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REVIEW

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Medicines regulatory harmonization: international collaboration as a key to improve public health

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ABSTRACT

Over the past 30 years, many national drug regulatory authorities have embarked on a process of gradual harmonization of all the technical aspects of studies, processes, and tests that generate the data necessary to support claims of quality, safety, and efficacy of medicines. This has been mainly a trade-driven process characterized by "region-specific" harmonization initiatives; the less-resourced authorities started this processes much later than the better-resourced ones. The immediate outcome of harmonized requirements is the eliminating of country-specific tests and studies, and the narrowing of gaps in the interpretation of data. This reduced the costs for pharmaceutical companies by enabling them to develop one single set of data and documentation to be submitted to several different countries. In addition, the harmonization processes are beneficial for public health: open-minded technical discussions and the exchange of ideas and experience among regulators of different countries contributes to strengthening the capacity of national authorities to expedite the assessment of priority medicines, and to filter out unsafe or substandard products.

Keywords: Medicines, Regulatory authorities, Public health

Introduction

Medicines are an essential component of our health systems. They are almost invariably the tangible outcome of a patient-prescriber encounter. They can change people's lives not only when they are effective, but also when they fail or cause adverse effects. They are also the source of other diverse outcomes, such as prestige for successful providers, and profits for those who have a commercial involvement in their development, manufacture, and trade.

Medicines are not common commodities. First, the assessment of their efficacy and safety is a difficult and specialized task that cannot be performed by individual health professionals or patients. Second, the assessment of their quality is a very complex technical task that requires specialized skills. Third, medicine consumption is ruled by a singular mechanism: those who determine the use of medicines – the prescribers – do not pay. Those who pay – be they patients, social security systems, or private insurers – usually have a very limited role in influencing consumption. Those who take medicines – the patients – most often substantially accept the advice they are given.

For all these reasons, in most countries, the pharmaceutical sector is highly regulated and the decision to make medicines available to prescribers and patients belongs to specialized entities: the national drug regulatory authorities (NRAs). At first sight, regulatory work should be based on a simple principle: only good quality medicines with a favorable benefit-risk ratio should be authorized for marketing. Unfortunately, the assessment of these parameters is not always a simple task, and pharmaceutical companies have shown an extraordinary ability to find ways to obtain the approval and to keep on the products market that do not really have a favorable benefit-risk ratio (e.g., see the cases of rofecoxib (1-3) and benfluorex (4)), or have significant quality defects (5-7).

Why approvals may be inappropriate

Many factors contribute to making these inappropriate approvals possible. One is the fact that the information available at the time of regulatory assessment is limited to the data obtained in the experimental context of clinical trials. While it is broadly accepted that clinical trials are the best available method for measuring the intrinsic efficacy of a drug, they are not suitable for representing the conditions of real use of medicines after the NRA's marketing approval. This provides regulators with a good opportunity to make wrong decisions when assessing benefit-risk ratios – decisions that are sometimes mitigated by the fig leaf of narrow indications

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or long lists of warnings and precautionary statements. However, these mitigating measures do not prevent intensive promotion, off-label use, and high numbers of prescriptions for population groups that are not represented in clinical trials. This means that it is only in an uncontrolled environment – the so-called "real life" – that large segments (if not the largest) of patient populations are exposed to a new medicine for the first time. These are, for example, patients that are older or younger than those included in clinical trials, patients with other concomitant diseases (which are generally excluded from clinical trials), patients taking other medications (also generally excluded), and patients that have been diagnosed using criteria or accuracy that are not the same as those used in the context of clinical trials. This situation implies that benefit-risk ratios can vary over time and in different contexts. Therefore, medicines should be constantly monitored to ensure that the experience of their use in real life does not contradict the initial benefit-risk ratio assessment. Unfortunately, this monitoring and the resulting decisions are not easy tasks: even in countries with efficient pharmacovigilance systems, monitoring the real-life use of medicines does not provide the same level of evidence offered by experimental evaluation, and brings with it a degree of uncertainty. This usually leads to leaving medicines on the market that have a poor benefit-risk ratio. (It is similar to criminal cases: when the judge is in doubt the accused is let free.)

Other factors, such as different manufacturing sites, different sources of active ingredients and excipients, and different packaging materials, all affect the quality of the final products and therefore may affect their efficacy and safety.

The NRA's work is further complicated by the involvement, at varying degrees, of (independent) experts, prescribers, public opinion, and politicians – all of whom consciously or unconsciously promote or fight vested interests.

It is against this background and within their national legal frameworks that NRAs discharge their duty. Needless to say, well-resourced NRAs can rely on highly skilled staff, advanced technical equipment and knowledge, effective market monitoring systems, and real decision-making capacity. Less-resourced NRAs are often in a more difficult position and have a greater need to develop creative and appropriate strategies to strengthen their capacity to make sound decisions. One way to do this is by intensifying international collaboration with other NRAs, and a prerequisite for this is the substantial similarity – or "harmonization" – of regulatory requirements; that is, all the technical aspects of studies, processes, and tests that generate the data necessary to support the claims of quality, safety, and efficacy of medicines.

Harmonizing regulatory requirements: recent history

Harmonization of regulatory requirements started as a trade-driven initiative in the European Economic Community (now the European Union [EU]) in the late 1970s. Its purpose was to develop a single body of pharmaceutical legislation and regulations among its member countries. In 1990, this was followed by the formal establishment of the International Council (formerly Conference) for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) (8), which involved the regulatory authorities and the pharmaceutical industry associations of the EU, Japan, and the USA. These huge, and extremely costly, initiatives have certainly brought benefits to the pharmaceutical industry by eliminating the need to perform different studies or by applying different methodologies to meet different national requirements. This has contributed to a reduction in paperwork and the time required to bring a new medicine onto the market. Some claim that this should have benefitted patients by lowering development costs and, therefore, the cost of medicines, but there seems to be no way to demonstrate this.

Less-resourced NRAs have recognized that harmonization can lead to greater collaboration among them, which can bring concrete benefits, such as a strengthening support for their decisions, learning from each other's experiences, sharing scarce resources, eliminating the duplication of work, and strengthening the confidence in outcomes of their assessments. This is generally welcomed by both the regulators and the industry and is believed to translate into improved public health protection by better regulatory performance.

Besides ICH, harmonization initiatives, with variable scopes and levels of implementation, have been established in different parts of the world by various institutions. Just to mention a few, from West to East: Mercosur (9), the Pan American Network for Drug Regulatory Harmonization (PANDRH) (10), the East African Community (EAC) (11), Zazibona (12), the Eurasian Economic Union (13), the Gulf Cooperation Council (14), the Association of Southeast Asian Nations (ASEAN) (15), and the Asia-Pacific Economic Cooperation (APEC) (16).

Harmonizing regulatory requirements: the importance of international collaboration

An interesting example of the possible benefits of international collaboration is offered by the NRAs of the 10 ASEAN member countries. Their technical discussions have gone deep into the background and rationale of stability testing, to the point of triggering the revision of the WHO's stability testing guidelines to include more appropriate storage conditions for hot and humid climatic zones (17) and the withdrawal of the relevant ICH guideline (18).

ASEAN includes 10 countries with very important differences in terms of population, per capita gross domestic product, industrial and rural development, and religion. Brunei Darussalam has the smallest population (420,000), and a per capita gross domestic product (GDP) purchasing power parity of over 70,000 international dollars (19-21). Indonesia has a population of 260 million and a per capita GDP of about 11,000 international dollars. Singapore has the highest per capita GDP of the region, over 80,000 international dollars, while Cambodia does not reach 3,500. Singapore is a major manufacturer and exporter of biotechnological medicines, while the less-resourced member states have no significant pharmaceutical manufacturing capacity.

ASEAN started harmonizing the pharmaceutical sector before the year 2000 within the scope of a trade-driven initiative, which virtually encompassed all sectors of the economy. The institutional entity leading the ASEAN pharmaceutical harmonization process is the Pharmaceutical Products Working Group of the ASEAN Consultative Committee on

Standards and Quality (PPWG). The PPWG comprises representatives from each of the 10 NRAs and is chaired by Malaysia. The most important difference, when compared to the European pharmaceutical harmonization process, is the absence of a common legal framework. This sets important limitations because PPWG must ensure that its deliberations are compatible with each of the 10 legal frameworks of the member countries. In addition, there is a significant gap concerning manufacturing: while the NRAs of Indonesia, Malaysia, Singapore, and Thailand are members of PIC/S (which means good manufacturing practice requirements and enforcement equivalent to those of, among others, the EU, Australia or the USA) (22). The other ASEAN NRAs, with the exception of the Philippines, cannot perform at recognized international standards.

Yet, in spite of this background of differences and limitations, ASEAN NRAs have been able to develop a single set of technical requirements for marketing authorization of pharmaceuticals, as well as a number of common guidelines for the application and interpretation of these requirements.

To grasp the benefits of the harmonized requirements, ASEAN NRAs have started joint assessments projects. These are formal procedures in which the same application is simultaneously submitted to all participating NRAs. Assessment work is then carried out by all participating NRAs together, and a joint assessment report is prepared. At the end of the process, the final decision on the application is taken – within established time lines – by each individual NRA through their normal decision-making process based on the joint report and, where applicable, nationally relevant considerations. The perceived benefits of conducting joint assessments are many. First, NRAs must agree on eligibility criteria for medicines to be admitted to the joint assessment procedure. This triggers fruitful discussions and an exchange of ideas about the priorities and purposes of the exercise. For many NRAs, these discussions are a novel, mind-opening experience. Second, NRAs must agree on procedures, report writing, and ways of exchanging correspondence with applicants. Experience shows that this is a good opportunity to critically review one's own practice. Third, the experience, knowledge, and skills of technical staff of the participating NRAs are not on the same level. Conducting joint assessments offers the possibility to learn from each other and to develop mutual trust. Fourth, joint assessments allow special situations to be looked at in a novel way. For example, the benefit-risk ratio of an antimalarial is not the same if one looks separately at the situation in a malaria-endemic country like Myanmar, or in a malaria-free country like Singapore. However, Singaporeans do regularly travel across malaria-endemic areas of other ASEAN countries. A joint assessment of antimalarials by regulators of endemic and nonendemic countries offers an opportunity to look at things from different angles and, possibly, to identify issues that may have been overlooked in assessments conducted in isolation.

A look ahead

With all their limitations, NRAs play an essential role in protecting public health from the potential harm caused by unsafe medicines. For many years, NRAs have worked in isolation and this has contributed to maintaining important disparities among countries in relation to the circulation of substandard medicines, irrational fixed-dose combinations, and other unsafe medicinal products. The development of international collaboration initiatives is certainly helping to reduce the gap in the outcome of regulatory work between well-resourced and less-resourced NRAs, and has encouraged even NRAs that are not participating in international harmonization initiatives to review their practice and remove unsafe products from their national markets (23, 24). This is good news for public health.

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