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ISSUES OF DRUG RESEARCH IN THE THIRD WORLD

"I was hearing of the frantic recruitment of third world 'volunteers' as cheap guinea pigs. Their role, though they may not ever know this, is to test drugs, not yet approved for testing in the US, which they themselves will never be able to afford even if the tests turn out reasonably safe. -- John le Carre[1]

Summary.

Multinational pharmaceutical companies stand accused of exploiting poverty in the developing world by failing to give priority to the development of drugs and vaccines needed by the poor (e.g. antimalarial drugs) because there is no profit in it; by preventing the manufacture and import of cheap generic drugs, by unethical use of the poor in drug trials, and by engaging in biopiracy[2].

Key Issues.

Only 1% of new medicines brought to market by multinational drug companies between 1975 and 1997 were designed to treat the tropical diseases that kill millions in the Third World[3]. Clinical trials of drugs and vaccines intended for poverty-related diseases such as malaria, tuberculosis and HIV/AIDS in developing countries under E.U. partnership programmes are commended as ethical, nevertheless, they require very strict control where documentation and clinical practice is less sophisticated. Elsewhere, medical trials involving HIV/AIDS attract heavy criticism[4], because this is a very vulnerable group, keen to have treatment which is not otherwise affordable. Women are particularly vulnerable, and in one trial to prevent transmission of HIV/AIDS to children, they were

1 www.heureka.clara.net/gaia/pharmas.htm

2 The charge by Third World countries that the multinational drug industry has "pirated" several billions worth of intellectual property in the form of plant-based traditional remedies from Africa, Asia and Latin America, has yet to be answered. And that "pirating" continues. It is important to state that the Paris Convention, an international agreement adopted in 1883 and revised six times and still in force, clearly states that non-protection of pharmaceutical patents is perfectly acceptable.

3 Doctors Without Borders.

4 Public Citizen, The US medical consumer group

given a placebo despite the fact that the drug AZT is already known to stop infection[5]. The defence would be that the priority is to developing cheap medication to stem the explosion of the disease in developing countries, and that maintaining placebo groups will increase the speed and effectiveness of the tests. If the right treatment can be developed quickly, they argue, hundreds of thousands of lives can be spared in the future. While it is regrettable that some women and their children must be consigned to a placebo group, they say, the overall benefit will outweigh this sacrifice.

While Western medicine might be attuned "hit and run" trials, the absence of sustainability and relationship exhibited in such research enhances denigration of rich nations in the eyes of peoples oppressed by a patronising culture of dependency and exploitation.

In the USA the average cost of a clinical trial is $10,000 per patient, in Russia it is $3,000. Figures are not available for underdeveloped countries, but it is probably much less. It can take $800 million to bring a new medicine to market, and thus the risk of exploitation is high. Insurance overheads are much less or non-existent in poor countries. Foreign drug trials have rapidly increased in Eastern Europe, Latin America and in Russia, where ethics review boards often are inexperienced and unsure of their roles. The FDA is unable to ensure that trial participants receive the same level of protection as those in the United States, and foreign Regulators cannot be relied upon to make sure patients are fully informed of risks and sign up willingly. There is the danger in extrapolating results from samples in a non-industrialised, poor environment to rich industrialised nations. There is the problem of extrapolating results from a different genetic pool.

The balance of bringing new drugs to market quickly to help people in need, and doing good science to protect the public from a drug's potentially dangerous side effects has been well rehearsed in systems such as the complex and elaborate Federal Drug Administration procedures. Such systems are poorly developed in poorer nations. Where health systems fail to meet demand, pharmaceutical trials can enhance care through provision of drugs, training, organization, buildings and equipment. But doctors and the sponsors of clinical trials, who include university departments as well as drug companies, say the changes needed to enhance provision cause research to become too expensive, and too onerous to continue after the study. Distinguished scientists agree with pharmaceutical companies that guidelines requiring researchers to provide the best proven treatment presents problems where demand exceeds provision. If interpreted literally, ethical guidelines to provide adequate levels of provision would make it almost impossible to do research.

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5 Tuskegee Experiment. a "textbook example of unethical research" conducted between 1932 and 1972: the Tuskegee Study of Untreated Syphilis. During the course of those infamous tests, 412 poor black farmers in Alabama were left untreated by government researchers -- even after penicillin, an effective treatment for syphilis, was discovered. New England Journal of Medicine published a much discussed editorial strongly criticizing a series of federally funded AIDS tests in developing countries. The editorial, by Dr. Marcia Angell, made the case that the studies constitute an unacceptable breach of medical ethics because they abandon those subjects in the "placebo group" to contend with untreated illness.

The World Medical Association (WMA) has asked pharmaceutical companies to ensure clinical trials are carried out to the highest standards. Amendments to the Declaration of Helsinki[6] have prioritised protection of participants in clinical trials in that participants must be fully informed of the risks and must be given proper medical care. UNAIDS has called for trials to be independently monitored to ensure they meet ethical standards. Amendments ask that patients who take part in a trial get the best treatment for their medical condition once the tests are over. The practicalities of this prove very difficult where health systems are rudimentary[7], and are impossible unless approved by the authorities in the host country. In the UK or USA patients in clinical trials continue to get successful new drugs on a compassionate basis after a study has ended, and before the granting of a licence.

Technological innovations are not "neutral"; they embody the values of their creators and sponsors. Billions of dollars are spent every year on weapons of destruction and luxury goods, consumerism rides high in the list of features of post-modern society. Technologies that would dramatically improve the quality of life in poor countries, such as nonpolluting energy sources, sustainable agricultural systems, basic health and sanitation measures receive minimal funding at best. Those who hold the reins of power exercise power over technological choice.

In the West, drug companies and their contractors offer large payments to doctors, nurses and other medical staff to encourage them to recruit patients quickly, and do not even have to conduct trials to get paid[8]. There are finder's fees for those who refer their patients to other doctors conducting research. Doctors who recruit the most patients receive additional benefits, such as authorship, even when the true author is a company employee using analysis from the drug company. Those who fail to meet the recruitment goals, query methodology, results, or analysis, are usually dropped from future studies. Thus, in a poor context and where bribes are an essential feature of the culture, the dual role of patient doctor and pharmaceutical investigator can easily promote corruption. There is a fine line between payment for work done and bribery, not always seen by regulatory systems.

In the USA, any company needs US FDA approval -entailing a regime of clinical trials-to be able to market a new machine or technique in the US. However, there appears to be no regulatory mechanism for conducting phase 1 and 2 of its trials in developing countries.

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6 World Medical Association Declaration of Helsinki; Ethical Principles for Medical Research Involving Human Subjects. Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the 29th WMA General Assembly, Tokyo, Japan, October 1975, 35th WMA General Assembly, Venice, Italy, October 1983, 41st WMA General Assembly, Hong Kong, September 1989, 48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996, and the 52nd WMA General Assembly, Edinburgh, Scotland, October 2000, with notes of clarification on Paragraph 29 added by the WMA General Assembly, Washington 2002 and Paragraph 30 added by the WMA General Assembly, Tokyo 2004.

7 "Neither sponsors nor researchers can take responsibility for deficiencies resulting from political mistakes and global economic circumstances".

8 For example, in 1996, a study of a migraine drug sponsored by Janssen Pharmaceutica, a unit of Johnson & Johnson, paid doctors $3,600 for each enrollment. Another study that year sponsored by Organon Inc. on a new birth control pill paid $1,100 for each patient. And a Wyeth-Ayerst study of drugs for hormone replacement in women paid $4,581.

There is no collaborating regulatory agency in India for monitoring clinical trials and one company, Surgilight, monitored its own trials in India and South America. India is a prominent recipient in the present climate of outsourcing of skills and talent by developed nations[9]. The Indian government's Health & Family Welfare department brought out new guidelines thereafter on 'good clinical practices for conducting clinical research in India', but very little is written about medical techniques. Guidelines on good clinical practices by the Central Drugs Standard Control Organization under the Ministry of Health, issued recently after cases of gross ethical violations by the Johns Hopkins Institute in collaboration with an Indian medical college went public are still inadequate. Clause 7.3 of the "Clinical Trials with Surgical Procedures/Medical Devices" states that the concept [of regulating medical devices trials] is new and admits that these do not come under the "strict purview" of existing regulatory bodies and vaguely shelves that responsibility to equally nebulous committees to be set up for such cases.

The Indian Council of Medical Research, which supports new intellectual property development only for research it specifically funds, is currently drafting a proposal for the establishment of an Indian Medical Devices Regulatory Authority. It is hoped that some guidelines and mechanisms of redress will soon come about.

In the rich world, "dumping" has become a very dirty word like "slavery" and "colonization." Classical "dumping" does not take place, instead it occurs as double standards in marketing practices. In their country of origin many potentially hazardous drugs may be promoted only for a restricted range of uses, and with certain mandatory warnings. If an importing country has no such requirements, the company can omit the warnings and can promote many more uses[10].

Since the mid-1980s, the Medical Lobby for Appropriate Marketing (MaLAM), based in Australia has carried out an enormous amount of lobbying drug companies about their marketing of certain drugs. Priority is given to misleading advertising in Africa, Asia and Latin America, where the practice is more common, more extreme and more dangerous. While many companies respond, the evidence indicates that misleading marketing practices continue.

The World Health Organization (WHO) started the Essential Drugs Programme (EDP) in 1981 with the aim of strengthening the national capabilities of developing countries in the

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9 In 2001, in India there was a controversy on issues of safety, efficacy and ethics when a non-medical scientist at the Baltimore, US-based Johns Hopkins University (JHU) conducted a clinical trial for an anti-cancer drug on Indian patients at the government Medical College Hospital at Thiruvananthapuram, Kerala, without proper authorization from any of JHU's regulatory institutional boards that ought to have considered if it was safe to use the drug on human beings. It also transpired that JHU had no knowledge of the scientist being granted $2m by a Minnesota-based start-up company called BioCure Medical for conducting the trials.

10 Hoechst withdrew Baralgan in West Germany potential toxicity. However, Hoescht markets it in several Third World countries. In India it is the ninth top selling brand-name drug. The indications for Organon's Durabolin in the British National Formulary are osteoporosis in post-menopausal women and aplastic anaemia. In Pakistan it is indicated for loss of weight, poor weight gain and malnutrition in children. The drug may produce precocious puberty, in a population which needs food and poverty relief for such indications as malnutrition and poor weight gain.

field of selection and proper use of essential drugs to meet the real needs of people in those countries. The programme also promotes and facilitates local production and quality control, where feasible, of such drugs[11]. The recent report, The World Medicines Situation, however does not mention the word exploitation, and the only reference to inappropriate use supports the widespread and dangerous nature of the problem[12].

To maintain fragile economies, indebted countries need loans to import basic essential needs such as food, fuel and pharmaceuticals. Loans are available only under conditions of structural adjustment laid out by the World Bank and International Monetary Fund (IMF). The structural adjustment policies usually demanded by these two institutions which have an adverse impact on health and pharmaceuticals include: currency devaluation - so that prices of imported goods such as pharmaceuticals go up; cuts in government spending - meaning that health subsidies are reduced or taken away altogether; removal of trade and exchange controls - resulting in the limited foreign exchange available being used up by the rich for importing luxury items and the disappearance of low-priced essential generic drugs from the market; and privatization of public sector enterprises, including health care[13].

In the United Kingdom human medicines are regulated by the Medicines and Healthcare products Regulatory Agency, and in Ireland by the Irish Medicines Board, in accordance with national and EU laws. The EU legislation has recently been changed to ensure that the system continues to protect public health in an enlarged Community and the UK Government are working on implementation. The Seroxat story reveals flaws in the system.

Summary.

The situation regarding the testing of drugs in the Third World, in general.remains unsatisfactory, in that testing can be carried out more cheaply but more importantly

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11 A progress report by the Director-General of WHO to the World Health Assembly in May 1992 reviewed the world drug situation. The progress report, "Implementation of WHO's Revised Drug Strategy: Action Programme on Essential Drugs" stated, among other things, "Approximately half the world's population still lacks regular access to the most needed essential drugs. Moreover, it is estimated that perhaps over 60 percent of the developing world does not have regular access - and socioeconomic deterioration in the developing world over the past decade has made progress difficult. This disturbing estimate for the developing world reflects a drug situation where poorly coordinated policies and strategies, inefficient procurement, uneven distribution, inadequate assurance of quality, unaffordable prices and improper drug utilization are often more the norm than the exception."

"It has become increasingly clear that the current level of cooperation is not sufficient to counter the socioeconomic decline in developing countries. The Director- General emphasizes that Member States will need to increase their efforts significantly to make the most of the present political will and momentum in the development of national drug policies and in the implementation of national essential drugs programmes."

12 The inappropriate use of medicines is not only widespread, it is costly and extremely harmful both to the individual and the population as a whole. Adverse drug events rank among the top 10 causes of death in the USA and are estimated to cost that country between US$ 30 and US$ 130 billion each year. The World Medicines Situation WHO 2004.

13 The per capita GNP of the bottom 20 percent of the people in Nepal , for example, is U.S.$25. If health subsidies are cut and prices of essential food grains go up by even a few cents, these people have to go without health care and food.

without the same safeguards expected in First Wowrld countries. Secondly there is no right of continuing to receive the drug once the trial is over.

The arguments over the ethics of drug research are well rehearsed in the literature and we would not want to demonise ethical attempts to advance science and technology. Underlying issues such as poverty and justice are more fundamental issues which underpin the reality of undertaking drug research. If these are not addressed, the arguments related to drug research might seem isolated and difficult to understand.

The Medical Ethics, Science and Technology Sub-committee