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Conference report

Challenges for the registration of vaccines in emerging countries: Differences in dossier requirements, application and evaluation processes ☆

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ABSTRACT

The divergence of regulatory requirements and processes in developing and emerging countries contributes to hamper vaccines' registration, and therefore delay access to high-quality, safe and efficacious vaccines for their respective populations. This report focuses on providing insights on the heterogeneity of registration requirements in terms of numbering structure and overall content of dossiers for marketing authorisation applications for vaccines in different areas of the world. While it also illustrates the divergence of regulatory processes in general, as well as the need to avoid redundant reviews, it does not claim to provide a comprehensive view of all processes nor existing facilitating mechanisms, nor is it intended to touch upon the differences in assessments made by different regulatory authorities. This report describes the work analysed by regulatory experts from vaccine manufacturing companies during a meeting held in Geneva in May 2017, in identifying and quantifying differences in the requirements for vaccine registration in three aspects for comparison: the dossier numbering structure and contents, the application forms, and the evaluation procedures, in different countries and regions. The Module 1 of the Common Technical Document (CTD) of 10 countries were compared. Modules 2–5 of the CTDs of two regions and three countries were compared to the CTD of the US FDA. The application forms of eight countries were compared and the registration procedures of 134 importing countries were compared as well. The analysis indicates a high degree of divergence in numbering structure and content requirements. Possible interventions that would lead to significant improvements in registration efficiency include alignment in CTD numbering structure, a standardised model-application form, and better convergence of evaluation procedures.

1. Introduction

The United Nations' System for vaccine procurement and supply is served by the United Nations International Children's Fund (UNICEF) and the Pan-American Health Organisation revolving fund (PAHO-RF). It relies on the World Health Organisation pre-qualification programme (WHO-PQ) to pre-select vaccines eligible for purchase as well as to monitor the quality, safety and efficacy of the vaccines supplied to receiving countries [1,2]. The UN system targets low middle income (LMIC) and low-income countries (LIC). Vaccines procured through this centralized system to support National Immunisation Programmes, have to fulfil three requirements: a valid marketing authorisation, evaluation by the WHO prequalification programme and, in some cases, marketing authorisation evaluation in the receiving countries.

Although these three levels of authorisation are required, the dossier review process should not need to be repeated at each level. Ideally, a vaccine that is well regulated in the manufacturing country and is prequalified by WHO, fulfils in principle the requirements of safety, efficacy and quality, and should be eligible for an accelerated and facilitated process for marketing authorisation in the receiving countries, based on recognition of the dossier

☆ This report summarises the views of an international group of experts as presented and discussed at a scientific meeting in a given time and context, and does not necessarily represent the decisions or the stated policy of any institution or corporation. It is a Report of the meeting on "Alignment of regulatory requirements for vaccine registration at global level", 15–16 May 2017, Geneva, Switzerland.

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evaluations performed by the manufacturing country competent NRA and the WHO. Although the WHO has developed and promotes a collaborative registration procedure for generic pharmaceuticals with the receiving countries' NRAs, recently extended in principle to vaccines [3], due to the need for adaptations, advocacy and intensive mentoring by WHO, which requires significant efforts and resources, its level of implementation remains low for vaccines.

Practically, this means that the manufacturers applying for registration of WHO prequalified vaccines undergo a similar process twice, and a third time in each individual country, being subject to different national requirements, in receiving countries. This repetitive registration process implies high number of dossiers prepared for one and the same vaccine, adding little value to the licensed products and delaying vaccine access for some populations.

There have been numerous attempts to align regulatory requirements between countries and regions, as well as attempts encouraging mutual recognition practices between regulators of different countries in order to save both resources and time, avoiding redundancy. One such international initiative is represented by the International Council for Harmonisation (ICH) of technical requirements for pharmaceuticals for human use, originally established by the European Union, Japan and the United States of America in 1990 and expanded to other member and observer countries [4]. The ICH developed and promoted the use of a Common Technical Document (CTD) which represents a common dossier for regulatory submissions for use in the ICH countries [5]. The CTD has subsequently been adopted by additional countries globally, which should have led to a harmonisation of requirements. Countries adopting the CTD have however made local individual adaptations of the ICH CTD template, thus defeating the original intention of harmonisation. Hence, the divergence of requirements between countries remains high and evident in two-areas: (a) dossier numbering structure and contents and (b) the registration application/evaluation procedure.

The existing divergence in content requirements and registration procedures seriously impact the timelines for registration, because manufacturers are required to comply with a diversity of country specific requirements and because the NRAs have different times for evaluation of the submitted information. This results in lengthy processes delaying unnecessarily the access to high-quality, safe and efficacious vaccines in developing countries.

The lack of awareness of the magnitude of the divergence in dossier requirements and regulatory approval procedures is such that vaccine manufacturers have considered it important to invest some effort and resources to analyse these differences. This paper describes the results of a systematic comparison of CTD numbering structure and contents, based on available guidelines from selected countries, showing the similarities and differences in the requirements. It also describes the application and evaluation procedures for registration experienced in different countries, highlighting the magnitude of the problem, as well as identifying opportunities for improvements in alignment.

2. Working methodology

The Developing Countries Vaccine Manufacturers' Network (DCVMN) [6], commissioned a comparative analysis of the CTD requirements in different countries in order to estimate the similarities and differences for the different CTD modules. The results of this work were presented to a group of registration experts from DCVMN and IFPMA affiliated vaccine manufacturers, in an informal workshop held in Geneva on 15 and 16 May 2017 [7], where the participants (a) reviewed the outcome of the comparative analysis for each of the CTD modules and made corrections and adjustments, (b) listed the procedural differences between 134 countries worldwide and (c) compared the application forms required by different countries.[2]

According to the ICH, the CTD includes 5 modules. Module 1 is not harmonised and contains regional/country information. Each country or region has its own numbering system and requirements [8]. Modules 2–5 are harmonised modules, and include information regarding quality, safety and efficacy.

To assess similarities and differences between countries' CTD structures, and in order to have representation across the globe, the following regions/countries technical dossiers were included in the comparison: Australia [9], the Association of Southeast Asian Nations (ASEAN) [10], China [11], the European Union [12], the Gulf Cooperation Council (GCC) [13], India [14], Jordan [15], the Pan American Health Organisation (PAHO) [16], the United States of America Food and Drug Administration (FDA) [17,18], Tanzania [19] and Thailand [20]. The WHO prequalification programme (WHO-PQ), has recently decided to adopt the CTD structure for the prequalification submissions, and has proposed requirements for Module 1 which were published for public comments [21]. This was also included in this comparison. The Module 1 of these countries or regions were compared to each other to assess similarities and differences. For simplicity of the comparative analysis, item 1.2 (application forms) was left out.

Assuming that Modules 2–5 are harmonised modules, it was decided to include fewer countries in the comparison of these modules. It included the ICH CTD and those proposed by two regions of the world (ASEAN and PAHO) in addition to India, as a major vaccine exporting country, Jordan, representative of countries in the Eastern Mediterranean region and Thailand (currently does not follow fully the ASEAN CTD). Each of these CTDs were compared against the ICH as implemented by the US FDA and similarities and differences evaluated.

For the analysis of Module 1, contents expressed exactly in the same terms or requiring the same information were considered "similar"; and contents that differed between the CTDs were considered "different". For the analysis of modules 2–5, requirements from different countries were considered "different" from the ICH CTD if one of the following situations applied:

(1) Country X does not require specific items required in the ICH CTD
(2) Country X requires information not required in the ICH CTD (other information)
(3) Country X contains in its requirements similar heading as in the ICH CTD but the information required under such heading is not specified, while specified in the ICH CTD.
(4) Country X contains in its requirements similar heading as in the ICH CTD but the information required under such heading is specified, while not specified in the ICH CTD
(5) Country X requires different information from ICH under the same heading
(6) Country X requires different information from ICH under the same numbering

The structure of the ASEAN CTD is different from the ICH CTD. Information required in Module 2 of the ICH CTD is embedded in other sections in the ASEAN CTD. Due to these structural differences, the comparison between the ICH and the ASEAN CTD was done separately from the other countries.

[2] Participants in the workshop were regulatory experts either from companies with WHO prequalified vaccines or registration experienced at global level.