FEATURE ARTICLE

Regulations and Guidelines Should Be Strengthened Urgently for Re-evaluation on Post-marketing Medicines in China

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ABSTRACT This paper reviewed the situation of regulations and guidelines on post-marketing medicines in the developed countries and in China. The developed countries have accumulated a lot of empirical principles and techniques on post-marketing surveillance (also named pharmacovigilance), therefore, their regulation systems are nearly perfect. In China, the regulations on post-marketing re-evaluation and relative technical guidelines do not cover the whole aspects, even lack in some important aspects, and long-term risk management mechanisms have not been established. So it is urgent to establish new regulations and improve the regulatory system in China based on the existing regulations and guidelines, by learning from the ideas of foreign advanced regulations, then fully integrating them with China’s actual conditions, and cooperating with multidisciplinary researchers.

KEYWORDS post-marketing medicines, re-evaluation, regulations and guidelines, pharmacovigilance

As we all known, re-evaluation on post-marketing medicines is very important to provide safe, effective and inexpensive medicines for the public. In China, it is very necessary to improve the relevant regulations and guidelines. In this paper, we reviewed the regulations and guidelines for re-evaluation on post-marketing medicines in developed countries, and the current situation in China. Ideas were proposed on the establishment and improvement of regulations and guidelines for the post-marketing re-evaluation in China.

Importance of the Re-evaluation Studies on Post-marketing Medicines

There are many disadvantages of clinical trials for the new drug applications, such as simple research purposes, populations with narrow age ranges, limited cases, stringent medication conditions, short follow-up periods, etc. Therefore, the researchers fail to find the adverse drug reactions (ADRs) due to low incidence rates, delayed ADRs, or drug interactions, which may lead to the failure to obtain comprehensive safety information of medicines. In the post-marketing clinical practice, these ADRs mentioned above may occur, and not only cause injury to the patients, but also severely restrict the development of the pharmaceutical enterprises. In order to avoid the serious ADRs, promote rational clinical medicine usage, and guarantee the public safety, the governments worldwide attach great importance to the safety re-evaluation on post-marketing medicines.

With a long history and abundant clinical experience, Chinese medicines still plays an important role in the field of public healthcare in China. Many aspects of Chinese medicines in clinical practice, including the long-term effectiveness, the best indications, the optimal dosage, methods of administration and dosage, drug interactions, new indications, as well as other factors affecting the effectiveness of medicines (e.g. age, physiological conditions, concomitant medications, etc.) are also important parts on the re-evaluation on post-marketing Chinese medicines.

Re-evaluation on the safety and effectiveness of
post-marketing Chinese medicines helps to constantly improve the pharmaceutical technology, reduce medicine costs, enhance the pharmaceutical industry, and earnestly safeguard the public health. Economic evaluation are carried out to evaluate the medicines’ economic advantages in the post-marketing clinical practice, which helps to provide safe, effective and inexpensive medicines for the public, promote public health and reduce the burden of the public and government, and promote the development of society.

Regulations and Guidelines for Re-evaluation on Post-marketing Medicines in Developed Countries

As a global organization, the World Health Organization (WHO) attaches great importance to the re-evaluation on post-marketing medicines, especially the safety monitoring, in order to ensure the safety of medication as far as possible. WHO issued a series of regulations and guidelines\(^{(1-3)}\) to stress the importance and necessity to carry out pharmacovigilance. A guideline was released to guide member states on how to establish and run a pharmacovigilance center.\(^{(4)}\) The safety of medicines: A guide to detecting and reporting ADRs provides the contents of the ADRs report form and the situations required to report,\(^{(5)}\) and it has become a basic principle and standard on the ADRs monitoring and reporting for the member countries. The WHO guidelines on safety monitoring of herbal medicines in pharmacovigilance systems\(^{(6)}\) aims for the safety monitoring of herbal medicines, and the contents involve the reporting entity, agencies collecting the ADRs, and reporting information. These guidelines are recognized by the majority of member countries, and serve as an important reference to develop post-marketing safety monitoring regulations.

The United States (US) is the country with the biggest pharmaceutical production and consumption, and the Food and Drug Administration (FDA) has not only committed to regulate the specification on pre-marketing medicines and administration of drug registration, but also paid great attention to the post-marketing safety monitoring. In the Code of Federal Regulations (CFR) Part 21, Chapter 314, procedures and requirements were set out for post-marketing report regulations, including the alert report and the annual report of the New Drug Application.\(^{(7)}\) On the basis of Federal Food, Drug, and Cosmetic Act\(^{(8)}\) and Food and Drug Administration Amendments Act of 2007,\(^{(9)}\) the American government agencies (including FDA) formulated and promulgated a series of laws, regulations and guidelines. Through the post-marketing commitments study,\(^{(10)}\) FDA can collect the additional information on the safety, effectiveness and best usage of the post-marketing medicines. FDA had established a post-marketing surveillance program in 1961, and established the MedWatch reporting system in 1993,\(^{(11)}\) which make ADRs reporting unprecedented systematic and efficient. US is the first country in the world to implement the product recall system, and also the country applies the product recall measures most frequently. The 21CFR7 Subpart C\(^{(12)}\) and Guidelines for Industry Product Recalls, Including Removals and Corrections Detail Provisions for Drug Recalls.\(^{(13)}\)

European Unions (EU) countries also pay much attention to the safety of the post-marketing medicines, and developed a series of laws, regulations and guidelines. The Regulation (EC) No. 726/2004\(^{(14)}\) and Directive 2001/83/EC\(^{(15)}\) set the legal framework for pharmacovigilance of medicinal products for human use in EU, and were amended respectively in 2010,\(^{(16,17)}\) as well as implemented in 2012.\(^{(18)}\) In order to better conduct the pharmacovigilance, EU enacted the Good Pharmacovigilance Practices (GVP),\(^{(19)}\) and the ten guidelines released cover the following regulations, technology and scientific methods: pharmacovigilance systems and their quality systems, pharmacovigilance system master file, pharmacovigilance inspections and audits; and set more specific and comprehensive requirements on the risk management systems, management and reporting of adverse reactions to medicinal products, periodic safety update report, post-authorization safety studies, signal management and so on.

Early in 1979, the post-marketing surveillance system (PMS) was established in Japan to assure the efficacy and safety of post-marketing medicines, and Japan was the first country to require pharmaceutical companies to carry out the post-marketing surveillance, which consists of three systems: the ADRs collecting and reporting system, the reexamination system, and the re-evaluation system. In 1993, Good Post-marketing Surveillance Practice (GPMSP) came into effect to assure proper implementation of PMS and is applied as standards when performing post-marketing surveillance or studies. In the revised Pharmaceutical Affairs Law (2004), GPMSP was divided into Good...