Lobbying by Big Pharma, bottlenecks for clinical research, and loosening of ethical standards in Brazil

Lobbying da indústria farmacêutica, gargalos para pesquisa clínica e afrouxamento das normas éticas no Brasil

Lobbying de la industria farmacéutica, los cuellos de botella para la investigación clínica y el aflojamiento de las normas éticas en Brasil

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As commented by Palácios & Rego [1], the Brazilian National Senate is currently reviewing a bill of law (*Projeto de Lei do Senado n. 200*, 2015) that proposes to amend the country's ethics review system for research in human subjects. The bill creates a second type of ethical review board, the Independent Ethics Committee (CEI), and provides that approval of a research protocol by either a Ethics Research Committee (CEP, linked to a public or private institution) or a CEI allows investigators to initiate a trial. The bill also introduces changes in ethical norms to include: (i) allowing the use of a placebo group even when there is already an effective treatment for the medical condition, as long as the placebo group is necessary "*…to meet a justifiable methodological requirement*" (*PL n. 200/2015*, Art. 27); (ii) exemption of study sponsors from the obligation to provide post-trial treatment at no charge to patients if there is no risk of death or "clinically relevant worsening" of the disease and if there is a "satisfactory therapeutic alternative" in the country for the same medical condition; (iii) authorization of sponsors to pay healthy volunteers to participate in phase I trials and bioavailability and/or bioequivalence studies; and (iv) "altruistic" enrollment of children if the "*clinical trial is essential for the population represented by the study subjects*" (*PL n. 200/2015* Art. 21, II). The latter change in ethical norms clashes with the current understanding that children and adolescents enrolled in a clinical trial must be suffering from the disease and should potentially benefit from the treatment. Minors' recruitment by clinical trials based on "altruism" is at best an ethically delicate issue and in any case should not entail any foreseeable risk, discomfort, and/or significant fear.

The bill's proponents claim unfavorable performance by the current CEP/CONEP (National Council for Research Ethics) system: "*…the current review system is slow and bureaucratic, with negative consequences for patients and researchers, thus hindering innovation in health*" (*PL n. 200/2015*, Justification, p. 22). The bill echoes criticism by researchers concerning excessive bureaucracy and slow ethical approval of trials. Researchers claim that the review process represents "a bottleneck for clinical research" in Brazil. Nonetheless, it is hard to foresee how changes introduced in ethical norms could shorten the review time; they merely loosen the country's standards for protection of research subjects' rights, safety, and dignity.

Big Pharma is a major player in lobbying to obtain Congressional support for the bill. For example, Interfarma (the "Brazilian Research-Based Pharmaceutical Manufacturers Association") has sponsored "Congressional study missions on innovation policies" to the United States and United Kingdom, including 36 Members of Congress who will presumably support the new bill of law 2.

The self-serving argument that "bottlenecks for clinical research" hamper drug innovation is fallacious. Clinical trials only occur in the final stage of drug development – prior to regulatory marketing approval – whereas the innovation itself (granting patent rights) takes place at the start of this long process, with innovative lab bench research by chemists, pharmacologists, and other scientists. Importantly, Brazil's overall innovative performance is mediocre, so lack of innovations in the pharmaceutical industry is no exception.

Ethical norms are intended to minimize harms and risks and maximize benefits, while ensuring respect for human values like dignity, privacy, and autonomy. However, researchers and sponsors have professional and/or financial conflicts of interest in this area and are expected to have a biased perception of acceptability within this delicate and complex context. The same holds true for Members of Congress that have received generous donations from pharmaceutical companies.

Sponsors and researchers are users of the CEP/CONEP system and as such are qualified to demand a faster and more streamlined review of study protocols. However, a revision of ethical norms does not make the review process "more efficient". Loosening standards for the protection of research subjects' rights could make Brazil "more attractive" to industry-sponsored multi-center studies, but such a strategy is unfair to the population and provides no stimulus for innovative research.

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Further debate on bill of *Law PL n. 200/2015* in the Brazilian Senate

The instigating comments by Paumgartten gave us food for thought: after all, what kind of research ethics system would result from the bill of law in the Brazilian Senate? [1]. The wording of Bill of *Law PL n. 200/2015* proposes to create Ethics Research Committees (CEPs) and Independent Ethics Committees (CEIs). According to the bill, these structures are similar in both their purpose and composition. They differ in terms of their affiliation: the CEP applies to a study associated with a research institution, while the CEI is independent from such an institution. Both would have to be registered with the Brazilian National Agency for Sanitary Surveillance (ANVISA), the role of which would be to accredit the committees, but not to coordinate the system, as done currently by the National Council for Research Ethics (CONEP).

The possibility of creating ethics committees that would be independent of research institutions opens the way for a contract research organization or research and development (R&D) division from within the industry itself to create an independent committee to review its research protocols in ample time. It might solve the issue of approval delays, but would that be all? Since the black box of research in human beings in the Nazi extermination camps, humankind has endeavored to introduce caution into scientific pursuits, as reflected in the time needed to effectively and impartially assess research and to protect research subjects, especially in clinical research, which intervenes in the human body.

The bill provides that an attribution of the CEP and CEI is "*to review and assess the medical, scientific, and ethical aspects of the proposed research*". It thus includes in the same act the technical assessment (the responsibility of ANVISA) and the ethical assessment, with the latter subsumed by the former.

The bill thus proposes a much simpler process, doubtless more agile, but also more bureaucratic, since it views the process of ethical discussion and reflection as included within the scientific assessment

(competent from the scientific point of view). That is, the bill proposes to reduce the assessment to nothing more than compliance with scientific requirements and submission of the required documents. If we consider the scientific literature that exposes conflict of interest in science publication and research conduct, we can assume that what is defended as competent from the point of view of science, without adequate social control, will actually be market-based interest, valuing the health industry's capital, often to the detriment of the population's interests.

Some researchers contend that the "delay" in the review process explains why Brazil occupies such a modest place in a purported "ranking" of clinical research [2]. This contention is surprisingly misinformed. The cause of Brazil's limited development in clinical research lies in the country's overall social, political, and economic backwardness and a policy that has failed to encourage the development of the domestic pharmaceutical industry. Even recent decisions in Brazil's pharmaceutical policy have failed to take advantage of the opportunities offered by the international agreement on patents and recognized them long before the deadline. It was only after enactment of the 1988 *Federal Constitution* that Brazil enjoyed some regulation of research with human subjects, a process that dates to the early 20th century in Germany (at the international level, the Nuremberg Code in 1947 already called the world's attention to the need for regulation). The United States passed a regulation in 1978 that influenced the rest of the world in setting criteria for ethical assessment of research with human subjects, and Brazil only achieved some degree of effective regulation in 1996. Unfortunately clinical trials in Brazil are mostly phase III and IV studies elaborated by foreign researchers outside our country, in which Brazil only participates with local study monitors in multicenter trials.

Our review system is in fact recent, and we still have problems with the turnaround time for research protocols. Such problems need to be adequately diagnosed and solved, but to limit the ethical concern to the time needed for final approval is to miss the point. Researchers and sponsors are inevitably dissatisfied with the turnaround time for reviewing a research project. Even assuming their best intentions, they will always feel that the safeguards they have established are effective guarantees for protecting research subjects. History shows that this is not true. Morin [3] wrote that "*science can only develop by obeying one ethics, the ethics of knowledge*" (p. 10-11) and thus proposes that science reconcile itself with philosophy. The generic view that protocol processing times are long and unjustifiable is not determined by the country's position in research ranking, but by the individual viewer's perspective. To reduce processing times alone is irrelevant to both research subjects and the general population. As for changes at ANVISA in recent years (hiring numerous new staff, digitization of processes, and more recently the time limit on processing phase III trials for synthetic drugs – 90 days with automatic approval in case ANVISA does not manifest itself) only fail to become more problematic because the RDC (Collegiate Directorate Resolution) emphasizes that authorization for a drug will only be issued after the study has received ethical approval.

The opinion section of the *Boston Globe* recently published a letter by a Harvard professor [4], defending the idea that a truly ethical bioethics should not bog down research based on such sweeping principles as "dignity", "sacredness", or "social justice". According to the author, patients' interests and the possibility of advancing scientific knowledge and occasionally anticipating treatments should compel bioethics to simply "get out of the way" of scientific research [4]. This example is intended to show that review time for research projects is not the real problem, but that this timeframe can never be short enough. The focus of analysis, criticisms, and proposals should not be the time for processing protocols, but the effectiveness of the analysis done by the CEP and the CONEP: are we actually improving the protection of research subjects or merely demanding more paperwork? For an appropriate discussion, we need to shift the focus away from the time issue towards the various requisites for effectively protecting research subjects: autonomy, guaranteed benefits, and respect for communities.

Contributors

Both authors planned, wrote and approved the final version of the paper.

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