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Universal ethical principles and their application in clinical drug trials

Los principios éticos universales y su aplicación a los ensayos clínicos de medicamentos

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ABSTRACT Since 1931, and especially since the Nuremberg Code of 1947, an increasing number of declarations, regulations, norms, guidelines, laws, resolutions, and rules intended to create conditions for better protection of subjects participating in research studies have been published, although some have meant setbacks in the human rights of vulnerable populations. As such, violations of the dignity of experimental subjects in clinical trials continue. What researchers investigate and how the research is done, the quality and transparency of the data, and the analysis and the publication of results (of both raw and processed data) respond to the financial interests of the pharmaceutical companies, coming into permanent tension with bioethical principles and the needs of society. The active participation of civil society is necessary to make it so that pharmaceutical research, results and applications subordinate economic benefits to the protection of human rights.

KEY WORDS Research; Human Rights; Scientific Misconduct; Bioethics; Ethics Committees, Research.

RESUMEN Desde el año 1931 y, especialmente, desde el Código de Núremberg de 1947, un creciente número de declaraciones, regulaciones, normas, guías, leyes, resoluciones y disposiciones pretenden generar condiciones para una mejor protección de los sujetos que participan en estudios de investigación, aunque también algunas implican retrocesos en el respeto a los derechos de poblaciones vulnerables. Sin embargo, todavía no se ha podido evitar la violación de la dignidad de los sujetos de experimentación en ensayos clínicos. Lo que se investiga, cómo se investiga, la calidad y transparencia de los datos obtenidos, el análisis y la publicación de los resultados (tanto de los datos crudos como de los ya elaborados) están sometidos a la lógica del lucro, la cual presenta una tensión permanente con los principios bioéticos y las necesidades de la sociedad. Es necesario el protagonismo activo de los pueblos para que la investigación farmacológica, sus resultados y aplicaciones avancen en un rumbo que subordine el beneficio económico a la protección de los derechos humanos.

PALABRAS CLAVES Investigación; Derechos Humanos; Mala Conducta Científica; Bioética; Comités de Ética en Investigación.

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INTRODUCTION

Research with human experimentation has a dark history and is full of grey areas, and it is a field in which progress in knowledge runs parallel to the exploitation of vulnerable subjects, given their economic, social, or cultural condition.

In order to avoid abuses, many groups elaborated laws, regulations, and proceedings aimed at protecting the rights of the participants in research studies. Nevertheless, clinical research is usually subject to the commercial purposes of the pharmaceutical companies, the companies hired to conduct the research studies – *contract research organization* (CRO) – universities and hospitals that receive economic benefits or equipment, and the researchers that not only gain prestige, but also receive a high remuneration from the trial sponsors.

In this context, the clinical research subjects become simple means that have their dignity reduced with the potential violation of their human rights.

The purpose of this paper is to show that the principles and rules established throughout history have not protected, as expected, the dignity and human rights of the clinical research subjects and that the capacity to reduce the risks they are exposed to has been limited.

The first part of this article provides a brief historical account with the aim of recalling that what happened during human research studies in the Nazi era did not happen due to a lack of codes or regulations to control the possible abuses of medical research studies, or because corrupt and terrible elements were hidden in German medicine. That is why we cannot think that the Nuremberg Code and the numerous declarations, regulations, and rules succeeded in controlling the abuses after the Nazi tragedy was over.

In the second part of this article, we will discuss the economic interests of those who participate in the development of drug therapies, and that may cause the medical trial sponsors and researchers to violate the human rights of the subjects involved in the studies and the methodology used. The economic interest may exceed the interest in finding a solution to health problems that most affect the population and encourage a bias in scientific publications.

Lastly, the agents that control the research and commercialization of medicine in the countries that produce innovative drugs – specifically the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) – are studied to decide if they are reliable enough so that the drug recipient countries may be able to automatically certify any product approved by them.

HISTORY OF CLINICAL RESEARCH AND THE BEGINNING OF REGULATIONS

The tension between the interest in science progress and the need to protect the subject participating in the research study is not something new and has pierced the different specializations of clinical research in all continents.

Syphilis studies and the response of the Prussian government

In 1898, Albert Neisser, who discovered in 1879 the gonorrhea transmitting agent (named *Neisseria gonorrhoeae* after him), published a clinical trial in which, with the aim of finding a method to prevent syphilis, he injected cell free serum from patients with such disease in patients hospitalized for other health problems. Most of these patients were prostitutes, whose consent to take part in such experiment was never requested. Some of them contracted the disease, which led Neisser to the conclusion that the experiment had failed, and that they had contracted syphilis because they were prostitutes.[1]

The case promoted a public debate that caused the public prosecutor to investigate it and the Prussia's Royal Disciplinary Court to fine the researcher for not getting the proper informed consent, even if the study did not actually represent any risk for the participating patients.[1]

In 1899, the Prussian Parliament discussed the problem and then, the Ministry of Religious, Educational, and Medical Affairs requested a report to the Scientific Medical Office of Health, whose members were renowned German doctors, including Rudolf Virchow. The committee concluded that studies that put a subject at risk

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of contracting an infection should not be carried out and that research studies should always be preceded by a proper informed consent. The Ministry also requested legal advice. Legal experts stated that, pursuant to criminal laws, conducting non-therapeutic research on a subject without consent fulfilled the criteria of physical injury and that the scientific validity of the experiment did not mitigate the damage caused. The problems of coercion, persuasion, and the unequal authority between doctors and patients were discussed in detail, and the legal experts came to the conclusion that rights and morality were as important for the humankind as scientific progress.[1]

As a consequence of these issues, in 1900 the Ministry sent guidelines to all hospitals and clinics. Medical directors were advised that any medical procedure other than diagnoses, treatments, and immunizations should not be carried out if "the human subject was a minor or not competent for other reasons," or if the person had not given their "unambiguous consent" following a "proper explanation of the negative consequences of the intervention." Any research study had to be performed with the authorization of the medical director and, in all cases, the compliance with these requirements had to be "documented in the medical history."[1]

Yellow fever

In 1881, Carlos Finlay published his theory about the role of the female mosquito *Aedes aegypti* in the transmission of yellow fever and its supporting evidence, although it was not completely conclusive.[2] In this study, he exposed five people (he himself was one of them) to the bite of a mosquito that had previously bitten infected people. Three of the five participants contracted the disease, but he and a fifth participant did not, although the time required to determine whether the latter had contracted the disease had not passed. None of the infected patients died. Before he started describing his experiments, he stated he had obtained the proper consent, but without specifying the data contained in them.

In 1897, the Italian bacteriologist Giuseppe Sanarelli, who was living in Montevideo, stated that yellow fever was produced by a bacillus he claimed to have discovered, and in order to prove it, he injected, without the necessary consent, cultures of the assumed bacillus in five patients hospitalized for other reasons, three of whom died. According to Sanarelli, those persons contracted a disease he described as a "classic yellow fever." One year after Santarelli's work was published, Osler rejected this study claiming that "to deliberately inject a poison of known high degree of virulence into a human being, unless you obtain that man's sanction is not ridiculous, it is criminal."[3]

Walter Reed, Arístides Agramonte, James Carroll, and Jesse Lazear confirmed Finlay's theory by subjecting healthy volunteers to the contact with infected patients' fomites, to the intravenous injection of infected patients' blood, or to the inoculation with infected mosquitoes (causing the disease in the latter two situations, but not in the first one). The experiments were carried out with the proper informed consent and with an economic compensation. In that consent, patients were advised that they were at risk of death. However, 15 of the volunteers were listed men, and 1 was an official and, at present, they would be considered a vulnerable population. The rest of the volunteers were two American civilians and 15 Spanish immigrants. Lazear, one of the researchers, died of yellow fever. None of the remaining study participants died.[3]

The informed consent that was delivered to the volunteers in English or Spanish, depending on the situation, stated that: "The undersigned understands perfectly well that, in case of the development of yellow fever in him, that he endangers his life to a certain extent; but it being entirely impossible for him to avoid the infection during his stay in this island, he prefers to take the chance of contracting it intentionally in the belief that he will receive from the said Commission the greatest care and the most skillful medical service."[3]

German regulations and Nazi experiments

In Germany, in 1931, a circular from the Federal Ministry of Interior established the "Guidelines concerning new therapy and human experimentation."[4] Apart from confirming the beneficence and non-maleficence principles, such regulations were based on the principle of patient's autonomy and on the legal doctrine of informed consent. Moreover, it made a

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difference between new therapy experimentation for the treatment, diagnosis, or prevention of diseases resulting from non-therapeutic human experimentation, which included the study of side effects and consequences that could not be suitably determined in the context of the knowledge of that time.

The Guidelines established that: 1) innovative therapies could only be initiated without proper consent to preserve live or prevent serious damage to health if its administration was proposed. However, under no circumstances could non-therapeutic research be performed without proper consent; 2) medical ethics rejected any exploitation of social hardship in the performance of such experiments; 3) experimentation involving children or young persons under 18 required special care; and 4) the use of live microorganisms required exercising an extreme caution.[4]

In Germany, in 1939, the miscalled "euthanasia" program started. In that period, the programs of human research studies were developed, and many researchers pretended to take indirect advantage of the destruction of "lives unworthy of living" (concept on which the Nazism attempted to "scientifically" base the need to separate from society those persons that belonged to such category, and which began with the mass sterilization of people that supposedly carried genetic defects, continued with the murder of disabled kids and then adults, and finished with the mass murder of those deemed racially inferior, political opponents, homosexuals, "dangerous religions," among others).[5]

One of the most prominent examples of this is Julius Hallervorden, from the Brandenburg State Hospital. He was an internationally known neuropathologist who was in charge of the Brandenburg-Grönen Chronic Care Institution, one of the six centers that developed the euthanasia program. Such situation gave him the possibility to study the neuropathology of rare diseases on a large scale.

In order to improve the quality of his studies, Hallervorden personally examined the patients before they were executed, in order to extract their brains at a later point. His moral indifference to the patients' fate was described after the war by Leo Alexander, an American neurologist and refugee in Central Europe, to whom Hallervorden told:

> "I heard that they were going to do that, and so I went up to them and told them, 'Look here now, boys. If you are going to kill all those people, at least take the brains out so that the material can be utilized'"; "There was wonderful material among those brains, beautiful mental defectives, malformations and early infantile disease"; "They asked me: 'How many can you examine?' And so I told them an unlimited number — the more the better"; and "I accepted the brains, of course. Where they came from and how they came to me was really none of my business."[6]

Japanese experiments in China and Manchuria

Although they were less advertised, the medical experiments performed by the Japanese Empire in Manchuria and China were equally terrible, which resulted in thousands of casualties. These experiments included causing prisoners gunshot wounds to train the army's surgeons, the development of biological weapons, the study of infectious diseases with germs insertion and the subsequent vivisection and death of the research subjects, and the performance of physiological studies of low pressure or low temperature exposure, in which babies took part. Many of these researchers published their studies years after war. One of them, named Hisato Yoshimura, even became head of the Kyoto Prefectural University of Medicine, and in 1978, Emperor Hirohito awarded him the Order of the Rising Sun 3rd Class, for his pioneer study in "environmental adaptation."[7,8] The moral apathy and impunity can be clearly seen by contrasting the prize reception with the statements made in the Khabarovsk Trials (former Soviet Union) in 1994 by Satoru Kurakazu, Sergeant Major of Military Police:

> When I walked into the prison laboratory, five Chinese experimentees were sitting on a long form [bench]; two of these Chinese had no fingers at all, their hands were black; in those of three others the bones were visible. They had fingers, but they were only bones. Yoshimura told me that this was the result of freezing experiments.[8]

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DEVELOPMENT OF INTERNATIONAL REGULATIONS

From the end of Second World War onward, many codes, declarations, regulations, laws, and rules aimed at protecting the rights of the study patients/participants were created with the purpose of avoiding the repetition of the atrocities that had occurred. Many of those resulted in progress towards the protection of people's integrity; several others in setbacks produced by the pressure applied by the lucrative needs of the innovative pharmaceuticals, though concealed under the disguise of the scientific development cost.

The regulations include the following documents: 1) the Nuremberg Code; 2) the Universal Declaration of Human Rights of the United Nations (UN); 3) the Declaration of Helsinki of the World Medical Association (WMA) with subsequent amendments; 4) the Belmont Report; 5) the International Ethical Guidelines of the Council for International Organizations of Medical Sciences (CIOMS); 6) the Universal Declaration on Bioethics and Human Rights of the UNESCO; 7) the Universal Declaration on Human Genome and Human Rights of UNESCO; 8) the Convention on Human Rights and Biomedicine of the Council of Europe; and 9) the Guidelines for Good Clinical Practice of the Pan American Health Organization (PAHO).

In Latin America there has been a large creation of laws, regulations, and rules about medical human subject research, specifically aimed at avoiding the violation of ethical rules and the human rights of the experimentation subjects. In almost all the countries of the region, there has been progress followed by setbacks because of the pressures applied by the clinical trial sponsors and their researchers. A recent work shows the vicissitudes of the legislation in Argentina, Brazil, Costa Rica, Mexico, and Peru legislation, countries where almost 80% of the region's clinical trials are performed.[9]

Despite the rules, violations persist

Researchers tend to find reasons to violate people's dignity by making scientific considerations. In 1967, Thomas Rivers, the renowned virologist who ran the Rockefeller Institute for New York's Medical Research, wrote in his memoirs:

> Well, all I can say is, it's against the law to do many things, but the law winks when a reputable man wants to do a scientific experiment. For example, the criminal code of the City of New York holds that is a felony to inject a person with infectious material. Well, I tested out live yellow fever vaccine right on my ward in the Rockefeller Hospital. It was no secret, and I assure you that the people in the New York City Department of Health knew it was being done. Unless the law winks occasionally, you have no progress in medicine.[10]

Following this section, for the sake of brevity, we will provide a summary of a few violations, many of them widely recorded.

Research studies in the USA

Although the case of the syphilis observational study in Tuskegee, Alabama, began prior to the Nazi experiments, it is described in texts as a paradigmatic example of post-Nuremberg violations, because it lasted from 1932 to 1972. Researchers expected to assess the natural development of syphilis in 400 black men. It was designed by the US Public Health Service, and in the last years of the study, the subjects were denied an efficient treatment.[11-13]

The same agency also took part in studies in Guatemala that involved the vaccination of *treponema pallidum,* a syphilis infectious agent, and other germs that cause sexually transmitted infections, and it also took part in experiments with treatments without the previous informed consent and without giving a proper subsequent monitoring (1946-1948). A total of 5,500 Guatemalans were subjects to the study, included prisoners, prostitutes, people with mental illnesses, and soldiers,[10] 1,300 of which were intentionally infected with syphilis, gonorrhea, and other sexually transmitted diseases. Around 700 received a treatment. Around 83 had died at the end of 1953.[14]

In the controversial studies performed at the Willowbrook State School, mentally disabled children were intentionally infected with the hepatitis virus (1963-1966). Such studies made it possible to distinguish two types of hepatitis (currently

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named A and B).[15] However, the ethical aspects that Beecher reported in his famous writing about ethics and clinical research[16] still prevail, despite the many unsettled discussions about the topic.[17-18] The truth is that Willowbrook's study can be ethically justified only from a narrow consequentialist and minimalist perspective, since nothing was done to fix, for example, the overcrowding problems that existed in such institution.

In 1963, in the New York Jewish Chronic Disease Hospital, 22 weakened patients were injected with cancer cells, with the purpose of researching the relation between immunosuppression and cancer.[20] The study, which clearly violated the "First, do no harm" rule because of the risk that it itself entailed, was performed without the proper informed consent by the subject involved in the research.

From the mid-1950s to the mid-1980s, the United States Army secretly experimented with soldiers, with the purpose of finding chemical weapons more humane than bullets and submachine guns.[21] They expected to fight against the enemy with clouds of psychotropic chemicals that incapacitated the mind during a certain period of time. The experiments were performed at a research center, and chemical substances were tested on thousands of soldiers insufficiently informed. Such substances included tear gas, LSD, 3-Quinuclidinyl benzilate (BZ), and VX, another agent that is highly lethal for the nervous system, developed in the research center. The research Military Chief was specialized in a family of molecules that blocked an important neurotransmitter and caused delirium. Researchers from John Hopkins University were hired to carry out sarin experiments. The drugs were basically known for the army's codes and were secret. The soldiers received no information about what they were given, or what the specific effects may be, and the army did not make the effort of monitoring the experiment participants.

Clinical trials in Africa and Latin America

Violations in Africa have been so frequent that they were used as material for the famous John Le Carré novel, *The constant gardener*. In a clinical trial, Pfizer had to come to a compensation and recognition agreement for performing, without the consent of the participants and their families, a research study with trovafloxacin (Trovan) in children during a meningitis epidemic in Nigeria in 1996. However, its value was notably lower than the originally claimed.[22,23] Such a trial contains all the ingredients of a human rights violation: 1) lack of proper informed consent (Pfizer argued that there was not any international rule demanding to obtain informed consent for experimental drug trials in Africa)[24]; 2) administration of a lower dose than the dose recommended for its comparative (ceftriaxone); 3) an incomplete monitoring during the treatment and nonexistent thereafter[25-27]; the sponsor resorted to investigators to uncover corruption links to the federal attorney general to expose him and make him drop the legal actions[28]; and 4) loss of the clinical records of the participant children[23]; 11 of whom would have allegedly died and many others suffered neurological after-effects.[27]

In Argentina, many ethical and normative violations that became public and required judicial intervention have been registered. Among them, we can mention oncological studies carried out without the authorization of the National Administration of Drugs, Food, and Medical Devices (ANMAT) [*Administración Nacional de Medicamentos, Alimentos y Tecnología Médica*], and clinical trials that violated other regulations. Such clinical trials included the *Clinical Otitis Media & Pneumonia Study* (COMPAS) of inoculation against the pneumococcus. It was performed in the provinces of Cordoba, Santiago del Estero (the poorest in the country), Mendoza, and San Juan, with 13,981 recruited children,[29] and it ended up in court proceedings where the National Judicial Branch imposed fines on the company and the main researchers.

The Ethical Hospital Committee [*Comité Hospitalario de Ética*] and the Research Studies Revision Board of the Mar del Plata Private Community Hospital [*Consejo de revisión de estudios de investigación del Hospital Privado de comunidad de Mar del Plata*] (Argentina) rejected a study to research the effectiveness and safety of a quinolone (moxifloxacin, a medicine that belongs to the same group of trovafloxacin) in pediatric patients that presented complicated intra-abdominal infections. This study had many ethical and methodological failures[30] and exposed vulnerable

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patients to disproportionate risks, in a pathology for which a proved effective treatment exists. This trial has been introduced in many countries, including the USA.

Many other instances of ethical and normative violations in Argentina, Brazil, Costa Rica, Mexico, and Peru are explained in the book *Ethics and Clinical Trials in Latin America* [*Éticas y normativas en ensayos clínicos en América Latina*].[31]

Double standard research studies

In 1994, the AIDS Clinical Trials Group (ACTG) protocol 076 was published, establishing that zidovudine administration during the antepartum, the intrapartum, and its administration to newborns reduced the risk of maternal-fetal transmission of HIV by 67%.[32] In 1997, Lurie and Wolfe[33] identified 18 controlled studies carried out after the publication of the ACTG study protocol 076, which involved 17,000 women. In the two studies performed in the USA, the access to zidovudine was unrestricted. In 15 of the 16 studies performed in developing countries, not all patients had access to zidovudine (whether because zidovudine was researched in less expensive and complex programs against placebos or because other methods to prevent HIV transmission were researched). Two of these studies, zidovudine against placebo, were published in such a prestigious journal as *The Lancet*.[34,35]

There is no doubt regarding the anti-ethical nature of these 15 studies that, as Lurie and Wolfe[33] highlight, transgressed the rules of the 1993 CIOMS International Ethics Standards for Biomedical Research Involving Human Subject, which states as follows:

> An external sponsoring organization [...] should submit the research protocol for ethical and scientific review in the country of the sponsoring organization, and the ethical standards applied should be no less stringent than they would be for research carried out in that country.[36]

Or, as explained by Marcia Angell,[37] in such cases there is a violation of the principles of the 1989 Declaration of Helsinki, one of which states as follows: "In any medical study, every patient – including those of a control group, if any – should be assured of the best proven diagnostic and therapeutic method."[38]

This double standard in studies was justified by researchers and by the regulating agencies with the argument that the prevailing law in the countries in which the study was being conducted was the "lack of treatment." Such way of reasoning assaults the state of inequality concerning the access to treatments aimed at developing studies, which in turn result in benefiting the industry and never solving the problem of lack of justice and symmetry in the distribution of the research results.

The issue of double standards in studies, just as the access to better treatments and methods developed after the clinical trial, promoted a profound debate in the field of bioethics. Continued modifications to the Declaration of Helsinki (the last of which was in 2013) have been subject to controversy that falls beyond the purpose of this paper. Nevertheless, it should be noted that both of the above-mentioned issues (double standards and post-research access) are indicative of the high-income countries' motivation to naturalize the exploitation of the population in the low-income countries and middle-income countries, and eventually, the exploitation of their own population that has no access to better proven treatments.

In 2001, the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), composed of the regulating agencies of the US, the European Union (venue of the massive innovative industry), and Japan, as well as representatives of the pharmaceutical industry of such countries, published the "Choice of Control Group in Clinical Trials,"[39] a guide in which section 2.1.3 reads as follows:

> When a new treatment is tested for a condition for which no effective treatment is known, there is usually no ethical problem with a study comparing the new treatment to placebo. Use of a placebo control may raise problems of ethics, acceptability, and feasibility, however, when an effective treatment is available for the condition under study in a proposed trial. In cases where an available treatment is known to prevent serious harm,

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> such as death or irreversible morbidity in the study population, it is generally inappropriate to use a placebo control.(39 p.16)

In section 2.1.7.1, the following is added:

> When effective therapy that is known to prevent death or irreversible morbidity exists for a particular population, that population cannot usually be ethically studied in placebo-controlled trials; the particular conditions and populations for which this is true may be controversial.(39 p.20)

In other words, the guide offers the possibility to resort to proven therapeutic methods that are effective in particular populations where no effective therapy exists to prevent death of irreversible morbidity.

The clinical trial with surfactants in Latin America

Similar characteristics displayed the controversy stemmed from the research protocol of surfactants vs. placebo that was being considered by the FDA for its acceptance in the year 2001, with a view of being implemented in four Latin American countries.(40) Such protocol involved the enrollment of hundreds of preterm babies, in spite of the fact that there were proven treatments reducing relative mortality up to 37%, intraventricular hemorrhage in the neonatal period to 12%, and first-year mortality to 20%.(41) Curiously, the company that was in charge of conducting the study against placebo in Latin America was designing at the same time a study against the surfactant approved by the FDA in Europe. Following the report made by Public Citizen and Latin American NGOs, the study in Latin America was finally performed under similar conditions as those in the European research.(42)

It bears no surprise that FDA decided, in 2008, to overlook the requirement of enforcing the Declaration of Helsinki in the studies conducted outside the US and merely request instead the application of the guides of the ICH.(43,44)

The aforesaid circumstances are not isolated accounts. A copious number of cases are reported in publications and books devoted to these topics.(45,46)

THE INTERESTS OF THE INNOVATIVE PHARMACOLOGICAL INDUSTRY

Research studies and the needs of the population

While treatments for certain conditions are profuse, there are other diseases that cause 35,000 deaths per day in low-income countries and middle-income countries that remain untreated, with a relevant morbidity rate.(47) Such conditions, known as the "neglected" diseases, include malaria, filariasis, onchocercosis, trachoma, trypanosomiasis, leishmaniasis, dengue fever, Chagas disease, and others.

The lack of investment in treatments for such diseases affecting populations that are unable to purchase them is known. During the period of 1975-1999, 1,393 new chemical entities or drugs (NCE) were launched into the market, only 16 of which were intended for these neglected diseases.(48) In 2004, the study costs surpassed 1 billion US dollars, but only 10% of this amount was used for research on the diseases that are responsible for the 90% of the disease load.(49) This disparity has been baptized "The 90/10 Gap," and its solution is one of the biggest challenges of humankind. The paradox is explained by the contradiction between the pursuit of economic profits that drives research studies and the needs of those who are in need of new treatments but are unable to pay for them.

Between 1998 and 2003, the FDA approved 487 drugs, 379 of which (78%) were considered to have therapeutic qualities similar to one or several existing in the market (*Me-too drugs*), and 333 (68%) were new products out of old combinations. Only 67 (14%) of the 487 drugs were truly innovative.(50)

The tragic epidemic produced by the Ebola virus in 2014, which caused thousands of deaths and an average fatality rate of 55%, conveys a reality of an ethically unjustifiable setback of the modern research and drug-developing system. According to Donovan, "the stark reality is that the pharmaceutical companies are in the business of producing therapies that people will pay for,"(51) and although the author tries to justify the situation from the viewpoint of the high research costs, the fact is that the economic benefits of the pharmaceutical industry surpass the research costs in

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a prominent way. However, Donovan has a point when he states that, if the disease relocates itself in developed countries, "a greater push for effective interventions might have been demanded, leading to the odious suspicion that the world cared less when the problem is confined to poor African countries."[51]

Lack of transparency in the publication of results

In 2009, an epidemic of the Influenza A virus (subtype H1N1) broke out. The WHO, the Centers for Disease Control and Prevention (CDC) and the US American Academy of Pediatrics, the UK National Institute for Health and Care Excellence (NICE), among others, recommended the use of neuraminidase inhibitors for the prevention of complications in patients at high risk of acquiring the disease.[53] These recommendations were delivered, in spite of the lack of sufficient evidence concerning its benefits and risks. As a result, national administrations spent billions of dollars in order to have enough stock of these drugs, given the occurrence of the pandemic.[54]

When all the data became available to the experts, it could be concluded that, on the one hand, there was no evidence that the administration of these drugs would reduce in-hospital stays or complications, and on the other hand, that it did increase adverse effects.[55,56] The questionable quality of data in the studies performed,[54] as well as the biased conclusions of the published papers and the undisclosed information,[57] serve to state that 20 billion US dollars were misspent,[58] resulting in abundant benefits for the industry. This is a scandal not very well-known by the public.

The case of rofecoxib (Vioxx) has been extensively documented.[59] The data manipulation in one of the clinical trials, the lack of transparency of the company, and the complicity of the FDA were uncovered when a judge requested information in the course of legal actions that were initiated by patients or their families when secondary effects could no longer be concealed and when death cases produced by the drugs came to surface. Since rofecoxib was launched into the market up to the time when it was withdrawn in 2004, Merck earned an average of 2.5 billion US dollars on an annual basis. An estimated 100 million patients have received the medicine. It is calculated that between 88,000 and 139,000 people suffered an Acute Myocardial Infarction as a result of using rofecoxib, 30%-40% of which died.[60,61]

Another example of intentional bias is the use of paroxetine to treat depression in pediatric population. A study conducted in the USA between 1993 and 1996 demonstrated that its use was no better than the placebo (study 329), while another study performed in Europe, South America, and other regions showed that it was inferior to the placebo (study 377).[62] Nevertheless, a team of the SmithKline Beecham laboratory advised to publish positive data because "it would be commercially unacceptable to include a statement that efficacy had not been demonstrated, as this would undermine the profile of paroxetine." Therefore, a favorable report of the medicine was issued at the meeting of the European College of Neuropsychopharmacology in 1998.[62] Although the publication informed that paroxetine is generally well-tolerated and effective for teenage depression, its administration to under 18-year-olds was later discouraged, because it increased the risk of suicide between 50-200% in comparison with the placebo.[62]

Data manipulation can be observed not only in the conclusions regarding the serotonin reuptake inhibitors and the risk of suicidal behavior, but also in the failure of the regulating entities at identifying the problem.[63,64]

According to Angell,[65] during the past two decades, the progress made in the pharmaceutical industry in the assessment of their own products has no precedents, and the bias observed in the clinical trials that used rofecoxib "is not unusual and by no means limited to Merck." In the case of sponsored studies, "as owners of the study database, sponsors have discretion to determine who will have access to the database. At its extreme, investigators have become little more than hired hands, supplying patients and collecting data according to the company protocol."[65] Researchers are more like technicians in charge of data collection, since they are not involved in the study design or the analysis.[66]

There are many ways of producing biased results without falsifying the source document data or the database, such as deciding to perform an

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"on-treatment" or an "intention-to-treat"[67] analysis, comparing the new drug with placebo (even where there is a drug with proven efficacy), or using a lower dose of the compared drug, or a higher dose to increase its adverse effects and minimize the effects of the drug that is being researched, or concealing part of the data, among other ways.[65]

Various authors call attention to the limitations in data access and the biased publication of results.[68] However, the fact that the very regulating agencies are part of the information concealment is noteworthy. Goldacre explains the difficulties that the researchers of the Nordic Cochrane Center endured in order to obtain the data related to the medicine for weight loss – orlistat and rimonabant – and the three and a half years which this took. It should be highlighted that during the wait time, one of the medicines had to be withdrawn from the market due to its adverse effects.[24] The increasing demand that the industry makes raw data available to independent researchers and not just the processed data, preserving the patients' privacy, is very valuable.[69-72]

Angell describes research, production, promotion, and marketing of drugs as a broken system that reaches the regulating agencies.[65] Gotzsche, a Nordic Cochrane Center member, conducted a study in which he accounts for fraud, hiding data on harms, misrepresentation of research results, marketing drugs for off-label uses. As result of this study, he states that corporate crime in the pharmaceutical industry is common, serious, and repetitive.[53]

The ability of agencies to protect research subjects and the quality of information

Angell observes that the FDA suffers from the pressure of the industry through their eighteen committees of permanent advisors that evaluate the registration of new drugs, because many of those committee members hold financial relationships with the interested companies. In accordance with USA Today, "at 92% of the meetings, at least one member had a financial conflict of interest" and that "at 55% of meetings, half or more of the FDA advisers had conflicts of interest."[52,73]

The clash of interests reaches the EMA as well. Goldacre states that in December 2010, Thomas Lönngren abandoned his post as executive director of the EMA and sent a letter to the Administration Council announcing that he would soon accept the position of advisor in the pharmaceutical industry within 4 days.[24]

David Healy explains that, although it is generally assumed that the FDA stores the clinical trials' raw data in case somebody observes a problem in a treatment and consults with them, this is not true.[64] He adds that, although companies do send a data file to FDA, the FDA does not process the raw data, but only works with the graphs that the companies designed.[64] Furthermore, he mentions that the FDA operates as an auditor: it produces samples of the clinical records in order to determine up to what extent these are coherent with the graphs and charts that the industry elaborated, and if further analysis is required, the FDA requests the company to undertake the task.

The inefficacy of regulating agencies may seem excessive. However, an audit of the inspector general of the US Department of Health and Human Services (HHS), who performed his duties in the period 2000-2005, concluded that the FDA members had no knowledge of the way in which many clinical trials were being conducted, because they audited less than 1% of the places where the trials were performed.[74] Further, he stated that the FDA not only monitored a few Research Ethics Committees (REC), also called Institutional Review Board (IRB), but also considerably overlooked the protection of the subjects involved in research studies.

The audit concluded that the FDA: 1) did not maintained a clinical trial registry of ongoing trials and of the Research Ethics Committees; 2) did not have a database in which the biomedical research inspections could be registered, which made it impossible to track them properly; 3) relied on voluntary compliance to correct violations of regulatory significance; 4) preserved uncertainty and lack of coordination, which impeded its members' ability to conduct biomedical research inspections.[74]

A second audit of the HHS to the FDA in 2008 questioned the quality of data, of research studies conducted abroad that are ordered by the sponsors with a view to obtain commercialization drugs in the US, and the emphasis with which the FDA monitors and inspects these research studies.[75] The audit concluded that 80% of approved drugs

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and biologics relied on data provided by the sponsors and that contained data from clinical trials performed outside the USA. Furthermore, they stated that, in that year, the FDA inspected less than 1% of the places in which these trials were being performed.[75] When the FDA or the EMA approve these medicines, the regulating agencies of other countries such as Argentina or Mexico also approve them, under the belief that these agencies are effective.

The RECs can be excellent instruments for the protection of patients/participants in research studies. However, they can also be used to legitimize studies in which rules, resolutions, provisions, laws, and principles that protect the dignity of patients are violated,[76] either in research protocols, in information factsheets, the informed consent, or in the course of the research study. A clandestine research of the US Government Accountability Office (GAO), in which an incredibly absurd protocol was presented to three Institutional Review Boards, documented that one of the committees had approved the study in less than a week and that the other two committees rejected it. Such difference illuminates the contradictory character of ethical reviews.[77] The committee that approved the study, with a view to make profit, reviewed 356 protocols in 5 years, rejected only one, and in 2008, earned 9.3 million US dollars for its "review services."[78]

The literature about the Research Ethics Committees is very copious, and it can be stated that, with the exception of a few cases, most of them explain that these committees have their limits to protect the subjects and ensure the quality of the collected data. In Latin America the volume of studies is scarce but sufficient to arrive at the same conclusion.

Very frequently in Latin America, the research subjects do not understand the informed consent forms, and the RECs are indifferent to this circumstance. In Costa Rica, an evaluation of the local bioethical committees conducted in 2009 found that they were unable to perform the duties required by the regulation guide.[79] In the same country, a clinical trial for cervical cancer inoculation was infested with ethical problems that the ethics committees were unable to avoid, and complaints were filed at the Legislative Assembly.[80,81] The seriousness of the situation regarding the clinical trials in Costa Rica led to a point in which, in 2010, the Supreme Court barred the approval of new clinical trials with human subjects until a law was passed to regulate trials with human experimentation.[79] This law was passed in April 2014. In Peru, a study showed severe failures in the evaluation performed by the RECs that could be attributed to the lack of training or negligence, as well as "deliberate and repeated" acts of omission of information.[82] In Mexico, the serious failures by the RECs were recorded in a number of exemplary and detailed research studies.[83-86]

The Institutional Research Studies Revision Board of the Mar del Plata Private Community Hospital (Argentina) revised, between 2005-2006, 33 protocols, information factsheets for patients, and informed consent forms. Such documents had been previously analyzed by "Independent Ethics Committees," which are for profit, and so their supply depends upon their clients' satisfaction. Three relevant objections per protocol were found.[76]

CONCLUSION AND PROPOSALS

It has been stated that the existence of laws and regulations is not sufficient to avoid the violation of human rights and universally accepted ethical principles. However, the violation starts from the very selection of the research topic, when research studies of diseases that kill or harm millions of people are abandoned because they are of no interest for the market. This is an aspect of clinical research that is not regulated.

The regulating agencies are accomplices in the lack of enforcement of the regulations. There are many reasons why the legislation and the rules are not complied with, but the influence of the pharmaceutical industry is the most prominent reason. As a result, not only are human rights violated, but also drugs that are not reliable or effective are still marketed, which amounts to legal and ethical violations.

The following points can be put forward to enhance the situation in Latin America:

1) It is necessary for society to become aware of the importance of medical research and of people's rights in order to avoid their exploitation.

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Without social participation, it is very unlikely that rules can be enforced.

2) Double standards in clinical research must not be accepted.
3) The FDA and the EMA are not reliable agencies. Other countries must not approve the commercialization of new drugs simply because these agencies have authorized them. It is unacceptable that regulating agencies in Latin America submit themselves to the decisions issued by the FDA and the EMA.
4) The Latin American regulating agencies of drugs – the ANMAT, the National Institute of Drugs and Food Revision (INVIMA) [*Instituto Nacional de Vigilancia de Medicamentos y Alimentos*], the Agência Nacional de Vigilância Sanitária (ANVISA), the Federal Committee for the Protection against Health Risks (COFEPRIS) [*Comisión Federal para la Protección contra Riesgos Sanitarios*], among others – must demand, as a necessary condition for the approval of the commercialization of any new chemical entity, that the raw data of the research studies be available for them and for the authorized institutions and agencies. The excuse of industrial secret cannot be invoked to hinder proper evaluation of the efficacy and reliability of a new drug.
5) The cost-benefit analysis should be assessed with social participation and with transparency before a drug is included in the public services and social insurance forms.
6) Action should be taken to prevent officers at the regulating agencies from having conflicts of interest with the pharmaceutical industry. Legislation must be passed to determine the number of years that must follow before an officer is hired by the pharmaceutical industry, after performing duties in an executive position, or an employee of the industry is hired by a regulating agency.
7) It is necessary to guarantee the transparency of the operation of agencies and create mechanisms to be audited and subjected to public scrutiny.
8) The operation of agencies must be subjected to bioethical principles, clearly framed in the compliance with human rights.
9) The agencies should keep a record of the clinical and epidemiological studies being developed in the territory over which they have jurisdiction. Research protocols, information factsheets, and informed consent forms, with their corrections, their different versions, and their languages, must be archived by the agencies, ensuring that they are publicly available.
10) RECs should be registered with the regulating agencies. The means necessary to fulfill the duties for which they have been created must be implemented. Neither commercial ethics committees nor organizations that define themselves as "not-for-profit" should be authorized, given that their creation depends on the income received by the approval of clinical trial documents, and are, therefore, dependent on sponsors.
11) Clear mechanisms for the authorization of the RECs must be implemented, as well as the instruments to ensure sanctions (administrative, economic, or even criminal) for those who do not comply or violate the current regulations.
12) The resolutions of each REC should be available at the agencies. Any act of rejection, modification, or approval of a protocol, information factsheet, or informed consent should be automatically sent to the rest of the RECs and other centers that conduct research.
13) Data alteration, manipulation of results, promotion of false information about efficacy and reliability of a new chemical entity or medicine should be considered to be crimes against human rights.
14) It is highly important for each country to pass national legislation concerning biomedical research that states punishments (administrative, economic, or even criminal) for the violation of norms that control clinical research in human subjects.

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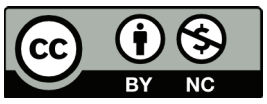

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