Clinical trials and the pharmaceutical industry

Ensaios clínicos e indústria farmacêutica

Los ensayos clínicos y la industria farmacéutica

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Authorization to market a drug is conditioned on submitting the results of clinical trials, proving that the product meets national and international standards and that it can be used to benefit human health. Who presents the proof? The manufacturer. Who authorizes use of the drug? The national regulatory agencies.

Clinical trials are the epidemiological approach that provides the best evidence of a drug's safety and efficacy. The first record of a controlled trial dates to the 18th century, on a ship whose crew was racked by scurvy. The trial was conducted in 1747 by James Lind, who compared different diets in 12 sick sailors. The best results came from adding citrus fruit to the diet, which led to the routine inclusion of lemons in sailors' rations on long seafaring voyages [1].

One virtue of clinical trials is that they compare different treatments, or treatments versus placebo (a just tribute to spontaneous cure!). They also randomly distribute study subjects between treatment arms, thereby guaranteeing that characteristics unrelated to the experimental drug do not influence the results (either for or against). Such virtues also allow less "contaminated" observation of the experimental treatment's effect and its role as compared to other therapeutic options.

The pharmaceutical industry has been referred to as "Big Pharma", possibly due to its enormous economic power. World pharmaceutical sales reached US$400 billion in 2002 [2]. Although manufacturers are required to submit their research results to the regulatory agencies, many clinical trials are conducted with government and university resources from the companies' home countries. For the ten largest companies, spending on research and development corresponded to 11% and 14% of sales in 1990 and 2000, respectively [2]. These percentages were exceeded by administrative and advertising expenditures.

The relationship between the two sides of the "clinical trials-pharmaceutical industry" dyad entails an obvious contradiction. On one side, drugs as a technology are used to cure diseases and relieve symptoms; on the other, they are produced mainly by corporations with a firm footing in the economic market and that are subject to the market's laws and driven by the pursuit of profit.

This contradiction produces devastating effects that have become progressively more visible to health professionals and citizens, triggering vigorous challenges. A movement among the editorial boards of respected biomedical journals currently aims to overcome manufacturers' resistance to publish their research results. Additionally, medicine and drugs have a huge role in spending, health, and life. And there is an in-

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creasingly critical stance towards the strategies used by the pharmaceutical industry to publicize purported therapeutic novelties which in fact are not new.

Among the 78 drugs approved by the U.S. Food and Drug Administration (FDA) in 2002, only 17 contained new active ingredients, of which seven represented improvements on products already on the market. The others were variations on old drugs or ones that failed to represent any therapeutic improvement [2]. Such results are obtained by lobbying the regulatory agencies and conducting countless trials (the majority with products already on the market) to find new uses and expand markets. The other side of the numerous purported therapeutic novelties is the expansion of the concept of disease and the drugs' therapeutic indications.

One of the most prestigious biomedical journals, the *British Medical Journal*, launched the campaign *Too Much Medicine: Too Little Care*, raising the current concerns among researchers and social activists [3]. Changes in the line between normal and abnormal have expanded the concept of disease and generated a troublesome boom in diagnoses. This has occurred with arterial hypertension, diabetes mellitus, osteoporosis, and cholesterol levels. Minor modifications in diagnostic definitions have expanded the proportion of the population classified as either sick or "carriers" of risk factors, and consequently the number of potential candidates for drug treatment.

Two examples justify these concerns. One comes from the field of diagnostic resources and the other from mental health. Pulmonary angio-CT, a new technology for the diagnosis of pulmonary embolism, is associated with an 80% increase in the detection of pulmonary embolism, many of which would not even need to be found [3]. In the case of mental health, despite controversies on the definitions of attention deficit and bipolar disorder, the new diagnostic criteria proposed by the American Psychiatric Association (APA) could lead to a veritable epidemic of false positives. Decisions on the distinction between the normal and the pathological may easily mask conflicts of interest: more than half of the APA panel members responsible for these psychiatric definitions have financial ties with the pharmaceutical industry [4]. The impact can be measured in millions of people being treated unnecessarily or even suffering adverse effects.

Not coincidentally, scientific journals require authors to disclose their conflicts of interest. Readers need to know who defines the new limits of the disease, and whether the definition separates the sick from the non-sick, or adds risk factor carriers to the sick. Caregivers need to know the natural course of the disease for various population groups, including which groups will benefit from the administration of given drugs. Patients need to know whether the benefits outweigh the risks, including adverse effects, additional expenses, and changes in social and psychological status.

The issues regarding lack of transparency in the results of research sponsored by the pharmaceutical industry are not limited to the professional sphere. An article by *The New York Times* [5] reports the efforts by renowned researchers to disclose the results of clinical trials in order to publicize the real benefits and hazards of new drugs.

One point of departure for this movement was the *Cochrane Collaboration* revision on the flu drug Tamiflu (oseltamivir), manufactured by Roche. The previous revision had concluded that the drug was effective in reducing the risk of complications from influenza, such as pneumonia, but the new revision showed that this conclusion had been based on incomplete data and studies that had not been published in medical journals. The request for access to the set of studies was initially conditioned on signing a confidentiality agreement, but the researchers refused. In December 2009 the *Cochrane Collaboration* team concluded that there was no proof that the product reduces complications of influenza (a self-limited disease that usually courses with spontaneous cure). That same year, Tamiflu purchases by national governments to stockpile for possible flu outbreaks already accounted for 60% of the US$ 3 billion in turnover on the product's sales. And the Tamiflu issue has not been resolved to this day [5].

Over time, similar episodes have involved a great effort to ensure transparency in decisive issues on the role of drugs in preventing and curing diseases. The inevitable result has been to shake society's convictions and reduce its expectations on the unlimited benefits of medicines. Independent researchers have studied and extensively documented their observation of distortions in the results of published studies that overstate favorable results of new products while omitting or downplaying unfavorable ones. To recall several episodes: the court cases involving claims of underreporting of heart attacks in studies on Vioxx (rofecoxib); publication of distorted data on the association between the antidepressant Paxil (paroxetine) and suicide risk in young people; non-disclosure of safety data on the lipid-lowering drug Avandia (rosiglitazone); postponement of removal from the market in the case of ineffective and harmful weight-loss products such as

sibutramine; and postponement of the decision to restrict therapeutic indications without scientific proof, as in hormone replacement therapy in menopause.

Several measures have been suggested for the patient care quality improvement agenda [3]. These include: maintaining healthy skepticism towards changes in disease thresholds; limiting the automatic ordering of tests to include only those that actually assist diagnosis; conduct screening selectively and with a scientific basis; and interpret abnormal results within the context of the overall clinical picture, repeating and reconsidering tests in light of treatments. Thus, clinicians and patients would be acting to contain the diagnostic avalanche.

Drugs should be valued when they are supported by robust scientific evidence for their efficacy and safety and are prescribed by well-trained and well-informed healthcare professionals, within the authorized therapeutic indications and only for the necessary time. A drug prescribed to relieve suffering and reduce pain should be employed sparingly, based on clear criteria, and when other measures are ineffective.

In individual patient care, a watch-and-wait approach, minimal intervention, counseling, and non-pharmacological measures should prevail over the uncritical acceptance of manufacturers' dictates. The pharmaceutical industry has less to do with health than with business, investments, stock prices, and individual gain. All this justifies the pressure for transparency, in order to make the results of clinical trials public.

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