiers	Source	Countries (no. of sites)	Title
NCT00206115 but also known as 'study 132' or D1444C00132	CT CSR.org	Bulgaria (4), Greece (4), India (4), Indonesia (3), Philippines 5), Romania (3), Russia (2), South Africa (7).	A 6-Week, multi-centre, double-Blind, double-dummy, randomised comparison of the efficacy & safety of sustained release formulation quetiapine fumarate (SEROQUEL) & placebo in the treatment of acutely ill patients with schizophrenia
D1444C0004, but also referred to as 'study 004'.	CSR.org	26 centres in Europe (not further specified) and India.	A one-year, international, multi-centre, randomised, double-blind, parallel-group, placebo-controlled phase III study to evaluate prevention of relapse in patients in stable condition with chronic schizophrenia receiving either sustained-release quetiapine fumarate (SEROQUEL) or placebo

Study 132 (or NCT00206115 or D1444C00132)
The first patient enrolled on November 2004 and the last patient completed the study on 12 December 2005. The sponsor's responsible medical officer was Martin Brecher. This study was conducted at 39 centres in South Africa, Russia, Romania, Bulgaria, Greece, India, Indonesia, and the Philippines. The distribution of the patients over the countries is unknown.

The primary objective of this study was to demonstrate superior efficacy of Seroquel XR for three doses, (400, 600 or 800 mg/day), compared to placebo in the treatment of patients with schizophrenia. Superior efficacy is proved when each of the doses demonstrates a higher response rate compared to placebo.[97] It should be borne in mind that this trial was not for a new experimental drug, it was to test a slightly different formulation of Seroquel (one-a-day formula with extended release)

> *Current ethical principles of conduct for biomedical research specifically prohibit designs that withhold or deny the best proven diagnostic and*

[97] Definition of placebo from Wikipedia: a treatment without intrinsic therapeutic value, but administered as if it were a therapy, either in medical treatment or in clinical trials.

therapeutic treatment to any participant in a clinical study, including those individuals who consent to randomisation into a control group[98]*.*

The patient group consisted of male and female patients between 18 and 65 years of age with acute schizophrenia. 115 patients were enrolled in the placebo group, 111 in the 400 mg/day group, 111 in the 600mg/day group, 117 in the 800mg/day group and 119 in the 40mg/day Seroquel IR group. The patients received a double-blind treatment for up to six weeks, at the end of treatment at day 42 the change in the 'CGI Severity of Illness Score' is measured.

It is clear that the trial design is in conflict with current ethical principles: in this trial 115 patients are denied the best proven diagnostic and therapeutic treatment. It seems unnecessary to expose 115 patients to risks only to test a different formulation of an already proven medicine. No justification is given for the placebo use.

Study 004 (or D1444C0004)
The first patient enrolled on 15 March 2005 and the last patient completed the study on 6 April 2006.

The trial was designed as a one-year trial (this is a long term treatment) but was stopped prematurely after 45 relapses. 327 patients had been enrolled when the study was stopped. 26 centres in Europe and India participated. Enrolment was competitive between countries and centres. In contrast with other Clinical Study reports the European countries are not specified in greater detail. In response to this, AstraZeneca adds that next to India patients from centres in Bulgaria, Poland, Russia and the Ukraine were enrolled.[99]

The primary objective of this study was to demonstrate superior efficacy of Seroquel XR to placebo by simply measuring the time to the first psychiatric relapse. In other words, to prove efficacy the patients in the placebo group must experience relapses in their psychiatric conditions more frequently and in shorter term than the patients in the Seroquel XR group.

The patients in this trial were chronic schizophrenia patients in a stable condition. The patients were scheduled to be treated for one year or until relapse. The study was terminated at the recommendation of the Data and Safety Monitoring Board (DSMB) after 45 observed relapses. The reason given was that at this stage of the study, the

[98] Theodore J. La Vaque and Thomas Rossiter, ' The Ethical Use of Placebo-controls in Clinical Research: The Declaration of Helsinki', in: Applied Psychophysiology and Biofeedback, 23-37, Subject Collection Behavioral Science, 3 November 2004. http://www.springerlink.com/content/v351387828jj33w4/

[99] Dr Martin Brecher MD DMSc, Executive Director, Medical Science, AstraZeneca . In an email dated 13 February 2008.

difference between Seroquel XR and the placebo had already achieved statistical significance.
After the open label stabilisation period 171 patients were randomised: 87 received placebo and 84 patients received Seroquel XR. The patients were predominantly diagnosed as paranoid schizophrenics. 36 patients in the placebo group experienced a psychiatric relapse (41.4% in four to seven months) and nine relapses (10.7%) in the Seroquel XR group. Recalculated for a six-month period: the estimated risk of relapse at six months was 68.2% for the placebo group and 14.3% for the Seroquel XR group, which proves the efficacy of Seroquel XR.
However, during the randomised phase, one patient died. A 25 year-old man committed suicide after 173 days of placebo treatment. Hospitalisation due to worsening of schizophrenia was required by 8.3 % of patients on placebo.

The risks of putting schizophrenic patients on placebo was demonstrated the hard way in this trial. But even in this case, no evaluative word in this Clinical Study Report was devoted to ethics or to a justification of the placebo use.[100] [101]

6.6. Case study analysis

Reading between the lines of Clinical Study Report of trial no. D1444C0004 you see a quite dramatic and unethical trial. However, market authorisation was granted on the basis of this trial . Study 132 was also unethical, taking the Declaration of Helsinki as benchmark.[102] The two pivotal trials described underline the fact that the ethics of drug testing is not a priority issue when granting drugs EU or US marketing authorisation.

In addition, the National Public Assessment Report for this case study is not available, even though this is required by law. This is a serious shortcoming of the Dutch regulatory authority that approved Seroquel XR for the European market. In the case of Seroquel XR, none of the regulatory authorities has provided data about the pivotal trials.
SOMO identified 20 Seroquel trials (including Seroquel immediate release as well as extended release) which were conducted in low and middle-income countries. There is a noticeable difference between the trials partly conducted in high-income countries and the trials which are exclusively conducted in low and middle-income countries.

[100] Website clinicalstudyresults.org, http://www.clinicalstudyresults.org/documents/company-study_3348_0.pdf (4 February 2008)
[101] Press release AstraZeneca,18 May 2007, 'SEROQUEL® Sustained Release Schizophrenia Data presented at ECP Congress in Madrid', http://www.astrazeneca.com/pressrelease/5310.aspx (4 February 2008)
[102] Astrazeneca refers in this respect to the EMEA Note for Guidance on the Clinical Investigation of Medicinal Products in the Treatment of Schizophrenia and the International Conference on Harmonisation (ICH) Topic E10, Choice of Control Group in Clinical Trials, EMEA. Dr Martin Brecher MD DMSc, Executive Director, Medical Science, AstraZeneca . Via email dated 13 February 2008.

The latter clearly have a higher risk profile: the placebo trials with schizophrenic patients or treating acute mania are almost exclusively located in low and middle-income countries[103]. AstraZeneca explains this by saying that almost all Western European Research Ethics Committees (RECs) no longer approve this kind of trials because of the ethical concerns and AstraZeneca is therefore compelled to look for locations outside Western Europe as these placebo-controlled studies are still required by the EMEA and the FDA for market authorisation.[104]

No reflections on ethical considerations can be found in the database records on Seroquel trials, which is a serious shortcoming. Ethical considerations can be found in medical journals.

[103] Except for the US.
[104] Spokesman AstraZenece Roeland van der Heide, by telephone 15 February 2008.

7. Outcomes of an expert meeting

On 6 November 2007, an expert meeting took place in the European Parliament to discuss the problems and risks of performing clinical trials in low and middle-income countries and the measures that can be taken at EU level to combat unethical trials. The expert meeting was organised by Ms. Dorette Corbey, Member of the EU Parliament for the Dutch Labour Party, in collaboration with the Dutch civil society organisation WEMOS. The participants included representatives of the EMEA and national drug authorities of EU Member States, the pharmaceutical industry, civil society organisations, research institutions, and other experts.

Several issues were discussed and some concrete suggestions were made by some of the participants. These suggestions included the following:

1. Ethics should become more of a priority issue when granting drugs EU marketing authorisation. Political and financial support is required to prioritise clinical trial ethics throughout the EU in a coordinated way.
2. The latest version of the DoH should be further operationalised. In consultation with experts from low and middle-income countries, tools should be developed to better assess the ethical aspects of clinical trials when granting a drug marketing authorisation.
3. Post-trial treatment arrangements are very complex, but this is a key aspect of the DoH that needs to be operationalised in cooperation with the involved countries as well.
4. Regulators in the EU and in low and middle-income countries should cooperate and mutually reinforce each others' capacity on clinical trial ethics.
5. It is unlikely that EU regulators have sufficient information to assess whether a drug has been tested in accordance with ethics guidelines, as they do not routinely seek access to audit reports nor do they have sufficient human and financial resources to check the ethical aspects of the registration file of a drug seeking marketing authorisation.
6. Penalties are needed to combat unethical research. If research does not fulfil ethical standards, it usually cannot fulfil scientific standards either. The legal framework for the imposition of penalties in the case of unethical clinical trials carried out in non-EU countries is unclear. Legislation and tools to implement this legislation need to be developed.[105]

[105] Outcomes copied from: 'Final Report of the expert meeting 'Clinical Trials and protection of trial subjects in low and middle-income countries', December 2007, by WEMOS.

Regarding the use of placebos, a pharmaceutical industry representative commented that the industry is not particularly happy about the use of placebo-controlled trials for schizophrenia drugs either, but that they are required by the EMEA for marketing authorisation. EMEA representatives, on the other hand, stated that for schizophrenia drugs the use of placebo-controls may need to be reconsidered.

The EMEA performed about 40 GCMP inspections outside Western Europe last year.

8. Conclusions and recommendations

The European authorities granting market authorisation for medicines require, in principle, that pharmaceutical companies conduct placebo-controlled studies (also for schizophrenia treatments); however, the Research Ethics Committees (RECs) in most Western European countries no longer approve this kind of trial due to the unethical aspects involved. As a result, the industry feels compelled to look outside of Western Europe, as these placebo-controlled studies are still required by the EMEA and the FDA for market authorisation. In doing so, the European authorities not only grant market authorisation based on unethical clinical trials, but they actually induce the offshoring of unethical trials to countries outside Western Europe, namely low and middle-income countries in Central and Eastern Europe, Latin America and Asia (India and China). SOMO's study reveals that this is indeed the case with placebo-controlled studies involving stable patients and acutely ill patients diagnosed with schizophrenia and acute mania.

→ Recommendations

- There should be no discrepancy between the requirements of the European authorities and the ethical criteria of national Research Ethics Committees. Discrepancies lead to unethical trial designs being necessarily offshored by pharmaceutical companies to countries outside Western Europe, including developing countries.
- Furthermore, there must be no discrepancy between the ethical criteria used to approve research protocols in Western Europe and in low and middle-income countries to avoid the creation of 'easy countries'. To achieve this it is necessary that RECs and regulators in the EU and in low and middle-income countries cooperate and keep each other informed about the criteria used.

By including the latest version of the Declaration of Helsinki, the European legislation for clinical trials states that placebo-controlled studies may only be conducted if no proven alternative therapy exists or in other special circumstances. This also applies to clinical trials conducted outside the European Community on medical products destined to be authorised within the EC. Yet the EMEA 'Note for Guidance on the Clinical Investigation of Medicinal Products in the Treatment of Schizophrenia' and the ICH guideline on the 'Choice of Control Group in Clinical Trials' state that, in principle, placebo-controlled studies are required although it is recognised that suitable alternative designs may be developed. In short, EU legislation says "no placebo trials unless…", and EMEA says "in principle placebo trials are required …". This inherent contradiction means that European legislation as set out in EU directives is not being fully implemented. Companies refer to the above-mentioned

EMEA Note and the ICH guideline as justification and explanation for their use of placebos, complaining that they are forced to conduct such tests even if they do not want to.

→ Recommendations

- The European directives for the ethical conduct of clinical trials for medicines destined for authorisation within the Community must be implemented in the EMEA's supporting guidelines and guidance and must be in line with the Declaration of Helsinki. European authorities should specifically ask for a justification for the use of placebos, and without a sound justification, submissions should not be taken into consideration.
- The pharmaceutical companies should take more responsibility and proactively develop alternative research methods to replace the placebo-controlled trials instead of hiding behind the requirements of the EMEA and the FDA. Some companies say they want to do things differently, but they should demonstrate this by submitting alternative studies to the EMEA as test cases. At this stage, the EMEA has unlocked the door, but it is up to the companies to open it.
- The pharmaceutical companies should, on their own initiative, address the ambiguous situation at the European authorities. They should seek for a solution on a European level rather than solving the problem themselves by off-shoring those trials to other countries, that are not approved by Western European ethical committees.

The offshoring of clinical trials outside Western Europe for medicines destined for the EU market has experienced a significant upsurge in recent years. Recent studies in Latin America and India show that local regulatory authorities and Research Ethics Committees have not been strengthened to cope with the increase; one-quarter of the research protocols are not approved by an REC, and none of the RECs investigated in Latin America monitor the implementation of the approved trials. The EMEA only performs about 40 GCMP inspections a year outside Western Europe.

→ Recommendations

- The European authorities can not blindly rely on local authorities, as is currently the situation.
- European authorities as well as the pharmaceutical companies should make efforts to strengthen local capacity for ensuring clinical trial ethics in countries where the upsurge has taken place; more cooperation and information sharing is needed.
- The EMEA should conduct more GCMP inspections outside Europe.

Transparency about clinical trials in low and middle-income countries is insufficient, both with regard to the amount of trials covered in public databases and with regard to the amount of information on ethical considerations for each trial. Online trial registries are far from complete, rendering it impossible to find information on trials conducted in low and middle-income for the major drugs on the EU market. The pharmaceutical industry's voluntary initiatives to increase transparency have clearly fallen short in this respect. Information from national medicines evaluation agencies in EU member states is also limited, despite the fact that current EU legislation requires that all assessment reports be published without delay. Furthermore, an important EU database with clinical trial information, EudraCT, is not available to the public.

→ Recommendations

- Registration of all clinical trials in public registries should be legally required.
- Data records in trial registries should include the locations of the trials.
- A timeframe for publishing National Public Assessment Reports (NPARs) should be determined.

It is not currently possible for external actors such as SOMO and WEMOS and their partners in low-income countries to monitor the ethical considerations made by companies. The data records of trial registries as well as the public assessment reports of the regulating authorities include little or no crucial information, such as the location of the clinical trials or a unique trial identification number. No database has separate data fields for ethical aspects. In a few cases, information on post-trial access provisions was included in trial descriptions. No explanation for the inclusion of vulnerable patient groups, mention of special protection measures, justification of placebo use or assessment of benefits for the population could be found in any of the trial descriptions, even though the nature of some trials raised serious questions about these issues. Most European Public Assessment Reports (EPARs and NPARs), if available, do not contain information about ethical conduct other than a statement by the applicant that Good Clinical Practice (CGP) was observed. Pharmaceutical companies claim that ethical considerations are included in the original trial protocols, but these are not publicly available.

→ Recommendations

- Sponsors of the trials should make it possible for external actors to check the ethical considerations and precautions taken to protect vulnerable trial subjects.
- Ethical considerations should be included in trial registries and in all communications about trials, such as public assessment reports.

Current EU legislation requires that results from unethical clinical trials that have not been conducted in accordance with the Declaration of Helsinki not be accepted for marketing authorisation. The case studies in this report reveal that this principle is being violated. The use of placebo-controls appears to be one of the most common problems. According to the Declaration of Helsinki, such studies should only be conducted if no proven alternative therapy exists or in other special circumstances. However, placebo-controlled trials were not questioned in any of the cases described in this report. More generally, the findings confirm that attention to clinical trial ethics in assessments for EU marketing authorisation is extremely limited. This not only applies to trials conducted in low and middle-income countries, but also to trials conducted in the EU itself. (For a summary of the case studies in this study, please see the executive summary).

9. Annex 1: EU legislation on clinical trials

Directive 2001/20/EC of 4 April 2001 sets standards for the conduct of clinical trials in the EU itself. The preamble mentions the following consideration:

(2) The accepted basis for the conduct of clinical trials in humans is founded in the protection of human rights and the dignity of the human being with regard to the application of biology and medicine, as for instance reflected in the 1996 version of the Helsinki Declaration.

Note that the Directive refers to the 1996 version of the DoH and not the to the 2000 version, as the Directive was drafted before the revision was completed. The reference is not exclusive, though, and at present the 2000 revision of the DoH, with the clarifications added to it in 2002 and 2004, can be considered the most accepted basis for the conduct of clinical trials.

Although Directive 2001/20/EC focuses on the conduct of clinical trials in the EU, article 15 also provides for inspections in other countries:

'4. 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.'

Directive 2001/83/EC of 6 November 2001 regulates marketing authorisation of medicinal products in the EU. This Directive provides stronger legal requirements for the ethical conduct of clinical trials outside the EU. Article 8 (3) specifies the information and documentation that must accompany the application for marketing authorisation in the EU, which need to be *'submitted in accordance with Annex I'*. The original version of article 8 (3) does not directly mention information on the ethical conduct of clinical trials. However, general standards for the conduct of clinical trials and for clinical documentation are set in Annex 1. In part four of Annex I, section B1 on 'Good Clinical Practice' includes the following paragraphs:

'1.2. All clinical trials shall be carried out in accordance with the ethical principles laid down in the current revision of the Declaration of Helsinki. In principle, the freely given informed consent of each trial subject shall be obtained and documented.

The trial protocol (including statistical design), the technical application and documentation shall be submitted by the sponsor and/or investigator for an opinion to the relevant ethics committee. The trials shall not begin before the opinion of this committee has been received in writing.'

Note that this paragraph explicitly refers to the current revision of the DoH and not to the 1996 version. The standards required by Annex I apply to all clinical trials for medicines that are approved for the EU market, including trials conducted in low and middle-income countries.

Directive 2003/63/EC of 25 June 2003 amends Directive 2001/83/EC. It replaces Annex I, but does not change the text of the articles of the Directive itself. The 'Introduction and general principles' section of the new Annex I includes the following paragraph:

'(8) All clinical trials, conducted within the European Community, must comply with the requirements of Directive 2001/20/EC of the European Parliament and of the Council 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. 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 other words, the Directive explicitly requires that clinical trials conducted anywhere in the world must be carried out in accordance with the DoH if they are to be taken into account for applications for marketing authorisation in the EU.

Directive 2004/27/EC of 31 March 2004 further amends Directive 2001/83/EC. It complements the previous amendment by modifying the text of the articles of the Directive without renewing Annex I. All EU Member States should implement the Directive before 31 October 2005. In the preamble, the Directive considers:

'(13) There is a need to provide for the ethical requirements of Directive 2001/20/EC of the European Parliament and the Council of 4 April 2001 (…) to apply to all medicinal products authorised within the Community. In particular, with respect to clinical trials conducted outside the Community on medicinal products destined to be authorised within the Community, it should be verified, at the time of the evaluation of the application for authorisation, that these trials were conducted in accordance with

the principles of good clinical practice and the ethical requirements equivalent to the provisions of that Directive.'

The Directive adds the following paragraph in article 8(3) to the list of information that must be submitted with the application:

'(ib) A statement to the effect that clinical trials carried out outside the European Union meet the ethical requirements of Directive 2001/20/EC.'

Thus, this explicitly requires that clinical trials conducted outside the EU, mentioned in marketing authorisation applications, meet the same standards for ethical conduct as trials in the EU. IN addition, in article 21, the Directive adds a requirement for national drug authorities to publicise the assessment report:

'4. The competent authorities shall draw up an assessment report and comments on the file as regards the results of the pharmaceutical and pre-clinical tests and the clinical trials of the medicinal product concerned. (…) The competent authorities shall make publicly accessible without delay the assessment report, together with the reasons for their opinion, after deletion of any information of a commercially confidential nature. The justification shall be provided separately for each indication applied for.'

Finally, Regulation (EC) No 726/2004 of 31 March 2004 establishes a Committee for Medicinal Products for Human Use (CMPHU) as part of the European Medicines Agency (EMEA). In the preamble, it considers:

'(16) There is also a need to provide for the ethical requirements of Directive 2001/20/EC of 4 April 2001 (…) to apply to medicinal products authorised by the Community. 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.'

The Regulation also sets standards for the centralised procedure for marketing authorisation. Article 6 states:

'1. Each application for the authorisation of a medicinal product for human use shall specifically and completely include the particulars and documents as referred to in articles 8(3), 10, 10a, 10b or 11 of, and Annex I to, Directive 2001/83/EC. The documents must include a statement to the effect that clinical trials carried out outside the European Union meet the ethical requirements of Directive 2001/20/EC. (…)'

The Directives 2001/83/EC and 2003/63/EC also mention ethical considerations regarding the use of placebos. In Directive 2001/83/EC, part four of Annex I, section F on 'Clinical efficacy and safety' includes the following paragraph:

'1. In general, clinical trials shall be done as 'controlled clinical trials' and if possible, randomised; 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; 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.'

As mentioned above, Directive 2003/63/EC replaced Annex I. The text on placebo use remained rather similar, though. In part I of the new text of Annex 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.'

Note that these EU Directives require that new medicines are normally tested in controlled trials, but not necessarily in placebo-controlled trials. On the contrary, the Directives state that the appropriate trial design will depend on ethical considerations and explicitly mention that testing against an existing medicine may sometimes be preferred.