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Pharmaceutical research: paradox, challenge or dilemma?

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Pharmaceutical research: paradox, challenge or dilemma?

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البحوث على المستحضرات الدوائية: مفارقة أم تحدٍّ، أم معضلة؟

عبد اللطيف شيخ

الخلاصة: يتم الآن إجراء العديد من البحوث على المستحضرات الدوائية في البلدان النامية مثل باكستان. فهل يؤخذ في الاعتبار تحقيق التوازن بين ضرورة إجراء البحث وبين فائدته للبلدان وللّذين يُجرَى عليهم البحث، وهم غالباً من الأميِّين والفئات المحدودة التعليم؟ إن البحوث الدوائية في باكستان قد تفيد المرضى والدولة على حد سواء، مع ضرورة التواصي بتعزيز الممارسات السريرية الجيدة وإعداد الدلائل الإرشادية الوطنية. كما يجب أن تقوم الحكومة والصناعة نفسها بدورهما في تحقيق التوازن المنشود والحفاظ عليه.

SUMMARY A great deal of pharmaceutical research is nowadays carried out in developing countries such as Pakistan. Is it, however, beneficial for the country and the participants, often the poorly educated and illiterate? Pharmaceutical research in Pakistan can bring benefits to both patients and country. Promotion of good clinical practice and the development of national guidelines are advocated. Government and industry both have a role to play to maintain the right balance.

Recherche pharmaceutique : paradoxe, défi ou dilemme ?

RÉSUMÉ Une grande partie de la recherche pharmaceutique est réalisée de nos jours dans des pays en développement tels que le Pakistan. Cependant, le pays et les participants, qui souvent sont les personnes ayant peu d'instruction et illettrées, en tirent-ils un quelconque bénéfice ? La recherche pharmaceutique au Pakistan peut procurer des avantages aux patients ainsi qu'au pays. La promotion des bonnes pratiques cliniques et l'élaboration de lignes directrices nationales sont préconisées. Le gouvernement et l'industrie ont tous deux un rôle à jouer pour maintenir le juste équilibre.

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Introduction

Globalization of health research and the conduct of clinical trials involving human participants over the past few decades has highlighted a number of ethical issues, especially in those situations in which organizations sponsoring research carry out studies in other countries. These may be done as a way of helping the host country address a public health problem; the research sponsor may consider the foreign location more convenient, more efficient, or less troublesome for a specific study; or the study may be carried out as a joint effort to address a specific health concern that is important in both countries.

The pace and scope of international collaboration in biomedical research have increased during the past few years, and now questions about the ethics of designing, conducting, and following up clinical trials have re-emerged. There is concern that research done by scientists from the richer countries but carried out in poorer nations that are heavily burdened by disease may be seen as imposing ethically inappropriate burdens on the host country and on the participants themselves. The potential for exploitation has engendered efforts to ensure that those who participate in international clinical trials are protected.

Pakistan is one of the developing countries where balance still needs to be attained between supply and demand in health care. Health care spending is escalating at a rate of US$ 0.3 billion per annum, which translates in to US$ 100 million per annum rise in pharmaceutical sales [*1*]. Unfortunately, the number of physicians per 1000 population remains static [*1*]. This is an indicator of the enormous burden of health care expenditure on the Indian subcontinent, where per capita annual income is equivalent to about $US 400. The public health system receives 0.8%–4.0% of the gross national product [*2*] (compared with 10%–15% in developed countries [*3*]). These hard facts, coupled with the general lack of third-party health insurance, mean that < 40% of our population has access to pharmaceuticals [*1*].

The major portion of our population, therefore, relies on alternative medicine, primarily practised by sidewalk practitioners, e.g. people practising the homeopathic system or *unani tibb* (Greek medicine); herbal or traditional healers; and spiritual healers (*pirs*, *aamils*, etc).

The pharmaceutical industry and research

The market in Pakistan

The role of the pharmaceutical industry needs to be explored. The Pakistani pharmaceutical market is estimated to be US $1.25 billion. There are 35 000 pharmaceuticals registered in the country [*4*]; prepackaged and formulated preparations are the mainstay of the industry. The usage, distribution, dispensing and administration monitoring aspects go unchecked, and the primary focus remains on production. The main share of the market is enjoyed by antibiotics (28%), followed by gastrointestinal drugs (14%) and respiratory medications (8%) .

The market shares of multinational and indigenous companies are converging quite rapidly. It could be depicted as an approximate 5% loss in local market share annually for the multinational companies, which are rapidly being overtaken by the local pharmaceutical companies. An analysis of the 7-year period 1998–2005 clearly shows a shift of market share from 30:70 to 50:50 for local and multinational companies. The annual growth rate for the Pakistani pharmaceutical market is estimated to be 5%,

with a 10% rise in institutional sales. This has a far-reaching impact on the research that is conducted in the country, and also on the quality of pharmaceuticals in clinical research.

Challenge: research and development

Most of the developing countries lack active research and development laboratories. The majority of industrial processing revolves around packaging and formulation. This, of course, leaves the pharmaceutical companies, primarily the multinational companies but some local ones too, at an advantage and allows them to proliferate in this area: research and development remains solely their realm. The research and development of a drug needs 3–4 times more capital today compared to 10–15 years ago. The graphical representation of the research and development expenditure of developed nations, particularly Japan, the United States of America and the European countries, provides a fair idea about this rise. Between 1990 and 2004, expenditure on drug research and development in Europe rose from 7941 to 21 500 million euros. In the United States of America during the same period, it rose from 6015 to 27 095 million euros, and in Japan from 1990 to 2003 expenditure rose from 3941 to 6743 million euros."

While analysing the data, it should be remembered that marketing expenditures are always embedded with research and development activities. A breakdown of research and development activities of 9 top pharmaceutical companies shows that 30% of expenditure is used for discovery research and 35% for clinical evaluation; 22 % is accounted for by non-clinical evaluation [*5*]. This 22% of the expenditure could be linked to marketing investment.

Additionally, when comparing the pharmaceutical industry with other industries, the research and development expenditure is proclaimed to be much higher [*5*]. This could be a result of the large marketing expenses component, which is obviously not an element of core research.

Paradox

The number of trials conducted in the developing countries is lamentable: 90% of medical research funds are spent on the richest, i.e. 10% of the world's population [*6*], and research and development expenditure for diseases of poverty (e.g. malaria, tropical diseases, tuberculosis etc.) is regarded as high risk (failure) and providing low returns. Drug trials in developing countries are usually initiated outside the country and dominated by the partner from the developed country, for example, Pharmacia-Upjohn has a research and development budget of US$ 2.2 billion per year, but only 6% is spent in Asia, mainly in Singapore, Taiwan, Hong Kong and Korea [*7*]. In his 1999 article, Silverstein says, "Many people of the Third World die of preventable, curable diseases. … malaria, tuberculosis, acute lower-respiratory infections claiming 6.1 million lives in 1998. People die because the drugs to treat those illnesses are nonexistent or are no longer effective, and they die because it doesn't pay to keep them alive" [*7*].

This unequal equation of overlooking diseases of the poor can be well illustrated when one identifies the origin of research money: in the United States of America, 70% of research is funded by industry and only 30% by the National Institute of Health [*8*]. It would be interesting to know the fringe benefits involved in the sponsored trials fuelled by the research and develop-

ment expenditure. The following rates will definitely serve as an eye opener [*9–11*]:

- paid speaking arrangements: ranging from $250 to $20 000/year;
- paid consultancies: mostly less than $10 000 but may be up to $120 000/year;
- paid positions on advisory boards, equity holdings: mostly over $10 000 and ranging up to $1 million/year.

Apart from these overwhelming incentives, the "luncheons" should not be left unaddressed. Across the United States of America, as a part of their research efforts, drug companies sponsor close to 300 000 events for doctors every year, many of them far more generous than a free pizza [*10*].

Dilemma

Millions of people die from preventable or curable diseases every week. But there is no market in the sense that, unlike Viagra, medicines for leishmaniasis are needed by poor people in poor countries. Pharmaceutical companies judge that they would not get sufficient return on research investment, so why, they ask, should they bother? Their obligation to shareholders, they say, demands that they put their effort into trying to find cures for the diseases of affluence and longevity: heart disease, cancer, Alzheimer's. Of the thousands of new compounds drugs companies have brought onto the market in recent years, less than 1% have been for tropical diseases [*12*].

Pharmaceutical companies may not be altruistic, but they may still have a powerful reason for sticking to ethical practices: "It's not in anyone's interest to do anything that would ultimately result in a drug being recalled," said Kate Robins, a spokeswoman for Pfizer. "You wouldn't spend a billion dollars if you're going to cut corners and it's going to ultimately be recalled. You're going to go into places where you can hold up to standards that are international," she said [*13*]. "There is no easier, softer way. There just isn't."

Drug trials in developing countries

Another area of concern regarding clinical trials is the vertical transmission trials conducted in a variety of developing countries by researchers from more-developed countries. These illustrate a variety of ethical issues. Three crucial issues are the injustice of the use of placebo control groups, the coercion used to recruit participants, and the exploitation of developing countries. A 2002 study examined each of these issues separately. It developed a new standard for when placebo control groups are acceptable and concluded that the issue of coercive offers was not well founded. and that concerns about exploitation are better addressed by assurances about the future care of the participants in the trial than by assurances of availability of the drugs in the country in general [*14*].

Against this background, it is hard to tie in ethics with research. Essentially, research requires expertise, diligence, honesty and integrity. Ethical research is vital to generate sound knowledge, but what does the ethical conduct of research involve? The concern regarding ethical consideration in research in developing countries could be expressed by the following questions. How does one obtain informed consent from people who cannot read and write? Who oversees the trials in areas where ethical review committees are unknown? Is the disease under investigation similar in different countries (epidemiological data are required to answer this question)? Is the trial relevant to the country? Are the risk factors the

same, is the treatment relevant and are the outcomes approximately the same? Do the culture and infrastructure exist to carry out this trial [*15*]?

The researcher may wish to stratify a method for obtaining genuine consent for participation, keeping in mind the standard of care locally and in developed countries.

There is always an abundance of vulnerable communities in developing countries, and this is so in Pakistan. Limited economic development; inadequate community/cultural experience with, or understanding of, scientific research; limited availability of health care and treatment options; and limited ability of individuals in the community to provide informed consent are some factors requiring much attention. In many countries, it is important for researchers to obtain permission from local leaders before seeking individual informed consent, and to discuss other aspects of the research. Although it may be difficult to identify the members of the community who should be consulted and to determine the level of authority they should have to permit researchers to approach potential participants, we believe that such consultations can be helpful in improving both the informed consent process and the overall research design.

Good clinical practice

What is the importance of good clinical practice? Ideally speaking, it protects the right of study subjects with respect to integrity and confidentiality. Good clinical practice also ensures that the data-driven results are credible. Scientifically, clinical trials are carried out for the testing of hypotheses, registering new drugs and devices, post-marketing surveillance in order to document efficacy and safety, and to obtain data for publication. Hence, the methodology of the clinical trial matters a lot. Study design, selection of appropriate subjects, adequate sample size, duration of the study and effectiveness of follow-up are some important aspects that may reflect on the credibility of the results.

Good clinical practice remains essential no matter where the study is conducted or who is conducting it. The prime concern is why developing countries are the favoured location for clinical trials. The large patient population, low incurred costs, a legislative vacuum or shortcomings, ignorance about legal and ethical issues and a strong desire among the developing countries to link up with institutions from rich countries at any cost could be the most likely reasons.

The developing countries do need clinical trials to be conducted—for the development of new medicines and regimens suitable for the local environment; to verify safety and efficacy on different ethnic groups; for academic interest and stimulation; and to generate income for institutions as well as individual financial reward. These are important considerations as far as developing countries are concerned.

Good clinical practice in Pakistan

In Pakistan, the government has definitely recognized the graveness of the issue, reacting to it by forming in 2002/03 a Ministry of Health/World Health Organization committee on good clinical practice, functioning as a Ministry of Health Research Cell. The final draft of the *Pakistan good clinical practices* has been sent to the World Health Organization for review.

On the part of our pharmaceutical industry, some issues still need to be resolved: lack of infrastructure and the overwhelming contribution of multinational industries in trials disturbs the equilibrium.

The way trials in Pakistan are conducted is deplorable. They are mostly phase IV (replicate) trials, which are more promo-

tional than evaluative. Company-sponsored clinical drug trials mostly use drugs supplied as samples. The majority of them are non-randomized, uncontrolled and open label. They are disguised as post-marketing surveillance, but in reality their anticipated outcome is to broaden the market share. The pharmaceutical companies have taken over the greater proportion of trials conducted; investigator-initiated trials and independent international publications are rare entities.

As has already been mentioned, local institutions in developing countries, particularly Pakistan, have an interest in tagging along on trials run by the multinationals; it is, however, worth noting the situation of our citizens participating in the clinical trials.

Access to healthcare facilities and pharmaceuticals is still a dream for most of the population. The lack of third-party insurance and governmental healthcare coverage policies may encourage people to participate in clinical trials as this may the only way they can obtain medical attention and get a chance to gain access to healthcare facilities. These poorly educated, and mostly illiterate, persons do not understand the consequences of being research subjects.

Role of the ethical review committee

In such a scenario, where a person is not aware of his or her rights and safety once inducted into the study, the ethical review committee needs to play a strong role in the interests of the population. The dilemma is that the ethical review committee in a developing country may overlook the importance of the local value system and also the adequacy of resources. The committee may fail to acquire the representation of social scientists, ethicists and other allied health professionals; thus, ethical review committees remain mostly physician-driven. Problems which initially appear minor, such as inadequate translation of informed consent in national languages, may turn out to be a nightmare for the study participants.

Involvement of clinicians

Clinicians have a complex relationship with the pharmaceutical industry, and need to critically evaluate their handling of samples and their contact with pharmaceutical company representatives to optimize this relationship and ensure quality patient care. Clinics with specific policies for interactions with drug companies appear to derive greater satisfaction from their encounters.

Gifts, no matter how small, produce a sense of reciprocity in the recipient; this is why pharmaceutical companies provide pens, notepads, name badge holders, etc. Social science has documented the way that gift recipients feel impelled to do something in return for the giver. However, this creates a conflict of interests: the desire to cure the patient versus the subconscious need to repay the drug company's generosity. While these 2 goals can be congruent, they may not be.

Entitlement is also an issue: students and resident physicians feel entitled to a good lunch and cool gadgets from the drug companies.

Role of the authorities

On the part of the regulatory authorities, a revolutionary transformation is required to provide the infrastructure to support research, ensure standards of care and safety, develop guidelines/legislation and implement standards. The Government of Pakistan has taken the initiative to formalize a National Committee on Good Clinical Practice and Good Prescribing Practice. The committee is to be a guideline-formulating body and will be responsible for training the health care community by organizing courses and seminars.

Conclusion

Promotion of good clinical practice in countries such as Pakistan requires mass awareness and education campaigns, training programmes or course development, the development of national guidelines, government and health ministry involvement at all levels and regular monitoring to evaluate benefits and ensure progress.

Pharmaceutical research is crucial to Pakistan. It brings benefit to the patients and wealth to the country. Government and industry have a definite role to play to keep the right balance between industrial policy and health policy. One should welcome and reward innovation, regulate less and better. The unprecedented movement between countries of people, goods and ideas has increased awareness of the imbalance in the global burden of disease among the citizens of developed countries. This is sometimes referred to as the 10/90 gap: less than 10% of global health care expenditure is devoted to conditions that account for 90% of the global burden of disease [*16*].

Initiatives to reduce the burden of disease in developing countries are urgently needed. Clinical trials responsive to the health care needs of developing countries are one such initiative. It is, however, neither necessary nor desirable to lower ethical standards in order to achieve this goal. On the contrary, standards should be maintained, and adapted specifically to the needs of developing countries.

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e-Health Code of Ethics

On Wednesday, May 24, 2000 the e-Health Ethics Initiative introduced a code of ethics for health care sites and services on the Internet. The "e-Health Code of Ethics" will help people worldwide realize the potential of the Internet for improving health and minimize its potential for doing harm. The e-Health Code is available in Arabic, Chinese, English, French, German and Spanish at: http://www.ihealthcoalition.org/. The Arabic version is also available on the EMRO website at: http://www.emro.who.int/his/medicalethics.htm