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Opinion

Medications Safety and The Development Process of Drugs or Vaccines for Human Use

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Introduction

The drug or vaccine development process has been perfectly established since decades, the pharmaceutical industry carries it out routinely in each drug/medicine that enters in the market with the prior authorization of the regulatory entities of each country such as the Food and Drug Administration (FDA) in the United States *(The Drug Development Process | FDA, n.d.)* [1], the European Medicines Agency (EMA) in Europe, or La Comisión Federal para la Protection contra Riesgos Sanitarios (COFEPRIS) in Mexico. This is a systematic process that consists of a preclinical stage which for most drugs or vaccines includes the following steps: the discovery of interaction (the design of the molecule by bioinformatic methods, the synthesis of molecules with the greatest potential for biological activity, and primary assays of hundreds of compounds that are carried out directly through a drug-receptor interaction *(Step 1: Discovery and Development | FDA, n.d.)* [2]; a second stage considers the bio evaluation in laboratory animals of the dozens of agents that have the greatest potential for pharmacological activity *(Step 2: Preclinical Research | FDA, n.d.)* [3]. In a second stage or clinical, medicine formulations are established in which the appropriate combination of active ingredient and pharmaceutical excipients is done in the correct proportion to facilitate administration to humans by a specific route. Clinical trials carried out in humans *(Step 3: Clinical Research | FDA, n.d.)* [4] are: main objective of phase 1 clinical trial is determinate the safety of the medicines by registering unwanted side effects or adverse drug reactions (ADRs) in dozens of healthy subjects, additionally in this phase pharmacokinetic parameters are stablished in humans; in phase 2 clinical trials an appropriate therapeutic regimen is established, by determining the doses and frequency of administration of medicines in approximately 100 patients; phase 3 is recorded in thousands of patients and are multicentric studies, in this phase the safety and effectiveness of the most appropriate therapeutic regimen established in the previous phase 2 clinical trials. The pharmaceutical industry submits its drug candidate to the regulatory entity for evaluation, with the information generated in clinical trials 1 -3 *(Step 4: FDA Drug Review | FDA, n.d.)* [5]. Once the drug is approved it can be distributed to hospitals of the country, and phase 4 clinical studies are continued, these consist of intensive pharmacovigilance in which the intentional search for ADRs and side effects are determined. In phase 4 clinical trials the medicines are administered to general population patients, new side effects that are still unknown can appear *(Step 5: FDA Post-Market Drug Safety Monitoring | FDA, n.d.)* [6]. Until that time, any incident related to lack of efficacy or problems with therapeutic administration or adherence is also included.

A medicine or vaccine is administered to humans with the aim of health recovery or health preservation, for that reason and logically the entire process of drug development is focused on the evaluation of effectiveness. However, despite how systematic, strict, and rigorous the drug development process is, the emergence or incidence of ADRs and side effects in patients is constant and seem to be increasing, both in new medicines in the market as vaccines against COVID-19 [7], or medicines marketed for a long time such as aspirin.

In the last decade, patient safety has acquired an institutional focus in the health systems of several countries in Latin America and the worldwide because ADRs are one of the ten main causes of

mortality and are also the cause of and prolongation of hospital stay [8-10]. The detection and registration of ADRs has increased due to the constant training of both doctors and nurses and the introduction of pharmaceutical professionals into health systems.

Medicines or vaccines are administered to healthy people to preserve their health and in patients to recover from an illness. Drugs are foreign substances that are introduced to the human body, causing changes at a biochemical and physicochemical level. These changes translate into mechanisms of pharmacological action, for example NSAIDs act by inhibiting cyclooxygenases I and II which results in an anti-inflammatory effect, but it also results in gastrointestinal irritation that can lead to the development of ulcers and intestinal bleeding. ADRs are inherent to medications even when they are administered at optimal conditions including doses, frequency and optimal time determined by the manufacturer. When making the prescription, physicians consider the health aspects of each patient such as: age, kidney disease, cardiovascular diseases, pregnancy, liver disease, and obesity, that is, they adequately carry out the prescription and administration. In consideration of the above described, this opinion article is issued since it is necessary to reflect on the drug development process, analyzing it with emphasis on the safety of the drug in terms of the lack of ability to predict the appearance of serious ADRs, both in the preclinical and clinical stages of the drug development process, from the computer-aided drug design to phase 4 clinical studies.

Opinion on the safety of drugs and vaccines with respect to the drug development process.

The pharmaceutical industry produces high-quality medicines that exceed the requirements of clinical studies in terms of safety and effectiveness, however, an undeniable fact is that all medicines that have been withdrawn from the market by instruction of regulatory entities is due to the presence of recently documented serious ADRs that that put the patient's life at risk, none of these were withdrawn due to lack of efficacy. Examples of medications withdrawn from the market for safety reasons are: Meridia/Sibutramine that Increased cardiovascular and stroke risk was withdrawn in 2010; Mylotarg/Gemtuzumab that Increased risk of death and veno-occlusive disease was withdrawn in 2010; and Darvon and Darvocet/Propoxyphene that causes Serious toxicity to the heart [11] (Narsis A. Kiani*, Ming-Mei Shang and Jesper Tegnér). Therefore, the question arises why just when a new drug or vaccine goes on sale, new serious adverse reactions that put people's lives at risk are also discovered. The explanation of the scientist and pharmaceutical community to this question is due to the frequency of appearance, mentioning that if the drug has ADRs with very low incidence rates, they will be difficult to observe in a few thousand people during phases 1 - 3 clinical trials.

Probably the most important limitation to consider in the detection of side effects during preclinical stage is the limited number of animals used in drugs bio evaluation, study groups made up of few elements are logically insufficient to detect low- frequency adverse reactions. The OECD Guidelines for the Testing of Chemicals (TGs) are generally used to evaluate general and specific toxicity of drugs *(OECD Guidelines for the Testing of Chemicals, Section 4: Health Effects | OECD Guidelines for the Testing of Chemicals | OECD ILibrary, n.d.)* [12]. In these assays the number of laboratory animals is very small, forming groups from 5 or 6 and up to a maximum of 100 animals. For example: in OECD 443 Guideline on "Extended one-generation reproductive toxicity study" the groups are of 20 animals and the maximum duration of the study is 25 weeks, necropsy of the animals is performed, and the general toxicity is clinically and pathologically documented with emphasis on the integrity and performance of the male and female reproductive systems and the health, growth, development and function of the offspring *(Test No. 443: Extended One- Generation Reproductive Toxicity Study, 2018)* [13]; in the OECD Test Guideline 451 on "Carcinogenicity Studies" the number of animals per group is 100 and the duration of the study is 12 months *(Test No. 451: Carcinogenicity Studies, 2018)* [14]. ADRs are classified according to the frequency of occurrence in humans as: very common ≥1/10 (≥10%), common ≥1/100 and <1/10 (≥1 and <10%), uncommon ≥1/1000 and <1/100 (≥0.1 and <1%), rare ≥1/10.000 and <1/1.000 (≥0.01% and <0.1%), very rare <1/10.000 (<0.01%) [15], this classification is assigned at post- commercialization stage but not during drug trials. Animal studies are not properly designed to estimate the frequency of occurrence unwanted side effects that potentially could be ADRs, in accordance with the above described, even when the number of animals is 100, this number is considerably low to detect uncommon, rare and very rare side effects, therefore these cannot be observed. Regarding the time of ADRs appearance, the OECD guidelines are appropriate since they would allow us to estimate reactions that appear immediately, such as anaphylactic or allergic reactions, such as Steven Johnson, or reactions that appear with chronic use of the medication, such as eye problems. such as glaucoma or cataracts caused by chronic use of corticosteroids such as prednisone.

In the computer-aided drug design stage, the assays are focus on predicting the pharmacological activity of the molecules using QSAR or DOCKING techniques, however, scientists should also focus on searching for the possible toxic effects of the molecule, since currently on the market there are several computer programs or software with great capacity to perform this task: QikProp, VolSurf, ADMET Predictor, q-TOX, ACD/ADME Suite, ACD/Tox Suite, TOPKAT, VirtualToxLab, Molcode Toolbox, Derek Nexus, PK-Sim, SimCYP, Know-it-all – ADME, TIMES, CAESAR, Lead scope, Toxmatch, PASS, Taxotere, T.E.S.T, Meta Drug, OSIRIS property explorer, MCASE, CT-LINK [11]. (Narsis A. Kiani*, Ming-Mei Shang and Jesper Tegnér The use of these computer programs by scientists should be carried out since the time invested is minimal and the resources are available on the market. In fact, the number of publications on the effects toxic effects of molecules with pharmacological activity is considerably lower than that of publications that report pharmacological activity, which is logical because molecules that present possible severe toxic effects will not be able to advance to the next stages of the process.

A disadvantage of the process in the bio evaluation stage in laboratory animals, is that in most studies the drug is evaluated alone

in solution, or through preliminary pharmaceutical formulations that are sometimes totally different from the definitive formulations of the medicine that goes on the market. A pharmaceutical formulation of medicines has the main purpose of promoting administration and bioavailability, however, excipients could also enhance the appearance of unwanted effects. Despite advances in tablet coating technology, there are currently medications which are available every day in pharmacies such as aspirin or ciprofloxacin that are irritants to the digestive tract [16] and are high-frequency reactions in humans.

A relevant aspect to detect possible and serious ADRs is that an intentional search for unwanted effects should be carried out, this is possible since the majority of new drugs of synthetic origin that come onto the market are molecules derived from others already known, such as the different generations of cephalosporins. Additionally, some new drugs are also structurally similar to other molecules with known adverse reactions, such as opioids. Therefore, it is logical to think or assume the possibility that, by increasing the potency of action, the undesirable side effects could also be preserved or even enhanced. The above raises the possibility of carrying out specific toxicity studies in laboratory animals of the most frequent and serious adverse effects like opioid addiction [17]. However, emphasis is rarely placed on this type of study by the pharmaceutical industry, which is focused on demonstrating the effectiveness of the medication in the initial stages of the process. Mainly, in clinical trials in humans, the pharmaceutical industry has the opportunity to perform specific studies on the unwanted side effects with common and very common frequency and severity, such as addiction caused by opioid agents. Or cardiovascular toxicity generated by antineoplastic agents such as trastuzumab.

Conclusion

In conclusion, it is undeniable that new medications constitute a hope of recovering patients' health, this subjective aspect of researchers and industry commercial interest to provide more powerful and effective medications, which must be promptly available in health systems, which has accelerated the drug development process as in the case of vaccine against COVID-19. In this case it was imperative and necessary to resist the global pandemic, however, now is evident the great need to perform intentional studies to investigate and predict the possible risk of serious ADRs. The responsibility falls on the regulatory authorities who are designated to establish the parameters with which drugs are evaluated to approve it.

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Conflict of Interest

No conflict of interest.

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