SOMO briefing paper on ethics in clinical trials

#1: Examples of unethical trials

February 2008 (updated)

Contents

Introduction

This briefing paper provides an overview of known examples of unethical clinical trials. It was prepared by SOMO, in collaboration with Wemos, and is based on secondary sources. Although the focus is on developing countries, it also includes a few cases from the US and Europe. By providing such an overview, the paper aims to illustrate problems in the ethical conduct of clinical trials. It does not provide an analysis of clinical trials in general or of the scale of ethical violations. Indeed, the scale of the problem is unknown, because it cannot be estimated how many unethical clinical trials escape public attention and therefore remain unnoticed.

There are some indications that underlying structural problems exist, though, as in several of the trials described in this paper, the operations of pharmaceutical research companies were not adequately controlled or authorities seemed unwilling to address unethical drug testing even after it caught media attention.

This overview is limited to clinical trials involving drugs and vaccines, as such recent controversies about trials of the Dutch company Occam in India involving stents, or circumcision trials or circumcision trials in Africa, have been excluded. Furthermore, the focus is on ethical issues related to the design and conduct of trials. Conflicts about intellectual property or illegal exports of blood samples are not described. Clinical trials with

dramatic outcomes but no apparent ethical or legal shortcomings, such as the probiotics trial in Dutch hospitals, fall outside the scope of the overview too.

For each trial, selected information sources are provided. Most sources are publicly accessible websites, but some require a subscription.

The first version of this briefing was published in November 2006. The present version, which is the second update, does not include new cases but adds more recent developments on several trials, takes into account feedback from three companies, and has updated sources.

Ethical norms

The case descriptions also refer to norms in widely accepted international codes that have (probably) been violated. The most cited reference is the Declaration of Helsinki (DoH) of the World Medical Association (WMA). 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 accepted basis for clinical trial ethics. Some important paragraphs from the declaration are briefly summarized below.

8. Vulnerable research populations require special protection.

11. Research must be based on knowledge of laboratory and animal experimentation.

13. The protocol for a clinical trial should be reviewed by an independent ethical review committee. The researchers must report any serious adverse events to this committee.

16. The design of all studies should be publicly available.

17. Investigations should be ceased if the risks are found to outweigh the potential benefits.

19. The 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.

20. Participation in a trial must be voluntary and participants must be informed.

22. Physicians should obtain freely-given informed consent from each participant.

24. Subjects who cannot provide informed consent themselves, for example children, should only be included in the research cannot be performed on other subjects instead.

29. The benefits, risks, burdens and effectiveness of a new therapy should be tested against those of the best currently available therapy. Placebo-controlled trials are only allowed if no proven therapy exists or under special circumstances.

30. At the conclusion of the study, all trial participants should be assured access to the best proven therapy identified by the study. Post-trial access arrangements must be described in the trial protocol.

31. When medical research is combined with medical care, the physician should inform the patient which aspects of the care are related to the research.

As placebo-controlled clinical trials (DoH §29) are currently a standard practice rather than an exception (for phase III studies), this overview does not include trials that could be considered controversial solely because drugs were tested against placebos where proven alternatives already existed.

Some examples of trials with controversial use of placebos can be found in:

- SOMO, “Ethics for Drug Testing in Low and Middle Income Countries: Considerations for European Market Authorisation,” Feb 2008, <http://www.somo.nl> (forthcoming).
- VBDO, “CSR voting advice: Discharge of executive board members,” Akzo Nobel case, Aug 2007, <http://www.somo.nl/html/paginas/pdf/VBDO_Sustainable_voting_advice_report.pdf> (Jan 2008), p. 20-21.

Furthermore, despite recent initiatives to increase transparency about drug trials, the design of most studies is still not publicly available (DoH §16). Therefore this principle was also not used as a selection criterion for the overview of unethical clinical trials in this

paper. The lack of transparency does limit the amount of information available on the studies described below, because in most cases it appears the study design is indeed not publicly available.

General observations

Even though the overview below is necessarily incomplete and biased towards unethical trials that have caught some publicity, some general observations can still be made.

Firstly, unethical trials have occurred around the world, in both developed and developing countries. In some cases, the trials had not been approved by an ethical review committee or institutional review board, or approval had be given for an unethical trial design. Hence there appear to be flaws, and sometimes rather serious ones, in the regulatory systems of various countries.

Secondly, the research organizations involved range from relatively unknown local companies to leading multinational corporations. This might be surprising, given that large multinational corporations usually have clear public commitments to high ethical standards in clinical trials.

Thirdly, some of the unethical trials are of a recent date, some were even being carried out in 2005 or later. Although it is sometimes argued that instances of unethical clinical trials are isolated and outdated, this is not always true. Note that some older cases have been included in the overview as well, mainly because the developments following these trials are still going on.

And finally, the nature of ethical concerns appears to be rather diverse and relates to all paragraphs of the DoH summarized above. The lack of voluntary, informed participation and adequately informed consent are probably the most common problems. Cases of trials that did not undergo adequate ethical review or failed to report serious adverse events indicate flaws in the regulation of clinical trials. Tests with experimental drugs of which the safety for testing in humans had not yet been fully established may be among the most alarming examples.

ART treatment interruption trials

Drugs:	lamivudine/zidovudine (Combivir) + tenofovir (Viread) or nevirapine (Viramune) or abacavir (Ziagen) (DART trial)
Treatment:	Anti-retroviral therapy (ART)
Sponsors:	UK Medical Research Council (MRC), Rockefeller Foundation, DfID (Uganda), GlaxoSmithKline, Gilead, Boehringer-Ingelheim
Period:	2003 – 2006 (DART trial)
Location:	Uganda, Zimbabwe, Côte d'Ivoire

Unethical aspects:
The Development of Anti-Retroviral Therapy in Africa (DART) trial was an open, randomised trial to compare standard continuous therapy (CT) with structured treatment interruption (STI) of 12 weeks on and 12 weeks off anti-retroviral therapy (ART). The trial had recruited 3,300 volunteers at the Joint Clinical Research Centre (Kampala, Uganda), the MRC/UVRI Uganda Research Unit on AIDS (Entebbe), and the University of Zimbabwe College of Health Sciences (Harare). On 14 March 2006, it was decided that all patients in the STI arm of the trial would be switched to continuous therapy as interim data demonstrated they had a greater rate of clinical HIV-related disease.

Critics say they had sounded alarms the year before already because of the relatively high number of fatalities in the STI arm in Uganda, but investigators replied their concerns were unfounded. Attempts to put patients whose situation deteriorated during treatment interruption back on ART failed and some of the patients died during the interruption period. There have also been complaints about enrolment of patients desperate to get free treatment, insufficient arrangements for post-trial treatment access, the use of a drug regimen that is not readily available to the general population, and omission of important risks in the consent forms.

Similar ethical concerns apply to the Strategies for Management of Anti-Retroviral Therapy (SMART) trial, which compared continuous ART with episodic drug treatment as well. The Data and Safety Monitoring Board (DSMB) also found that treatment interruption was associated with a higher risk of disease progression. Enrolment in the SMART trial was halted two months earlier, in January 2006, and re-initiation of interrupted therapy was recommended.

Trivacan is another ART trial with two treatment interruption arms. For one group of patients the treatment interruption is determined by CD4 cell counts, a measure for the functioning of the patients' immune system. For a second group the treatment is interrupted according to a fixed schedule. The Trivacan trial enrolled approximately 840 patients in Côte d'Ivoire since 2002 and still ongoing.

Violated norms (DART trial):

- DoH §17: Investigations may not have been ceased in time after a negative risk/benefit balance for STI was identified.
- DoH §19: The population is which the research was carried out might not benefit from the results of the study, as tenofovir is not readily available in Uganda and Zimbabwe.
- DoH §22: Voluntary informed consent was obtained for each patient, but this may have been compromised by patients being desperate to get access to free treatment, and risks may not have been sufficiently explained.
- DoH §30/20: Post-trial access arrangements were unclear and apparently not described in the trial protocol. This would also effectively inhibit patients to leave the trial.

Outcome:

The investigators of the DART trial denied lethal side-effects of treatment interruption and ethical shortcomings in the trials. On 17-19 July 2006, the Office of AIDS Research (OAR) of the US National Institutes of Health (NIH) and the Treatment Action Group (TAG) held an international workshop to discuss the conduct of STI and intermittent therapy trials. A review of available evidence confirmed that some trial participants were at increased risk of adverse events, including death. It was concluded that STI trials cannot be recommended until the findings from past trials have been better understood.

Sources:

- R.M. Kavuma, "AIDS research kill 50 – angry activists claim," Weekly Observer (Uganda), 8 Jun 2006.
- MRC, "DART trial moves patients from interrupted to continuous antiretroviral therapy (ART)," 14 Mar 2006, <http://www.ctu.mrc.ac.uk/dart/files/DARTPressreleaseFINAL14Mar06.pdf> (Jan 2008).
- DART website, last updated 15 Mar 2006, <http://www.ctu.mrc.ac.uk/dart> (Jan 2008).
- NIH, "Clinical Alert: International HIV/AIDS Trial Finds Continuous Antiretroviral Therapy Superior to Episodic Therapy,"<http://www.nlm.nih.gov/databases/alerts/aids_smart.html> (Jan 2008).
- Correspondence about DART and SMART trials, ITPC discussion group, <http://health.groups.yahoo.com/group/internationaltreatmentpreparedness> (Jan 2008).
- ANRS, Press release, "Côte d'Ivoire: La recherche continue," 24 Apr 2006, <http://www.anrs.fr/index.php/anrs/rubriques_transversales/presse> (Jan 2008).
- "Report from the Workshop on HIV STI /Intermittent Therapy", held 17-19 Jul 2006 in London, <http://www.oar.nih.gov/public/NIH_OAR_STI_IT_Report_Final.pdf> (Jan 2008).

Tenofovir trials on HIV transmission

Drugs:	Tenofovir (Viread)
Treatment:	Prevention of HIV transmission
Sponsors:	Gilead, US CDC, Bill and Melinda Gates Foundation
Research organization:	Family Health International (FHI) in Africa, US NIH in Cambodia
Period:	2004 – 2005
Location:	Cameroon, Thailand, Nigeria

Unethical aspects:

In Cameroon five women became HIV-infected while enrolled in the Tenofir-study. Non-governmental organisations (NGOs) claim the 400 sex workers participating in the trial were not adequately informed about the risks and only English information was given to mostly French speaking volunteers. There was a lack of ARVs for patients infected during the trial.

In Thailand, key community groups including the Thai Drug Users Network (TDN) and the Thai AIDS Treatment Advocacy Group (TTAG) claim their concerns have been ignored by the trial investigators and they were not consulted about the trial design and conduct until a very late stage. They are concerned that intravenous drug users participating in the trial in Thailand will not have access to free, clean syringes through needle exchange programmes. In case the drug would be effective, the researchers had not ensured a roll-over study to take care of trial participants in the interim period between study closure and marketing approval. Furthermore, only one year of free post-trial access was negotiated, even though in Thailand at least two years of post-trial drug access would be the norm.

In Cambodia, the Women's Network for Unity, a local union of sex workers protested as they perceived that medical insurance for trial participants would be insufficient. FHI cancelled the study in Nigeria giving as a reason that the quality of the local study team was inadequate, but activists claim that FHI wanted to avoid another scandal and cancelled the trial a few days before the release of the Nigeria HIV Vaccine and Microbicide Advocacy Group (NIHMAG) report (see sources). Similar trials were planned in Ghana, Peru, Botswana, and Malawi.

Violated norms:

- DoH §8: Vulnerable subjects may not have received the required special protection.
- DoH §22: Participants had not been adequately informed.
- DoH §30: Post-trial access arrangements were insufficient.

Outcome:

The trials were cancelled in Cameroon in March 2005. Trials in Cambodia were cancelled in 2004 by Cambodian authorities. The impending study in Nigeria was cancelled by FHI. Community groups in Thailand asked for establishment of a broad committee to address key HIV issues, involvement in trial outreach and education and ensuring at least two years of post-trial tenofovir access to trial participants.

Sources:

- "FHI ends clinical trial of ARV drug Tenofovir," Plus NEWS, 10 Aug 2005, <http://www.plusnews.org/AIDSreport.asp?ReportID=5118&SelectRegion=West_Africa&SelectCountry=CAMEROON> (Jan 2008).
- "Ethical issues involved in the Cambodia Tenofovir trials," Global Campaign News, Issue 41, 14 Sep 2004, <http://www.global-campaign.org/clientfiles/GCNews41(1).pdf> (Jan 2008).
- Kaiser network, "Cambodian Prime Minister Says He Opposes Testing HIV/AIDS Drugs on Residents," 4 Aug 2004, <http://www.kaisernetwork.org/daily_reports/print_report.cfm?DR_ID=25099&dr_cat=1> (Jan 2008).
- A. Chua, N. Ford, D. Wilson & P. Cawthorne, PLoS Medicine, 25 Oct 2005, "The Tenofovir Pre-Exposure Prophylaxis Trial in Thailand: […]," <http://medicine.plosjournals.org/perlserv/?request=get-document&doi=10.1371/journal.pmed.0020346> (Jan 2008).
- "The trial of tenofovir trials," The Lancet, Vol. 365, 26 Mar 2005, p. 1111, <http://www.thelancet.com/journals/lancet/article/PIIS0140673605718501X/fulltext> (Jan 2008).
- A. Jack & A. Kazmin, "Thai Aids campaigners question new clinical trials," Financial Times, 12 Mar 2005, <http://news.ft.com/cms/s/0bcd9024-929b-11d9-bca5-00000e2511c8.html> (Jan 2008).
- NIHMAG, "Report of the outcome of dialogue […]," 2005, <http://aidsvaccineclearinghouse.org/pdf/advocacy/Nigeria_HIV_Vaccine_Report.pdf> (Jan 2008).
- Correspondence about tenofovir trials, ITPC group, <http://health.groups.yahoo.com/group/internationaltreatmentpreparedness> (Jan 2008).
- CDC website, "CDC Trials of Daily Oral Tenofovir for Preventing HIV Infection," <http://www.cdc.gov/hiv/PUBS/TenofovirFactSheet.htm > (Jan 2008).

Hepatitis E vaccine trial in Nepal

Drugs:	Hepatitis E vaccine
Sponsors:	GSK, Walter Reed Army Institute of Research
Period:	2001 – 2003
Location:	Kathmandu, Nepal

Unethical aspects:

In 1998, GSK and the Walter Reed Institute, which conducts medical research for the US army, started cooperating to develop a Hepatitis E vaccine. Hepatitis E is a comon disease in poor countries and there have been outbreaks in countries where US troops are deployed. Preparations for phase II trials were made in February 2000. Before launching the trials, GSK had already decided the vaccine would not be commercially developed for a travellers' market, while Walter Reed decided it would be unsuitable for US soldiers. Still, GSK and Walter Reed went ahead with phase II trials and wanted to test the candidate vaccine on 8,000 Nepalese volunteers in Lalitpur, without a plan to further develop the vaccine and make it available to the local population if the trials were successful.

The Nepalese NGO Lumanti and municipal officers protested against the tests in Lalitpur because the majority of its population is illiterate and highly vulnerable. Walter Reed then decided to test the vaccine on 2,000 soldiers offered by the Royal Nepalese Army as volunteers. However, the soldiers were also considered a vulnerable group as they are poor and potentially subject to coercion by their superiors.

Violated norms:

- DoH §8: Vulnerable subjects may not have received the required special protection.
- DoH §19: The population where the research was carried out is unlikely to benefit from the study.
- DoH §22: Consent may not have been fully informed and freely-given.
- DoH §30: Post-trial access arrangements were apparently lacking.

Outcome:

In March 2006, civil society groups sent a letter to GSK demanding that the vaccine is made available for free to the Royal Nepalese Army and the Lalitpur community and offered to the Nepali Ministry of Health at not-for-profit prices. Furthermore, GSK should sign prior agreements with the communities impacted by the research to ensuring post-trial access if the vaccine is approved before further testing takes place. Apparently, the company did not publicly respond to the letter.

In March 2007, the results of the study were published in the New England Journal of Medicine (NEJM). In June 2007, the NEJM published two letters to the editor, reiterating the need to further develop the vaccine and make it available to the Nepalese community, and a response from GSK. The company explained that measures had been taken *'to remove the influence of military commanders over participation by subordinates'* and that most soldiers approached for the trial refused to participate. GSK affirmed that it is committed to continue development of the Hepatitis E vaccine so that it can be available in Nepal, but calls for external financing for the introduction of the vaccine through partnerships.

Sources:

- Letters to the Editor by S. Basu & P. Lurie and by A. Bhattarai; Reply by the Authors B.L. Innis, M.P. Shrestha & R. McNair Scott, NEJM 356(23), 7 Jun 2007, p. 2421-2.
- S. Sarkar, "Nepal questions US Army vaccine experiments," ISN Security Watch, 12 Jan 2006, <http://www.isn.ethz.ch/news/sw/details.cfm?id=14309> (Jan 2008).
- M. Logan, "Nepal: Guinea Pigs in Hepatitis E Vaccine Trials," IPS News Agency, 6 Feb 2006, <http://ipsnews.org/news.asp?idnews=32047> (Jan 2008).
- A. Jack, "GSK is criticised for army drug test," Financial Times, 1 Mar 2006.
- J. Andrews, "U.S. Military Sponsored Vaccine Trials and La Resistance in Nepal," The American Journal of Bioethics, Vol. 5(3), May-Jun 2005, <http://www.bioethics.net/journal/j_articles.php?aid=713> (Jan 2008).
- J. Andrews, "Research in the Ranks: Vulnerable Subjects, Coercible Collaboration, and the Hepatitis E Vaccine Trial in Nepal," Perspectives in Biology and Medicine, Vol. 49(1), winter 2006, p. 35-5.
- K. Fleming-Michael, "Hepatitis E vaccine trials: compilation," INSN, 1 Nov 2001, <http://66.116.151.85/?p=2878> (Jan 2008).

Nevirapine PMTCT trials in Uganda

Drug:	nevirapine (Viramune)
Treatment:	HIV prevention of mother to child transmission (PMTCT)
Sponsors:	Boehringer Ingelheim (BI), US National Institutes of Health (NIH)
Period:	1997 – 2003
Location:	Uganda

Unethical aspects:

In the HIVNET 012 trial, investigators failed to get patients' consent about changes in the experiment and administered wrong doses. There were serious problems in record keeping and delays and underreporting of fatal and life threatening problems. Fourteen deaths were not reported. Researchers acknowledged thousands of side effects and adverse reactions were not disclosed. Procedures for divulging Serious Adverse Events (SAEs) were not followed. Boehringer Ingelheim, the company that markets the drug and audited the trial, asked the US National Institutes of Health (NIH) to destroy an early copy of the research report in case the study would be audited by the US Food and Drug Authority (FDA).

Violated norms:

- DoH §13: Serious adverse events were not reported.
- DoH §22: Informed consent from participants about changes in the trial protocol was not obtained.

Outcome:

Problems were revealed in early 2002 and Boehringer Ingelheim withdrew its FDA marketing application. In 2004, the FDA recommended the NIH to stop using the drug with certain patients in Africa and issued warnings about side effects. Boehringer Ingleheim (BI) stated that *'the trial was conducted under the sole responsibility of*

the NIH. BI at no point covered up any information or destroyed any documents.'

Sources:

- J. Solomon, "AP Exclusive: Top U.S. officials warned of concerns before AIDS drug sent to Africa," AP, 13 Dec 2004, <http://www.lubbockonline.com/stories/121304/upd_075-4013.shtml> (Jan 2008).
- "Selected documents AP obtained in the investigation of nevirapine's use in Uganda," from AP website, <http://www.honestdoctor.org/documents.html> (Jan 2008).
- Author's correspondence with BI, Apr 2007.

SFBC Miami test centre

Drugs:	Various
Sponsors:	Pfizer, Merck & Co, Johnson & Johnson, Schering-Plough, Theravance, Purdue Pharma, AstraZeneca, and others
Research organization:	SFBC
Period:	2000 – 2005
Location:	Miami, US

Unethical aspects:

In November 2005, a special Bloomberg report revealed inappropriate testing at that the SFBC test centre in Miami. The US Food and Drug Administration (FDA) had already discovered significant violations in 2000 and 2002. SFBC is a contract research organization (CRO), a company that carries out clinical trials for large pharmaceutical companies. The trial participants are largely poor immigrants from Latin America.

In some cases, trial participants had not been fully informed about the risks of the trials and received misleading and confusing explanations. Consent forms were not fully read and informed consent was not adequately verified by SFBC employees. Furthermore, participants were not always allowed to leave the trials at any time. Payments were heavily back loaded towards the end of the trial, causing inappropriate pressure to complete a trial. Finally, there existed conflicts of interests regarding the approval of trials. One of the Institutional Review Boards (IRBs) charged with the review of protocols for trials to be carried out at SFBC was owned by the wife of the SFBC Vice President.

Violated norms:

- DoH §8: Vulnerable subjects may not have received the required special protection.
- DoH §13: Ethical review committees were not fully independent.
- DoH §20: Participants were not allowed to leave the trials.
- DoH §22: Participants had not been adequately informed.

Outcome:

SFBC denied the allegations. The company threatened to arrange federal deportation of Latin American immigrants who disclosed unethical aspects of the clinical trials and tried to make them sign false statements. Several top officials of the company resigned. In May 2006, SFBC announced that it will close down the test centre in Miami and move planned drug trials to Canada. The US Senate performed investigations into the company's conduct.

Sources:

- D. Evans, M. Smith & L. Willen, "Big pharma's shameful secret," Dec 2005, <http://www.bloomberg.com/specialreport/pharma.pdf> (Jan 2008).
- Bloomberg website, "Special Report: Big Pharma's Shameful Secret," <http://www.bloomberg.com/specialreport/bigpharma.html> (Jan 2008).

Letrozole trials in India

Drugs:	letrozole
Treatment:	Inducing ovulation
Sponsors:	Sun Pharmaceuticals
Period:	2003
Location:	India

Unethical aspects:

Letrozole, which belongs to the group of aromatase inhibitors, was tested by Sun Pharmaceuticals to induce ovulation. The drug has been approved globally for the treatment of breast cancer in post-menopausal women, but it is not approved for any other use in any country. More than 400 women who had been trying in vain to conceive were enrolled in 2003 without their knowledge or consent to take part in clinical trials conducted at nine or more centres across India.

Violated norms:

- DoH §20: Subjects were not informed they were participating in a trial.
- DoH §22: Informed consent was not obtained.

Outcome:

A complaint on the letrozole case was filed in the Supreme Court by the Delhi-based NGO Social Jurist. Novartis, who was not involved with the study but markets letrozole under the brand name Femara, sent a clarification letter to all infertility experts in India to remind them of the approved indication.

Sources:

- J. Padmini, "Social Jurist to slap criminal suit on nimesulide makers," Express Healthcare Management, 15 Apr 2004, <http://www.expresshealthcaremgmt.com/20040415/pharma01.shtml> (Jan 2008).
- J. Padmini, "Social Jurist to file PIL on illegal letrozole trials," Express Pharma Pulse, 8 Jan 2004, <http://www.expresspharmapulse.com/20040108/coverstory01.shtml> (Jan 2008).
- I. Basu, "India's clinical trials and tribulations," Asia Times, 23 Jul 2004.
- T.V. Padma, "India's drug tests," Nature, Vol. 436, 28 Jul 2005, p. 485.
- "Letrozole trials: Misdeeds of self-styled 'Researchers', Hundreds of Women Used as Guinea Pigs," Editorial, Monthly Index of Medical Specialities (India), Dec 2003.
- C.M. Gulhati, "Needed: closer scrutiny of clinical trials," Indian Journal of Medical Ethics, Vol.12(1), Jan-Mar 2004, <http://www.issuesinmedicalethics.org/121ed004.html> (Jan 2008).

Alosetron trials after marketing withdrawal

Drugs:	alosetron HCl (Lotronex)
Treatment:	Treatment for Irritable Bowel Syndrome (IBS)
Sponsors:	Glaxo Wellcome (now GlaxoSmithKline)
Period:	2000
Location:	Various countries

Unethical aspects:

In November 2000, Glaxo Wellcome withdrew its drug Lotronex from the US market because of FDA safety concerns. Serious complications and three deaths potentially linked to Lotronex had been reported. However, 7,500 trial participants in other countries continued to take the drug after it was withdrawn in the US.

Violated norms:

- DoH §17: Investigations were not ceased after the risks were found to outweigh the potential benefits.

Outcome:

The company responded that it would take until the end of December 2000 to phase out the studies.

Sources:

- M.P. Flaherty, D. Nelson, and J. Stephen, "The Body Hunters: Overwhelming the Watchdogs," Washington Post, 18 Dec 2000, <http://www.washingtonpost.com/ac2/wp-dyn/A11986-2000Dec15, http://www.washingtonpost.com/ac2/wp-dyn/A11976-2000Dec15> (Jan 2008).

Streptokinase trials in India

Drugs:	streptokinase (Streptokinnese / Streptase) and insulin
Treatment:	Clot-busting drug used in heart attacks, diabetes
Sponsors:	Shanta Biotechnics (streptokinase), Biocon (insulin)
Period:	2003
Location:	Hyderabad, India

Unethical aspects:

The companies had openly conducted illegal phase III clinical trials of new drugs on unaware patients and had conducted improper clinical trials without permission from the Genetic Engineering Approval Committee (GEAC). Eight patients died. Shanta Biotechnics denied the allegations.

Violated norms:

- DoH §13: The trial protocol was not reviewed by an ethical review committee.
- DoH §20: Subjects were not informed they were participating in a trial.
- DoH §22: Informed consent was not obtained.

Outcome:

A litigation was filed by the Delhi-based NGO Aadar Destitute and Old People's home. In March 2004, the

Supreme Court of India confirmed that the trials had been illegal.

Sources:

- I. Basu, "India's clinical trials and tribulations," Asia Times, 23 Jul 2004, <http://www.atimes.com/atimes/South_Asia/FG23Df03.html> (Jan 2008).
- S. Srinivasan, "Indian Guinea Pigs for Sale: Outsourcing Clinical Trials," India Resource Center, 8 Sep 2004, <http://www.indiaresource.org/issues/globalization/2004/indianguineapigs.html> (Jan 2008).
- C.M. Gulhati, "Needed: closer scrutiny of clinical trials," Indian Journal of Medical Ethics, Vol.12(1), Jan-Mar 2004, <http://www.issuesinmedicalethics.org/121ed004.html> (Jan 2008).

Fortified ORS trials in Peru

Drugs:	Oral rehydration solution (ORS) with added lactoferrin and lysozyme (proteins)
Treatment:	Diarrhea
Sponsors:	Ventria Bioscience
Research organization:	Institute for Child Health, Nutrition Research Institute
Period:	2004-2005
Location:	Two hospitals in Peru

Unethical aspects:

Starting in August 2004, a fortified formulation of Oral Rehydration Solution (ORS) was tested on 140 Peruvian babies and young children of age 5 to 33 months hospitalized with serious diarrhea. The enhanced ORS contained two synthetic human breast milk proteins produced by genetically modified (GM) rice. Ventria reports that the children who received it on average had a shorter duration of the diarrhea and a higher rate of recovery. One of the proteins was also studied in the US among hospitalized elderly patients that receive large doses of antibiotics, to try to halt diarrhea.

Two children participating in the trial in Peru suffered serious allergic reactions and one of them would have become allergic to fruits and other foods. There exist previous studies that pointed out the dangers of GM rice proteins, including immune reactions, and the proteins of Ventria Bioscience had not yet been approved for testing in the US or abroad and studies on children in the US were not allowed. There are some doubts whether the parents that gave their consent were properly informed.

Violated norms:

- DoH §11, Peruvian and US law: the proteins were not yet approved for testing.
- DoH §22: There are doubts as to whether the consent of parents was fully informed.

Outcome:

The Peruvian Medical Association, a local NGO, denounced the trial. On request of a parliamentarian, a legal inquiry started in July 2006. The company insists that the study met all legal requirements, including approval from 3 independent scientific groups before the trial started.

Sources:

- S. Burcher and M.W. Ho, "FDA in Third World Drug Trial Scandals," Institute of Science in Society, 1 Sep 2006, <http://www.i-sis.org.uk/FDAinDrugTrial.php> (Jan 2008).
- "International Academy of Life Sciences Applauds Novel Product for Diarrhea," PRWeb Press Release, 24 June 2006, <http://mediaserver.prweb.com/pdfdownload/403604/pr.pdf> (Jan 2008).
- R. Vecchio, "Uproar in Peru over genetically-engineered diarrhea treatment," USA Today, 14 Jul 2006, <http://www.usatoday.com/tech/science/genetics/2006-07-14-diarrhea-treatment_x.htm?csp=34> (Jan 2008).
- P. Díaz, "Condenan experimentos con bebés, " La República, 8 Jul 2006, <http://www.larepublica.com.pe> (Jan 2008).
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- P. Leighton, "Study on infants in Peru sparks ethics inquiry," SciDev.Net, 18 Jul 2006, <http://www.scidev.net/content/news/eng/study-on-infants-in-peru-sparks-ethics-inquiry.cfm> (Jan 2008).

Risperidone trials in India

Drugs:	risperidone (Risperdal)
Treatment:	Treatment of acute mania
Sponsors:	Johnson & Johnson
Period:	Unclear, probably 2003
Location:	Gujarat, India

Unethical aspects:
During a trial for the treatment of acute mania, psychiatric patients were taken off their existing medication and told that it was discontinued and no longer available. They subsequently received risperidone or a placebo. This was controversial because the patients receiving a placebo could suffer unnecessary harm by being taken off their medication. One patient explained that he signed a form because the doctor required it, but had no idea that he was participating in a clinical trial.

Violated norms:
- DoH §20: Not all subjects were informed they were participating in a trial.
- DoH §22: Informed consent was not properly obtained from all participants.
- DoH §29: The use of a placebo was controversial because it was unnecessarily dangerous.
- DoH §31: It was not explained to all patients that the provided medical care was linked to a research.

Outcome:
Johnson & Johnson denies the allegations and stated that consent had been obtained from every patient. It defended that placebo-controlled trial expose less patients to a potentially ineffective treatment. However, this does not explain while patients have to discontinue a proven existing treatment.

Sources:

- "Drug trials outsourced to India," BBC News, 22 Apr 2006, <http://news.bbc.co.uk/2/hi/south_asia/4932188.stm> (Jan 2008).
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VGV-1 trials in China

Drugs:	VGV-1
Treatment:	Anti-HIV therapy
Sponsors:	Viral Genetics (US)
Period:	2003
Location:	Ditan Hospital, Beijing, China

Unethical aspects:
HIV-positive patients were not told about the risk of side effects from the investigational drug. Participants did not understand the informed-consent forms and the physicians made no effort to explain them. In addition, participants complained expenses were not covered as agreed and they were not informed about the trial results despite asking.

Violated norms:
- DoH §22: Informed consent was not properly obtained from all participants.

Outcome:
Following complaints from trial participants, the Institutional Review Board (IRB) of the National Center for AIDS/STD Prevention and Control recommended that trials must be better explained in the future and expenses should be paid. However, it concluded there were no serious problems with the trial.

Sources:

- D. Cyranoski, "Chinese clinical trials Consenting adults? Not necessarily..." Nature 435 (11 May 2005), p138.

TGN 1412 trials in London

Drugs:	TGN 1424
Treatment:	Rheumatism treatment
Sponsors:	TeGenero
Research organization:	Parexel International
Period:	March 2006
Location:	London, UK

Unethical aspects:
When the anti-inflammatory drug candidate TGN 1412 was tested in animals, it showed no significant side effects. When it was first administered to six healthy volunteers in subsequent phase I trials, however, within minutes it caused potentially fatal multi-organ failure and they had to be taken to intensive care. The trials were carried out by the US-based CRO Parexel International in a private research facility in London and had been approved by the UK Medicines and Healthcare Products Regulatory Agency (MHRA). After the event, ethicists who were shown the consent from for the drug trial found that the trial participants had not been adequately informed about the risks involved. Dutch experts later found that essential information, substantiating claims on how the drug would affect humans compared to monkeys, was not available to the MRHA when the trial was approved.

Violated norms:

- DoH §11: Key information from preclinical testing was missing in the documentation for approval of the trial.
- DoH §22: Participants had not been adequately informed.

Outcome:

The MHRA suspended the clinical trial authorization for the drug. It performed an exhaustive inquiry of Parexel and confirmed that the trial was run according to the approved protocol. However, the MHRA investigation did not include a review of the consent form. All six participants survived, but one had toes and fingers amputated.

Sources:

- Circare, overview of sources provided in "Tegenero AG TGN1412 Clinical Trial," last updated 7 Dec 2007, <http://www.circare.org/foia5/tgn1412.htm> (Jan 2008)
- "Key data 'missing' in drug trial," BBC News, 13 Oct 2006, <http://news.bbc.co.uk/2/hi/health/6044634.stm> (Jan 2008)
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Imatinib trials

Drugs:	imatinib (Gleevec)
Treatment:	Treatment for chronic myeloid leukaemia (CML)
Sponsors:	Novartis
Period:	From 2001 onwards
Location:	South Korea, Hong Kong and other countries

Unethical aspects:

After the launch of imatinib in the US and Europe in 2001, 7,500 patients received the drug during clinical trials for regulatory approvals in other countries. Novartis had announced free supplies to people around the world that could not afford its costs of US$ 27,000 per year. However, donations were only provided to small numbers of patients and sometimes cancelled during pricing disputes.

After approval, Novartis threatened to end free supplies to 53 patients who had participated in trials in Hong Kong to press the government to provide the drug through a subsidised programme and negotiate a higher price. There has also been a dispute in South Korea over the pricing of imatinib. The company defended that its Expanded Access Programme in South Korea was not a clinical trial, but that argument was later invalidated. In India, where market exclusivity was obtained in 2003, costs became unsustainable for former generics users and aid groups were forced to withdraw their support for CML patients. After market exclusivity of Gleevec in India was cancelled in 2006, Novartis challenged this decision in court.

Violated norms:

- DoH §30: Post-trial access arrangements were insufficient.

Outcome:

Disputes over the pricing of the drug continue. In India, the People's Health Movement of Karnataka called for a boycott of Novartis products after previous appeals to withdraw the court case had failed.

Sources:

- "Call to boycott Novartis products," The Hindu, 3 Dec 2007, <http://www.hindu.com/2007/12/03/stories/2007120360940300.htm> (Jan 2008).
- Berne Declaration & Pronatura, "Shortlist 2007 Public Eye Swiss Award: Novartis AG," <http://www.evb.ch/cm_data/Novartis_e.pdf> (Jan 2008).
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- V. Landon, "Pricing dispute leaves patients without drugs," Swissinfo, 5 Aug 2002,

<http://www.swissinfo.ch/eng/Swissinfo.html?siteSect=511&sid=1257326> (Jan 2008).
- Jinbo website, "Life first before making profit!" <http://glivec.jinbo.net/english.html> (Jan 2008).
- Author's correspondence with Novartis, Feb-Apr 2007.

Ragaglitazar trials in India and other countries

Drugs:	ragaglitazar
Treatment:	Diabetes treatment
Sponsors:	Novo Nordisk
Period:	2002
Location:	32 countries, including India

Unethical aspects:
Indian scientists questioned the ethics of the phase III clinical trials of the drug before it was fully tested on animals. The trials were conducted in 32 countries, inlcuding EU countries and the US, and involved 2,500 people. Novo Nordisk stated that prior approval had been obtained in each country. The trials were suspended by the company after it discovered a mouse (and several rats) treated with the drug had developed urinary bladder tumours. In India, 130 people from eight centres participated in the trials. Half of them received the experimental drug.

Violated norms:
- DoH §11: It was disputed whether required animal experiments had been completed.
- Under Indian Council of Medical Research (ICMR) regulations, the results of toxicity studies on drugs for chronic diseases had to be available before phase III clinical trials begin. In the EU and the US, this is not required.

Outcome:
The trials were suspended in July 2002. Novo Nordisk refuted allegiations that it had not acted appropriately and stated that long-term carcinogenic study data were only required when filing a marketing application. The company conducted a clinical follow-up programme, which indicated no relation between ragaglitazar exposure and cancer in the trial participants.

Sources:
- G. Mudur, "Researchers question ethics of diabetes drug trial," BMJ, Vol. 325, 17 Aug 2002, p. 223, <http://bmj.bmjjournals.com/cgi/content/full/325/7360/353/a> (Jan 2008)
- S. Srinivasan, "Indian Guinea Pigs for Sale: Outsourcing Clinical Trials," India Resource Center, 8 Sep 2004, <http://www.indiaresource.org/issues/globalization/2004/indianguineapigs.html> (Jan 2008).
- EPP News, "Rodent studies not commenced late: Novo," Express Pharma Pulse, Aug 2002, <http://www.expresspharmaonline.com/20020808/research2.shtml> (Jan 2008).
- K. Maggon, Ups and downs in drug development," Express Healthcare Management, 16-31 Oct 2002, <http://www.expresshealthcaremgmt.com/20021031/edit2.shtml> (Jan 2008).
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- Novo Nordisk, Press release, 26 Jul 2002, <http://www.novonordisk.com/images/opencmsexport/03_Investors/SEA/English/Attachments/PR020722_NN622_UK.pdf> (Jan 2008).
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Trovafloxacin trials in Nigeria

Drugs:	trovafloxacin (Trovan)
Treatment:	Treatment of bacterial meningitis
Sponsors:	Pfizer
Research organization:	Pfizer
Period:	1996
Location:	Kano, Nigeria

Unethical aspects:
During an outbreak of meningitis in Kano, Nigeria, in 1996, Pfizer arrived several weeks after Médecins Sans Frontières and performed a trial of trovafloxacin, a new quinolone antibiotic. The drug was tested on children without parents' informed consent, patients were unaware of the experiment, and the trial was not approved in advance by an ethical review committee. Out of 190 children that were enrolled in the trial, five receiving trovafloxacin and six receiving the existing treatment ceftriaxone died. Others suffered brain damage and paralysis.

Violated norms:
- DoH §13: The trial protocol was not reviewed by an ethical review committee.

- DoH §20: Subjects were not informed they were participating in a trial.
- DoH §22/25: Informed consent was not obtained.
- DoH §31: It was not explained that the medical care that provided was linked to a research.

Outcome:
A lawsuit was filed against Pfizer in the US in 2001. The suit was dismissed in 2002 on the grounds that it should be handled in Nigeria. The 2nd US Circuit Court of Appeals repealed this in 2003 because the Nigerian court system was not an adequate alternative due to bias and corruption. In 2005, a federal judge in Manhattan dismissed the claims for a second time for lack of subject-matter jurisdiction under the Alien Tort Claims Act. A further appeal is in process.

In 2005, the Kano state government started a domestic court case. In May 2006, an anonymous source provided a copy of a report by a panel of Nigerian medical experts that had remained hidden since it was written in 2001. The panel concluded that the trials had been illegal and exploitative and violated Nigerian law, the Declaration of Helsinki and the UN Convention on the Rights of the Child. In June 2007, the federal government of Nigeria filed separate charges against the company seeking US$ 7 billion in compensation. In January 2008, the Nigerian High Court issued a warrant of arrest against eight former directors of Pfizer. Pfizer continues to deny that the drug trial was unethical.

Sources:

- I. Uwugiaren, “Nigeria: Pfizer Directors Declared Wanted,” AllAfrica, 10 Jan 2008, <http://allafrica.com/stories/200801100283.html> (Jan 2008).
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- “Nigeria sues drugs giant Pfizer,” BBC News, 5 June 2007, <http://news.bbc.co.uk/2/hi/africa/6719141.stm> (Jan 2008).
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- Alliance for Human Research Protection (AHRP) website, “Appeals Court reinstates Nigerian research case against Pfizer,” 23 Oct 2003, <http://www.ahrp.org/infomail/03/10/14.php> (Jan 2008).

Cilansetron trials in India

Drugs:	cilansetron (Calmactin)
Treatment:	Treatment for diarrhoea from Irritable Bowel Syndrome (IBS)
Sponsors:	Solvay Pharmaceuticals
Period:	Unclear, probably around 2000
Location:	India

Unethical aspects:
Phase III trials involving cilansetron, a new molecule of Solvay Pharmaceuticals, were cleared by the Drugs Controller General of India (DCGI) even though only Phase II trials had been conducted abroad. At the time, trials of foreign drugs were permitted in India only at one step below the phase completed abroad.

Violated norms:
- Before 2005, the Schedule Y of the Indian Drug and Cosmetic Act prohibited clinical trials in India of drugs developed outside the country before Phase II trials were completed abroad. Phase III trials of such drugs were only allowed if the drug had already been fully tested elsewhere.

Outcome:
In April 2005, the FDA issued a non-approvable letter regarding Solvay’s marketing application for cilansetron and requested additional clinical trials. In November 2005, Solvay withdrew its New Drug Application (NDA) in the US. Discussions with EU authorities continued, but attempts to obtain EU marketing authorisation may also have been abandoned.

Sources:

- C.M. Gulhati, “Debate: Should clinical trials be allowed in India?” Business Standard, 18 Feb 2004.
- C.M. Gulhati, “Needed: Closer scrutiny of clinical trials,” Indian Journal of Medical Ethics, Vol.12(1), Jan-Mar 2004, <http://www.issuesinmedicalethics.org/121ed004.html> (Jan 2008).
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Zoniporide trials in India

Drugs:	zoniporide
Treatment:	Perioperative cardiac events
Sponsors:	Pfizer
Period:	Unclear, probably around 2000
Location:	India

Unethical aspects:
The Drugs Controller General of India (DCGI) approved Phase III trial of Pfizer's zoniporide while Phase II trials had not been completed in the USA and carcinogenic and reproductive studies on animals mandated by Indian law had not been completed.

Violated norms:
- DoH §11: Required animal experiments had not yet been completed.
- Before 2005, the Schedule Y of the Indian Drug and Cosmetic Act prohibited clinical trials in India of drugs developed outside the country before Phase II trials were completed abroad. Phase III trials of such drugs were only allowed if the drug had already been fully tested elsewhere.

Outcome:
Not known.

Sources:
- C.M. Gulhati, "Needed: closer scrutiny of clinical trials," Indian Journal of Medical Ethics, Vol.12(1), Jan-Mar 2004, <http://www.issuesinmedicalethics.org/121ed004.html> (Jan 2008).

Maxamine trial in Russia

Drugs:	histamine 2HCl (Maxamine)
Treatment:	Treatment for Hepatitis C
Sponsors:	Maxim Pharmaceuticals (US)
Period:	Around 2000
Location:	Russia, also in Israel, Belgium, and UK

Unethical aspects:
The US FDA insisted on more animal tests before testing the drug Maxamine on human subjects. Because the company could not get approval for Phase III trials in the US and wanted to proceed with the testing, it moved trials to Russia where the research plan was approved in 30 days. In Russia, researchers were not aware that the FDA required more animal testing.

Violated norms:
- DoH §11: Animal experiments may have been insufficient to continue with testing on patients.

Outcome:
In August 2000, Maxim announced a USD 100 million deal with Roche for further development of the drug.

Sources:
- M.P. Flaherty, D. Nelson, and J. Stephen, "The Body Hunters: Overwhelming the Watchdogs," 18 Dec 2000, <http://www.washingtonpost.com/ac2/wp-dyn/A11986-2000Dec15, http://www.washingtonpost.com/ac2/wp-dyn/A11976-2000Dec15> (Jan 2008).

Trials on foster care children in New York

Drugs:	Various ARV drug combinations and vaccines: didanosine, zidovudine, nevirapine, ritonavir, valacyclovir, Live-Attenuated Varicella Vaccine (Varivax) Seven Valent Pneumococcal Conjugate Vaccine, Recombinant Interleukin-2 (rIL-2) Recombinant Envelope Proteins of HIV-1 gp160 and gp120
Treatment:	ARV therapy, vaccination against infectious diseases
Sponsors:	US National Institute of Allergy and Infectious Diseases (NIAID), US National Institute of Child Health and Human Development (NICHD), Genentech, MicroGeneSystems, Lederle-Praxis Biologicals
Period:	1997 – 2002
Location:	New York, US

Unethical aspects:
Phase I and II clinical trials were conducted on HIV-infected children and infants in the guardianship of New York City Agency for Children's Services (ACS), living at Incarnation Children's Center in Harlem, a foster care facility under contract with ACS. The ACS provided consent for their participation. Children were forced to take the experimental medication that made them severely ill and had potentially lethal side effects.

Violated norms:
- DoH §8: The children were vulnerable subjects and did not receive the required special protection.
- DoH §24: The research should not have been performed on children without justification.

- The US Code of Federal Regulations prohibits the use of children who are wards of the state from being subjected to experiments involving greater than minimal risk.

Outcome:
The trials were suddenly halted in 2002. The Office for Human Research Protections (OHRP) conducted an investigation and confirmed noncompliance with legal regulations for the protection of human research subjects.

Sources:

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Cilostazol trials in India

Drugs:	cilostazol (Pletal)
Treatment:	Treatment of intermittent claudication
Sponsors:	Otsuka
Period:	Unclear, probably around 1999
Location:	India

Unethical aspects:
Drug trials were cleared by the Drugs Controller General of India (DCGI) based on incomplete, inadequate information on adverse effects. Common serious side-effects such as angina and myocardial infarction were not mentioned.

Violated norms:
- DoH §13: Serious Adverse Events were not reported.

Outcome:
Unknown.

Sources:

- C.M. Gulhati, "Needed: closer scrutiny of clinical trials," Indian Journal of Medical Ethics, Vol.12(1), Jan-Mar 2004, <http://www.issuesinmedicalethics.org/121ed004.html> (Jan 2008).

NDGA trials in India

Drugs:	nordihydroguaiaretic acid (NDGA)
Treatment:	Treatment for oral cancer
Sponsors:	Johns Hopkins Hospital (US)
Research organization:	Regional Cancer treatment Center (RCC)
Period:	1999 – 2000
Location:	Trivandrum, India

Unethical aspects:
The drug was tried on 26 cancer patients before its safety was established in animal tests. The patients were not informed that they were taking part in an experiment or that they were being denied an established treatment and two of them died. Subsequently, a 60-year-old woman was again included for a trial in which the RCC provided five doses of the experimental drug. The woman's condition turned critical before the fifth dose but she survived.

Violated norms:
- DoH §11: Required animal experiments had not yet been completed.
- DoH §20: Subjects were not informed they were participating in a trial.
- DoH §22: Informed consent was not obtained.

Outcome:
Under pressure from the media and NGOs, the government was forced to take action but only uspended the research for six months. The Indian Council of Medical Research conducted an inquiry into his trial but the results have not been made public. The John Hopkins University admitted that previous drug safety testing and the trial's consent forms had been inadequate and barred the involved scientist from serving as principal investigator on any future research involving human subjects.

Sources:

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- C.M. Gulhati, “Needed: closer scrutiny of clinical trials,” Indian Journal of Medical Ethics, Vol.12(1), Jan-Mar 2004, <http://www.issuesinmedicalethics.org/121ed004.html> (Jan 2008).

Cariporide trial in Argentina

Drugs:	cariporide
Treatment:	Protection against further heart damage after angina, artery-clearing or bypass surgery
Sponsors:	Hoechst Marion Roussel (now Sanofi-Aventis)
Period:	1997
Location:	Naval Hospital, Buenas Aires, Argentina

Unethical aspects:

None of the 137 patients participating in the trial at the Naval Hospital in Buenas Aires consented to the trial. The signatures on at least 80 informed consent forms were forged, and those who did sign the paper themselves did not know its contents. In total 13 patients died and at least three of them were considered murders because they were not given the right treatment. Data in medical records was changed and key documentation disappeared. In total, the drug was tested in more than 11,500 patients at nearly 400 study sites in 23 countries.

Violated norms:

- DoH §20: Not all subjects were informed they were participating in a trial.
- DoH §22: Consent was not obtained or fully informed.

Outcome:

A criminal lawsuit was started and the company decided not to apply for US marketing approval because of the disappointing outcomes of the trials.

Sources:

- K. DeYoung and D. Nelson, “Latin America is ripe for Trials and fraud,” Washington Post, 21 Dec 2000, <http://www.washingtonpost.com/ac2/wp-dyn/A31027-2000Dec20> (Jan 2008).

Colophon

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