

Herbal Medicines Pre-Marketing Registration Process in the State of Kuwait: An up-to-Date Overview of the Process

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Abstract

All herbal medicines (HMs) in Kuwait are imported from other countries and are registered by the Kuwait Drug and Food Control and Administration (KDFC). In order for a HM to be approved into the Kuwaiti market, several steps must be taken consisting of agent and company registration and herbal product registration. Each step requires that specific regulatory and scientific documents be submitted, assessed and evaluated in the relevant unit at the KDFC. Some concerns and safety issues have been identified in the current HM registration process because of the absence of important regulatory measures. Therefore, this review aims to describe the most up-to-date pre-marketing process and procedures carried out to assess the approval of imported HMs into the Kuwaiti market and address the current challenges of the process.

Keywords: Herbal medicine registration, Kuwait, Challenges, Medicines regulation

Introduction

The use of herbs for the prevention and treatment of illnesses is historical. With the development of science, the popularity of herbal medicines (HMs) has widened. It is estimated that 80% of the world's population use HMs as their source of primary care [1]. With the growing consumption of HMs, complications associated with their use have become widely acknowledged. A single medicinal herb can contain hundreds of constituents with different properties that are difficult to identify. Reported incidents of consuming some kinds of HMs vary from allergies, liver and kidney dysfunction, cancer and even death [1].

In some national markets, such as Austria, Germany and France, herbal preparations are well defined and the HM registration system is well established under existing laws [2]. However, in other markets, such as Kuwait, sufficient regulatory measures for HMs registration are inadequate resulting in safety issues to the consumer [3]. For the purpose of this review, HMs are defined as "Herbal preparations that are industrially manufactured in which the active ingredient(s) is/are originated from pure plant substance(s) which is/are not chemically altered and is/are responsible for the overall therapeutic effect of the product".

Background of the State of Kuwait

Kuwait is a small emirate of 17,818 sq. km located at the top of the Arabian Gulf between Iraq and Saudi Arabia (as shown in Figure 1). The country has a small population of 4.4 million (with 30.5%

being Kuwaiti) [5]. Kuwait is wealthy, as it possesses about 10% of the world's reserves of crude oil. However, as a result of the small population, there is limited pharmaceutical manufacturing capacity and therefore, all HMs are imported. The exact prevalence rate for HMs consumption in Kuwait is unknown as there is scarcity in published studies around this area. However, in a study that was conducted in 2014 on the usage of complementary and alternative medicine (CAM) among medical and pharmacy students in Kuwait, it was found that 55.2% of participants are CAM users with HMs being the most commonly consumed [6].



Figure 1: Map of Kuwait and surrounding countries [4]

The regulation of HMs in Kuwait with the introduction of specific laws for HMs started in 1989 by the Islamic Medicine Centre [7]. In 1990, the Iraqi invasion of Kuwait caused a seven month long Iraqi occupation of Kuwait that led to the collapse of the entire healthcare and pharmaceutical regulatory system. In 1991, the war ended and relations between the two neighbouring countries turned friendly. Since then, the healthcare system in Kuwait and the registration and regulation of all kind of medicines including HMs are in the process of developing. All HMs imported into Kuwait are currently registered and regulated by the Kuwait Drug and Food Control and Administration (KDFC), a division under the Ministry of Health (MOH). Current literature related to HMs regulation in Kuwait is limited, as it only describes the regulations of the Centre for Islamic Medicine, which used to regulate HMs [8]. KDFC's HMs registration process, documents required for their registration and the decision process of approving the products are scarcely addressed in literature. Therefore, the aim of this review is to describe the current most up-to-date HMs pre-marketing process and procedures carried out to assess the approval of HMs into the Kuwaiti market and address the current challenges of the process.

HMs pre-marketing registration process in the KDFC

KDFC is the responsible body for registering all pharmaceuticals, herbal products, homeopathic products, medical devices, veterinary medicines, cosmetics and food supplements in Kuwait. The Drug Registration and Release Superintendent (DRRS) is the person responsible for approving the registration of all products in the market. The registration departments in the KDFC consist of five separate registration units and two additional units (as shown in Figure 2): The pharmaceutical unit, herbal unit, veterinary unit, unclassified unit (borderline), cosmetics unit and food supplements unit.

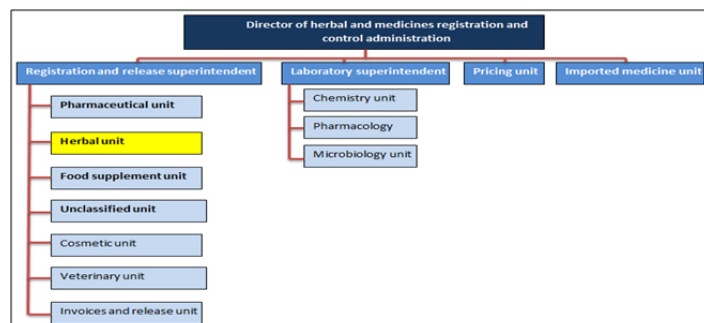


Figure 2: Organisational structure of the KDFC

All registration units include scientific reviewers who perform a scientific assessment of each product as part of the pre-registration phase. The additional units are quality assurance (QA) and invoices and release. The QA unit is considered a newly established department which is responsible for monitoring the safety of registered medicines. The invoices and release unit is responsible for issuing receipts for applicants who submits new products for registration and are responsible for providing release approval for the product into the market after the products are assessed, tested and approved by the DRRS.

The laboratory unit is divided into three sections: chemistry, pharmacology and microbiology. Workers in the laboratories are considered analysts; they perform the quality control (QC) of all medicines required for registration. The analysis involves analysing the finished product sample against quality standards. The pricing

department is responsible for regulating the price proposed by the manufacturing companies for medicines to be sold in Kuwait. The Kuwaiti government set an exact fixed profit margin for all pharmaceuticals including HMs, which is a maximum profit value of 55%.

The imported medicines unit is responsible for sorting all samples received from local agents and distribute them to the different departments for the purpose of assessment and analysis according to the product registration status in the country of origin.

The registration process

The herbal unit consists of five scientific reviewers who are responsible for assessing new HMs prior to their registration. The herbal unit registers herbal teas, herbal coffees, homeopathic medicines and HMs. For a HM to be approved into the market, two main steps must be carried, agent and company registration and product registration. Figure 3 illustrates the overall registration process of HMs in the KDFC.

Agent and company registration

Since all HMs in Kuwait are imported from other countries, the manufacturing company must appoint a local agent to represent the product in Kuwait. This process is a one-off procedure that is required for the registration of all products. In addition to the registration of the local agent, the manufacturing company must also be registered, which requires the submission of an original good manufacturing practice (GMP) certificate that is authenticated by the Kuwaiti embassy and the health authority of the country of origin. This certificate must state that the manufacturing company has been inspected by the relevant health authority and that it follows the current GMP (cGMP) guidelines which ensures the production of products with high quality standard. Another requirement for the registration of the company is to provide an original manufacturing licence from the health authority, which must also be authenticated by the Kuwaiti embassy of the country of origin.

Herbal product registration

The overall registration process of HMs in KDFC is described in Figure 3.

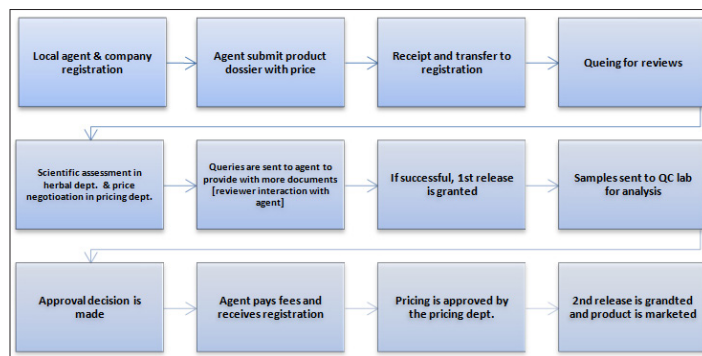


Figure 3: Overall registration process of HMs registration at the KDFC

Submission of the dossier

After the local agent and company registration, the review of the product file process starts with the agent submitting the registration dossier along with a covering letter to the Director's administrative staff requesting the registration of the herbal product. The dossier

contains hard copy documents and materials required for the registration of HMs in accordance with Ministerial Decree 201/97. The administrative staffs then transfer the registration dossier to the herbal registration department and the DRRS acknowledges receipt and appoints a scientific reviewer to undertake the assessment of the dossier. The reviewer places the product in a queue for review.

Scientific assessment

The scientific reviewer starts with the validation of the submitted documents making sure that the agent and manufacturing company are registered in the KDFC. This is followed by validating the original Certificate of Pharmaceutical Product (CPP) or Free Sale Certificate (FSC) which must be submitted in a World Health Organisation (WHO) format, and authenticated by the Kuwaiti embassy in the country of origin where the product needs to have been registered in the country of origin for at least two years. The reviewer then ensures that evidential documents of quality, safety and efficacy are submitted and are clear.

There are other requirements including the patient information leaflet (PIL), artwork of the finished product outer pack and label and original proposed price certificate authenticated by the Kuwaiti embassy in the country of origin. The safety and efficacy documents are based on toxicological and safety studies, clinical studies showing pharmacological effect of the product on the human body or evidence of acknowledged scientific references. The safety and efficacy studies are not investigated unless a query is raised on a specific product. The reviewer, however, assesses the quality documents thoroughly. This includes product specifications and detailed methods of analysis of the finished product with the reference pharmacopoeias, full stability studies addressing the proposed product shelf life, raw material specifications and their methods of analysis as well as the reference pharmacopoeia. This type of assessment is called an abridged review, where the documents are not fully reviewed. It is different from the full review where an extensive full evaluation of quality, pre-clinical and clinical data are required where access to appropriate experts is essential. The department considers the abridged assessment as it saves time and effort by not reassessing all scientific data that has been reviewed, assessed and approved in the product's country of origin. If any of the required documents are missing, the reviewer requests the missing documents for the agent to provide which the head of the department and the DRRS must sign off.

Approval

Once the scientific assessment of the dossier is completed and the reviewer is satisfied with the documents, approval decision is made and another scientific reviewer is asked to validate the assessment and decision. The decision is then signed off by the DRRS. The agent will therefore be given a first release form to sign declaring that the product can enter the country and be kept in a storage place. The agent must also present with a storage licence before receiving the first release. The product will then be sent to the pricing department for pricing and price negotiation between the agent and pricing department begins. The product must not enter the market until a second release is given for the product to be marketed. To gain the second release, the agent will be asked to provide with a sample of the batch in order to test the product in the QC laboratory. The QC tests depend on the certificate of analysis of finished products that the agent provides in the initial submission of the dossier. This certificate is used to compare the

information with the QC analytical results. If the product passes the QC analysis and the pricing negotiations are complete, the agent will pay the registration fees, second release is granted and product registration certificate is issued. There are currently 191 HMs registered in the KDFC.

Challenges of the current HMs registration system in Kuwait

The regulatory status of HMs varies from one country to another [9]. Where it may be defined as a dietary supplement in one country, it may be defined as a herbal or a conventional medicine in others. This results in HMs imported into Kuwait being registered under different units in the KDFC, as the allocation is not based on the nature or characteristics of the product itself, but its regulatory status in the country of origin. The lack of a clear definition of what constitutes a HM and a classification system for HMs causes an uncoordinated registration process. Consequently, some HMs are registered under the unclassified unit as dietary supplements or as functional food under the food supplements unit (as shown above in Figure 2). Products under these units require very few and less stringent requirements for registration. As a result, some products are marketed with poor quality and safety, causing safety issues to the public's health [3].

Conclusion

Kuwait has established clear registration requirements for the assessment of HMs. However, the current process lack a classification and definition for HM registration, which is resulting in some imported products being regulated under different units with less stringent registration requirements. Proposed action would be to introduce a clear definition of what constitute a HM in the KDFC, and require that all products under this definition must be classified under one department; the herbal department. This action would allow a standardised approach for evaluating safety, efficacy and quality of HMs imported into Kuwait.

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