Pharmaceutical Colonialism – Ethical Issues for Clinical Research in Africa

By

Dr. Tanya Lyons,

School of Political and International Studies, Flinders University.

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Pharmaceutical Colonialism is the term used to describe the activities of some of the big pharmaceutical companies and their contract research organizations (CROs), that involves exploiting the sickness and poverty of citizens of weak and/or developing states. This is enabled because there is a failure or lack of ethical policies and rules within those states that are implemented and designed to protect against unethical clinical drug trials. It is also caused by the CROs that can justify their study designs within various ethical loop holes in current international ethical guidelines. This paper will examine the issues of research with vulnerable populations, and their ability to make informed consent; and the use of placebo controlled clinical trials, where international best practice or standard of care is denied, simply because it would not be available in the local African context, because health care systems are non-existent or not functional.

I have previously argued that the activities of pharmaceutical companies in Africa amounts to "Globonialism,"[1] a combination of globalization hindering state strength to benefit only global corporations, in the process of extracting clinical data from sick patients in vulnerable communities, to support scientific evidence to gain approvals for drugs mainly designed to be marketed in western countries, but in drug trials that would either not be approved ethically in the west, and if they were, receive no volunteers. Where some African states have allowed international clinical trials to proceed, they

[1] Tanya Lyons, "Globalisation, Failed States and Pharmaceutical Colonialism in Africa", *Australasian Review of African Studies*, 30:2 (2009) - forthcoming

justify this 'investment' and 'intervention' on the basis that "something is better than nothing."[2]

Placebo controlled research

In their essay on the use of 'placebo' in AIDS research, David and Sheila Rothman have drawn a strong connection between human rights and medicine with "a commitment to informed consent and freedom from coercion"[3]. They provide a substantial amount of evidence in support of claims of pharmaceutical colonialism. Rothman and Rothman explain that the 1990s saw an increased shift in conducting medical experiments from America to the Third World, for two main reasons. 1: AIDS – "the first modern infectious disease to strike the developed and developing world simultaneously and to give both a large stake in finding a cure"; 2: "the mounting financial and regulatory burdens of research in the rich nations" [4]. Rothman and Rothman point out that both the 1947 Nuremberg Codes and the 1964 World Medical Association Declaration of Helsinki "say that the well-being of the subject always should take precedence over the needs of science of the interests of society, and that doctors must obtain 'the subjects' freely informed consent'"[5]. The problem is however, how can these principles be ensured and guaranteed when the levels of poverty and disease are so high and the access to relevant drugs is so minimal in the third world[6]? Their debate is outlined in relation to the clinical trials for anti-retroviral drugs aimed at reducing HIV transmission between mother and baby[7], where in many trials the active drug was only compared to placebo. This type of

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[2] Lyons, forthcoming.

[3] David Rothman, and Sheila Rothman, *Trust is Not Enough: Bringing Human Rights to Medicine*, New York Review of Books, New York, 2006.

[4] David Rothman and Sheila Rothman, 2006, p.53

[5] David Rothman and Sheila Rothman, 2006, pp.53-54

[6] Sonia Shah describes the history of medical experimentation on humans in the developed world. Ranging from the Nazi tests on Jewish victims if the Holocaust, the Tuskegee Syphilis trials on poor black Americans, drug trials on prisoners, and even children in state care (up until 1973), and The lack of testing, lack of regulations and approval of Thalidomide in 1957-1962. See Sonia Shah, *The Body Hunters: Testing New Drugs on the World's Poorest Patients,* New Press, New York: London, 2006, Chapter 4 Uncaging the Guinea Pig.

[7] The Rothmans also provide other examples of unethical placebo trials, for example, 'genital shedding and intrapartum transmission of HIV-1, in 1997-8 conducted in Nairobi. The investigators argued that they needed to "understand the mechanism of vertical [mother to infant] HIV-1 transmission" and they couldn't do this if the disease was treated with the standard care, AZT. In another study 3 different doses of gamma globulin were trialed for the same purposes. No patient received AZT. "The expense of AZT, compliance and toxicity considerations … make widespread use of this approach in developing countries impractical".

trial design can be unethical when a known effective treatment or better standard of care is available. Shah notes at least "15 different trials testing experimental interventions to block mother to child HIV infections in developing countries"[8], where all compared the active drug, even half doses of it, with a placebo. In these cases, the justifications were simple – the women would otherwise receive no treatment. This situation really highlights the ethical debate on placebo trials in the developing world, when an effective treatment is known of, and available in the west, but just unaffordable in the poor developing country. Instead, thousands of children were condemned to HIV infection. The ethical principles were compromised because the control groups were not given any effective therapy against HIV transmission, even though they existed. Researchers should have a "clear ethical obligation to provide them"[9]. By using a placebo arm in the trials the researchers "violated the Helsinki standards and demonstrated a 'callous disregard of their welfare'"[10]. By not providing the 'standard of care' to the research subjects a double standard is created, which further creates "an incentive to use as research subjects those with the least access to health care" [11].

Marcia Angell outlines the role that 'me-too' drugs play in the need for placebo controlled trials. These drugs are only a slight variation on existing successful drugs on the market, when patents expire, however, they are usually only tested against a placebo, so there is no way of telling if they are any better or worse than other existing drugs, just better than nothing[12]. This is obviously of benefit to the drug industry, but not necessarily to participants in trials. Therefore, any suggestion that convenient double

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The double standard here is noted by the fact that such a trial wouldn't be approved in the US, "because it withheld from the women a drug of known efficacy. By adopting a different set of rules, it could be conducted in Uganda". David Rothman and Sheila Rothman, 2006, p. 61.

[8] Sonia Shah, 2006, p.90

[9] Sonia Shah, 2006, p.91. Also see Neal Halsey et al. "Ethics and International Research: research Standards are the same throughout the world; Medical care is not", *British Medical Journal*, October 18 1997.

[10] Marcia Angell "The Ethics of Clinical Research in the Third World", in *New England Journal of Medicine*, Vol. 337, 1997, pp.847-849: cited in David Rothman and Sheila Rothman, 2006, p. 57

[11] Peter Lurie and Sidney Wolfe, "Unethical Trials of Interventions to Reduce Perinatal Transmission of the Human Immunodeficiency Virus in Developing Countries", *New England Journal of Medicine*, Vol. 337, 1997, pp.853-856: cited in David Rothman and Sheila Rothman, 2006, pp. 57-58.

[12] Marcia Angell, "Excess in the Pharmaceutical Industry", in *Canadian Medical Association Journal*, December 7, 2004, 171(12), p.1451

standards would be curtailed due to new ethical requirements worried the pharmaceutical industry that placebo trials for 'me-too' drugs would become too difficult.

As Shah has pointed out, there has already been "years of tortuous debate within the biomedical community" regarding the ethics of placebo controlled clinical trials in developing country settings[13]. Nonetheless, evidence that these types of trials continue is voluminous. The policies, institutions and organizations that are needed to pursue this type of pharmaceutical colonialism can be seen in a culmination of attempts to create double standards of care and ethical principles between people in developing and developed countries. For example, there have been various attempts since 1999 to update or qualify the Helsinki code to allow research to be conducted in developing countries (that couldn't otherwise be conducted in the west), that would ensure third world participants do not need to be offered first world standards of care[14]. In 2000, however the World Medical Association instead "strengthen[ed] protections of research subjects...by pointing out that placebos were only permissible when there was no known effective treatment"[15]. This was good news for potential trial participants and ethics committees to prevent any dangerous placebo trials.

The WMA's Declaration of Helsinki policy states at Note 29 that

> 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.[16]

In 2001 a clarification noted on this paragraph in the policy also states that

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[13] Sonia Shah, 2006, p.132. The debate was opened in the pages of the *New England Journal of Medicine* in 1997.

[14] See David Rothman and Sheila Rothman, 2006, pp.66-68. Rothman and Rothman have also been critical about a statement issued by the Nuffield Council of Bioethics in 2005 that states "wherever appropriate, participants in the control group should be offered a universal standard of care. Where it is inappropriate ... the minimum that should be offered is the best intervention currently available as part of the national public health system". This would also mean that researchers do not even need to meet the usually superior private health systems in those countries. See Nuffield Council of Bioethics, "The Ethics of Research Related to Healthcare in Developing Countries", 2005, cited in David Rothman and Sheila Rothman, 2006, p. 86.

[15] Sonia Shah, 2006, p. 133

[16] World Medical Association, Declaration of Helsinki, www.wma.net/e/policy/b3.htm (accessed January 2009)

> 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:
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> - **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
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> - 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.
>
> All other provisions of the Declaration of Helsinki must be adhered to, especially the need for appropriate ethical and scientific review (emphasis added).[17]

However, according to Shah "the FDA has been slowly trying to distance itself from the WMA and Declaration of Helsinki ... refus[ing] to incorporate new restrictions on placebo trials in 2001"[18]. Attempts to circumvent these strict codes include arguments in favour of **only needing local ethics committee's approvals for clinical trials**, rather than both home (the USA) and host countries. Such lax requirements would be problematic for many African countries where there are either no ethics committees (such as in Morocco), or corruption and bias has infiltrated the ethical review process (such as in Uganda)[19]. According to Shah, "one quarter of clinical trials conducted in developing countries went through no ethical review"[20]. Apparently, the US National Bioethics Advisory Committee finally recommended that approvals were required from both home and host sites "unless US officials decided that the foreign site was sufficient on its own"[21].

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[17] World Medical Association, Declaration of Helsinki, www.wma.net/e/policy/b3.htm (accessed January 2009)
[18] Shah, Sonia, "Outsourcing risks: testing new drugs on the world's poor", in *Le Monde Diplomatique*, June, 2007, accessed from www.global-sisterhood-network.org/content/view/1800/59/ March 25th 2008; and Sonia Shah, 2006, p.135
[19] Sonia Shah, 2006, p.135
[20] Sonia Shah, 2006, p.136
[21] Sonia Shah, 2006, p.136

In the 2007 *Australian National Statement on Ethical Conduct in Human Research*, Chapter 4.8 deals with "people in other countries" and reinforces the need for one standard of ethical conduct in both home and host countries in relation to respect, justice and beneficence - "the research should not be exploitative" (4.8.11), and the research should be conducted in "a way that accords the participants no less respect and protection than this national statement requires" (4.8.10). If there are no local ethics committees in the host country then the Australian Statement applies, and if local ethics approvals are required then the details of these need to be reported in Australia as well (4.8.4; 4.8.5).[22]

The Helsinki Declaration was again updated in 2004 with another footnote, this time to permit the drug industry not to offer ongoing access to a drug even if it was proven effective. 'Ethically' all they had to do was 'identify' and 'describe' whether they would offer a successful drug or not after a trial ended, before the trial began (presumably in the participant information sheet).

Thus while note 30 of the Helsinki Declaration states

> 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.[23]

The note of clarification on paragraph 30 of the WMA Declaration of Helsinki states

> The WMA hereby reaffirms its position that it is necessary during the study planning process to identify post-trial access by study participants to prophylactic, diagnostic and therapeutic procedures identified as beneficial in the study or access to other appropriate care. Post-trial access arrangements or

[22] However, for the purposes here, I do not have any data on Australian trials overseas and their ethical outcomes. This could be the subject of further research. The *Australian National Statement on Ethical Conduct in Human Research, 2007.*

[23] World Medical Association, Declaration of Helsinki, www.wma.net/e/policy/b3.htm (accessed January 2009)

other care must be described in the study protocol so the ethical review committee may consider such arrangements during its review.[24]

Shah has argued that participants in trials should be offered "access to the medicines whose approval they have helped secure". They should not be "priced prohibitively" and they should be relevant to the nations' needs. Others may argue however, that providing the drug at the completion of a trial may also provide an incentive to participate beyond altruism. Thus Shah concludes that now a host of "influential institutions ... [were] on record supporting double standards in medical research ... if there is solid scientific reason to believe trial subjects will not be harmed and can possibly benefit, then researchers should feel free to lower their ethical standards for impoverished patients"[25].

The ethical issues also come down to the question of informed consent, particularly in light of the unethical use of placebo trials. Rothman and Rothman question if participants from developing countries (where illiteracy levels are often quite high) actually can be fully informed and give their consent to trials, when even in the US a study found that 25-50% of participants "do not understand what it is that they have agreed to". They argue that "no-one ought to justify placebo-based protocols simply because Ugandan or Thai subjects consented to join them" [26].

Shah also demonstrates the difficulties in claiming informed consent has been achieved in these cases especially when participants are poor, have no choice, are in a powerless position in the relationship with doctors, and often are not even aware of the western scientific understanding of "bacteria or virus"[27]. In Thailand for example, there is no simple and direct translation for the word placebo[28], and "in some African languages

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[24] World Medical Association, Declaration of Helsinki, www.wma.net/e/policy/b3.htm (accessed January 2009)

[25] Sonia Shah, 2006, p. 139. These institutions include UNAIDS, NBAC, WMA, Council for International Organisation of Medical Sciences, European Group on Ethics in Science and New Technologies.

[26] David Rothman and Sheila Rothman, 2006, pp.70-71.

[27] Sonia Shah, June 2007.

[28] In the Thai language the word - *ya wiset* – translates as 'magic medicine', and may explain placebo only in terms of the 'placebo effect', while the word – *ya lork* – can be translated as a 'trick medicine', and may be more suitable to use when explaining placebo arms of trials in Thailand.

'there is no word for 'research' or 'science' ... [and] no concept of an experiment or placebo"[29].

Tenofovir

One example can be seen with Tenofovir, a drug aimed at reducing the transmission of HIV, which was trialed in Cameroon, Thailand and Nigeria for 12 months in 2004. In Cameroon, 400 sex workers were enrolled, 5 died. The study involved comparing the active drug with a placebo among sex workers most at risk of contracting HIV. However, the ethical considerations were questionable as the information given to mostly illiterate and French speaking volunteers, was in English. "Some of the women thought they were receiving a vaccine. Those who were given a placebo did not receive any advice on AIDS prevention or medical follow up"[30]. While the trial was approved by the Cameroon National Ethical committee, Chippaux argues that where many African ethics committees may exist in some form, they "still lack the necessary expertise and funding"[31]. Furthermore, even though this trial was sponsored by the drug manufacturer Gilead, the US Centre for Disease Control and the Bill and Melinda Gates Foundation, with their 'good intentions' to ease the health crisis in the third world, the actual relevance of this drug in this population was questionable. Even if it did prove effective, who could afford to take it everyday for the rest of their lives? Condoms also prevent HIV transmission and are cheaper, but these were not promoted in the study. The double standards evident in this placebo based trial on the world's poorest is indeed a clear case of Chippaux's 'strategic imperialism'[32], or at best, a misguided 'do-gooder colonialism'.

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[29] Sonia Shah, 2006, p.151.

[30] Jean-Phillipe Chippaux, "Pharmaceutical Colonialism in Africa" *Le Monde Diplomatique*, August 2005, translated by Donald Hounam, accessed from http://mondediplo.com/2005/08/11pharma, accessed March 25, 2008

, also See Somo, "Briefing paper on ethics in clinical trials, #1 Examples of Unethical Trials", February 2008, http://www.somo.nl/html/paginas/pdf/Examples_of_unethical_trials_dec_2006_NL.pdf, accessed May 14th 2008

[31] Jean-Phillipe Chippaux, 2005, suggests the Pan African Bioethics Initiative website as a source for this claim, but an examination of this does not immediately draw the same conclusions, www.pabin.org. "In the UK, the running costs of an ethics committee are about £36 000 a year and in the USA they can be as high as $500 000. Many developing countries lack regulatory mechanisms and a legal framework for biomedical research; moreover, poverty, poor pay and ignorance breed corrupt practices". See Alimuddin Zumla and Anthony Costello, "Ethics of healthcare research in developing countries" *Journal of the Royal Society of Medicine*. 2002 June; 95(6): 275–276.

[32] Jean-Phillipe Chippaux, 2005.

However, some have argued that such placebo trials are worthwhile to conduct in places where patients would otherwise get no treatment[33].

Those defending the above AIDS drug trials argued that local ethics committees were competent to review the protocols, and any criticism of that process would be patronizing (and racist)[34]. Thus, if this is part of pharmaceutical colonialism then it is by the request of the locals. However, it can be argued that a weak state is not able to negotiate on a level playing field with a powerful, globalised corporation, both colonizing and profit seeking (and bearing gifts!). Furthermore, in relation to political funding for medications, "no country wanted to spend significant amounts of money on second-class treatment"[35], so these trials needed to compare something to nothing, otherwise the something would not look as good as the most effective treatment (available in the developed world), and thus something is better than nothing, and these drugs could then be legitimately purchased by PPPs or national health authorities to assist their sick populations, profiting the pharmaceutical industry only.

CONCLUSION

What is the ability of "sick, poor subjects lining up at their clinic doors in Asia and Africa, to make informed and voluntary consent"[36]? Are we actually being paternalistic (in a colonial mindset) even to question their ability to do this? Sonia Shah demonstrates that the issue of "informed consent is an emperor with no clothes"[37]. That is, there seems to be a cynical attitude among some researchers and doctors of its effectiveness, because patients trust their doctors to advise them, and because there is no alternative to achieve

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[33] Jerry Menikoff and Edward Richards refer to this as *clinical equipoise.* Jerry Menikoff and Edward Richards, *What the Doctor Didn't Say: The Hidden Truth About Medical Research,* Oxford University Press, Oxford: New York, 2006, pp.67-68

[34] In support of such trials being conducted in the developing world, the Chairman of the Uganda Cancer Institute Research Committee, argued in an open letter that, "These are Ugandan studies conducted by Ugandan investigators on Ugandans ... It is not NIH conducting the studies in Uganda but Ugandans conducting their study on their people for the good of their people". Quoted by H. Varmus and D. Satcher "Ethical Complexities of Conducting research in Developing Countries", in *New England Journal of Medicine,* Vol. 337, 1997, pp,1003-1005, and Vol. 338 pp.836-844: cited in David Rothman and Sheila Rothman, 2006, p. 59.

[35] David Rothman and Sheila Rothman, 2006, p. 59.

[36] Sonia Shah, 2006, p.143

[37] Sonia Shah, 2006, p.163

an ethical façade/standard, we keep using it[38]. Informed consent needs to be considered more carefully. There are ways to get informed consent in poor and illiterate participants, using various methods, including translators and pictures for example. If consent still cannot be informed then the tests must be 'abandoned'. Shah, quoting bioethicist Jonathan Moreno, argues, "not all knowledge is accessible ... it is one of the trade-offs between realizing there is a moral difference between people and lab rats"[39].

[38] The outcome of the class action taken against Pfizer by 30 Nigerian families involved in the drug trial for Trovan in 1996 in Kano state may change these attitudes. However, in 2005 after being dismissed twice in the US court system, further avenues of appeal are being investigated. When forced to take the complaints through the Nigerian courts, "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". See Somo, February 2008.

[39] Sonia Shah, 2006, pp.150-151; and Sonia Shah, "Body Hunting: The Outsourcing of Drug Trials", January 31, 2007, www.theglobalist.com/DBWeb/StoryId_aspx?StoryId=5637 accessed May 2nd 2008

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