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Review Article

RISK-BASED MODELLING IN MONITORING THE QULITY OF PHARMACEUTICAL PRODUCTS

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ABSTRACT

According to WHO reports, low quality medicines represent about 10% of the global pharmaceutical market of which about 40% were substandard medicines. Most of the studies of quality of medicines recommend development of additional innovative techniques to control the existence of substandard medicines in the market. Based on recent assessment by WHO, systems applied to detect substandard and/or counterfeit medicines in developing countries were not effective enough. A strong post marketing surveillance system would be a more powerful tool for detecting sub standard medicines. In some countries, it was proven that strengthening the system by applying risk-based model for supporting the decisions is useful and possible approach. This exploration work aimed at exploring possible options to develop a risk-based quality monitoring model for pharmaceutical products. The model proposed based on this review work should help medicines regulatory authorities in resource limited settings to improve surveillance systems. The model was tested for its usefulness and effectiveness and the results obtained showed potential applications of the model in improving the system. This would include its use in the selection technique of products for inclusion in post-marketing quality monitoring. It can also be applied to increase the detection rate of low quality products.

Keywords: Quality of medicines, quality assurance, post-marketing surveillance, testing, risk management, modelling.

INTRODUCTION

Partners in areas related to pharmaceutical services are focusing their efforts intensively on assuring the safety, efficacy and quality of pharmaceutical products. By reviewing the global policy directions of most of the initiatives introduced during the last two decades, it is possible to observe a clear focus on safety and efficacy as important dimensions, with safety always put first [1, 2]. Among the three dimensions, quality receives relatively less attention, not because it is less significant but usually due to complicated management systems. Quality management systems rely greatly on national authorities on the one hand and on manufacturers on the other hand. As part of a quality monitoring system, post-marketing surveillance (PMS) for monitoring quality is no exception and has received little consideration in relation to drug monitoring information systems. Unlike the monitoring of adverse drug reactions (ADRs) which has improved markedly during the last 10 years, PMS has not been the subject of major changes aimed at improving the process or outcomes. However, there have been some specific and exceptional initiatives in some countries that have aimed to improve PMS and develop new approaches. The justification for establishing PMS in most countries is that the authorities have only a slight influence on premarketing quality management, which relies rather on the compliance of the pharmaceutical industry with regard to quality assurance schemes. The need for strong PMS was the driving force for all of these initiatives.

The main goal of this review is to encourage countries to develop risk-based quality monitoring schemes in relation to pharmaceutical products, and to examine potential options and practical models to increase the efficacy of quality monitoring systems using routinely available data [2]. The review team under took a systematic review of current projects to compare different approaches attempted in this area. The review focused primarily on measures currently implemented by the European Union member states and members of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (known as ICH). This helped, to a great extent, to inform the way in which this review was designed and recommendations were formulated to expand PMS in resource-limited settings.

Review outcomes

European Union (EU) member states have implemented mutual recognition procedure for the provision of marketing authorization (MA) of pharmaceutical products since 2005. This procedure is usually coordinated by the European Medicines Agency (EMA) but the authorities in each member state should issue MAs separately. Monitoring the quality of any registered product is maintained as part of the responsibilities of each individual member state [3]. EMA created a voluntary surveillance scheme at the EU level in the field of the independent official control of registered products [4]. The design of the surveillance scheme under this initiative is a risk-based model and uses risk evaluation approaches to target medicinal products for surveillance testing [5, 6]. The scheme began with a pilot phase in 2007. The most remarkable outcome of implementing this risk-based approach is its use in establishing more 'informed testing plans' [7]. The new system has enabled member states to focus on certain trade products with sufficient available evidence to justify testing-targeted decisions. By implementing this strategic change, member states are able to avoid unnecessary tests and reduce the load on individual laboratories.

The Food and Drug Administration (FDA) in the United States currently uses the Drug Quality Reporting System (DQRS).In this system, there are both voluntary and mandatory reporting schemes that enrich the data contributing to quality risk management (QRM). This was initially used in the premarketing phase of product lifecycles and was extended later to include the post-marketing phase. Based on the FDA experience, it is clear that to build a risk assessment model many factors may need to be considered in terms of the assumptions to support the model. Decision making based on this model is similar to that in 'problem tree analysis' in which different decision nodes can be identified based on the anticipated risk(s) at each stage. The FDA includes QRM as part of its routine regulatory operations, especially inspection and assessment activities. This model was considered for many reasons, particularly its ability to assist in allocating resources and prioritizing testing activities. In addition, it becomes less complicated to evaluate the significance of quality defects, potential recalls and inspection findings, for example [8].

In 2010, the World Health Organisation (WHO) published an overview of the findings from 26 assessment reports of regulatory systems governing medicines in sub-Saharan African countries. One of the weaknesses identified in this review is the poor implementation of PMS (WHO, 2010).The report states: 'Quality monitoring was not prioritized based on risk, but was generally performed in case of complaints if at all' [9]. In addition: 'Fourteen of

26 NMRAs (54%) lacked a quality monitoring programme altogether; 7 tested samples in case of complaints or in the framework of specific programmes, and only 5 (19%) had a systematic approach' [9]. These findings are highly significant. The report makes the following recommendation: 'A risk-based system of inspections and sampling should be in place to monitor the quality of pharmaceutical products on the market. Manufacturers should be obliged to report complaints and quality problems to the NMRA. An effective recall procedure should be in place to remove defective products from the market.' [9].

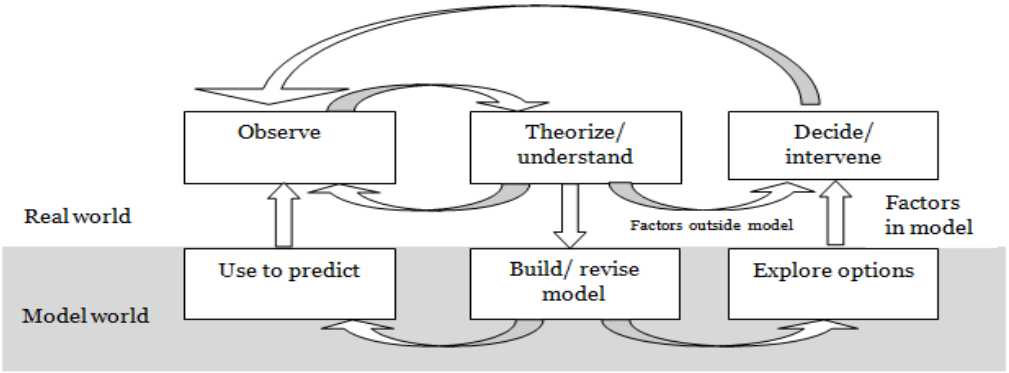
Theoretical background on risk management

When considering different risk analysis processes in any industry or service, the definition of risk is an important step in managing risks. In general, risk can be defined by ICH as a 'combination of the probability of the occurrence of *harm* and the *severity* of that harm' [10]. This definition is found to be relatively valid for all fields or areas – including pharmaceutical management – and it covers a wide range of risk categories. In the context of medicines quality, regarding sampling and testing schemes, the 'risk' is any unsatisfactory testing outcome and an 'event' is applying a sample selection process that does not maximize the possibility of identifying the undesired outcome. Thus, identifying the best way to detect unwanted event – a process – ensures the maximum detection rate of low quality products. As mentioned previously, many regulatory authorities have started to apply the concepts of risk management in their regulatory decisions. ICH member states started to apply this concept a few years ago, but there are different guidelines on the application of this technique in the field of medicines quality control and quality assurance. Its application in inspection and assessment activities has been shown to make a significant contribution to improving management systems that have applied this approach. However, its uses in the post-marketing phase of product lifecycles are still limited and countries adopting this risk management approach are still in the process of developing and improving it. The experience of EU countries in relation to the usefulness of this approach can be summarized as follows: (i) risk management assists in resource allocation among different activities, including inspection planning, inspection intensity and assessment intensity; (ii) it is useful in evaluating the significance of quality defects detected, evaluating the possibilities for potential recalls and determining the significance of inspection findings at manufacturing sites; (iii) it helps authorities to determine the appropriateness and type of post-inspection regulatory follow-up [5].

In general, any quality risk management should be based on two fundamental principles. First, scientific knowledge should be applied when evaluating risk and this should be linked to the concept of patient protection. Second, when decisions are taken to respond to identified risk(s), the efforts in this management process should be proportional to the level of risk (Bar one, 2008). The application of these principles in this exploration was considered part of an analytical approach used to arrive at the conclusions drawn. It is common proactive practice to use both formal and informal risk assessment tools, as both have been proven to be effective. Formal tools use well-known techniques that follow a more formal and structured process; these may include preliminary hazard analysis techniques, risk ranking and filtering techniques, amongst others. Informal tools, on the other hand, may make use of routine data in building models that help the organization to identify potential risks in its systems. Whatever the tool used to evaluate risk, it should include clear identification of the vulnerability of the factors and outcomes being evaluated. In this process, a key set of information needs to be identified prior to any analysis. This includes information concerning the vulnerability of different aspects of the system (especially things that might go wrong) and the possibilities of remedying these, as well as the likelihood (probability) that they will go wrong and the severity of impact [11]. In the area of medicines quality, the triggering factors that might lead to the suspicion that the product is substandard need to be identified. This process may include qualitative and/or quantitative methods related to the probability of occurrence and the severity of the potential risk(s). In other fields, the use of a 'relative risk measure', combining multiple levels of severity and probability within an overall estimate of relative risk, is also acceptable [12]. In this exploration work, this technique was used to generate a model that can help in detection of more low quality medicines circulated on the market. The aim of any medicines authority in terms of quality assurance is to reduce the risk to public health if low quality medicines find their way onto the market. Accordingly, the purpose of using this technique is to support regularity authorities in making the best use of routine sampling and testing plans to increase the detection rate of these low quality medicines. The outcome of this process will help to prioritize products for testing using a risk ranking approach that takes into account the available information to rank all categories of registered products.

Applications of risk management in quality monitoring

In this technique, the selection of products is usually based on the evaluation of a range of criteria that includes, among others, therapeutic categories, market availability, stability of the products, the manufacturing process and previous experience concerning the quality of the products. The decision to target any product combines these factors together with input from the technical staff in the regulatory authorities and general medical practice inspectorates, similar to the system in EU [6]. The final selection depends on the ranking of the products according to risk probability related to assessment criteria. This ranking process should be undertaken considering not only the risk factors but also their weight; the selection of products for inclusion in any analysis is then based on the assigned risk level. After completing the assessment of the potential risk factors, these are critically evaluated considering the probability of obtaining unsatisfactory test results and the possible consequences of this outcome, based on the profile of the products being evaluated. Then the products (or categories) are ranked against these factors and the list of products to be tested every year should take account of this ranking. The important part of this process is its simplicity as it uses extant information from different sources.



The following graphical demonstration described the logic behind building any decision support model; based on Sanderson and Gruen [13].

Fig. 1: Analytical Models Development Process*

* Sanderson, C. & Gruen, R. Analytical Models for Decision Makin. Open University Press; 2009.

Model logic

Management decisions in relation to monitoring the quality and efficacy of medicines in the post-marketing phase are usually difficult and complicated. Using risk-based management in monitoring quality is a tool that can facilitate and support a strong decision-making process. Recently, there has been a remarkable growth in the use of descriptive and analytical models for decision making in health services [13]. The models tend to use routine data and information generated from within health systems to support and increase the efficiency of the quality improvement process. Different types of model can be used in this area, depending on the objectives of the process and the data available. Considering the context of this work, a risk-based model is the most appropriate and feasible approach. Below, we discuss the possible use of a risk-based descriptive and analytical model to support decisions related to the monitoring of the quality of medicines in the post-marketing phase.

Upon the application of this concept, the model developed in this work will be useful in improving the PMS of medicines. The general characteristics of this model are as follows: i) it is essentially descriptive in nature but, based on the robustness analysis, it provides a very strong starting point for developing an advanced analytical model in the future; ii) although descriptive, the model is sufficiently strong to show the relationships between the causes and outcomes of PMS systems currently in place in pilot country (Sudan);iii) the description generated from this model is of great help in building a hypothesis concerning the most at-risk items that should be the subject of further quality evaluation or assessment (as detailed below);iv) this model includes a framework for the risk management of pharmaceutical quality, which should contribute to more consistent and science-based decision making; v) the model supports the establishment and vision of quality-related practices, guidelines, requirements and standards regarding the testing scheme of medicines in a PMS system.

The model-building process

In all risk identification procedures, the core concept is the prioritization of a large number of risk scenarios according to their individual contributions to the overall risk in the system [14]. Thus, the basic assumptions in this model were developed based on available data concerning the quality of medicines in Sudan contained in an unpublished report on a Quality Monitoring Survey (QMS) conducted in Sudan in the period 2009–2010. In addition, the team used other data from different sources to estimate the overall risk probability. The following factors were considered in estimating the severity of risk for each category of pharmaceutical products: i) therapeutic groups, ii) dosage forms, iii) manufacturing origins. The data required for this process were generated from the unpublished QMS report. In addition, other sources were used to extract data from currently published reports by the National Medicines and Poisons Board in Sudan [15]. To generate the probabilities related to the severity of risks associated with the three variables, the calculations were built based on weighting these probabilities against the total number of events reported. In addition to these factors, it was fundamental in this process to consider the impact of identified risks on public health. As it was difficult to establish the impact without precise data, it was decided to consider the 'consumption rate' of the products as an indicator of harm that could result from each category of substandard products. Based on this, products with a high consumption rate were expected to entail more harm than those with a low consumption rate. In relation to this, the (80:20 rule) was useful [16]. The concept is simple: 20% of registered items are expected to have 80% of the market share and accordingly the expected harm is represented by this ratio.

Having obtained these outcomes, the same approach was applied in a large-scale decision tree (trial) that considered the different possible categories of products based on combinations of the four factors, i.e.: i) Therapeutic group of the product, ii) Dosage form of the product, iii) Country of origin, and iv) product utilization rate. The output of this process provided the primary data for the descriptive model. Then risk ranking and filtering techniques were used to obtain the final outcomes of the model; this technique was found to be very useful in obtaining the final results [17]. The statistical package used for this process was the cumulative sum (CUSUM) control chart ISO-7871[18, 19]. The results of this process generated a model that could be used to support decision making to select specifically targeted medicines for quality checks based on the anticipated risks.

Main outcomes of the model

The following outcomes were noted, and these were very specific to the context of the market in Sudan:

1. The medicines reported with quality problems in the QMS were found within the first 64 categories (this represents 17.5% of the total 360 categories). All of the items that did not comply with reference standards are within the first 44 categories (representing 11.20% of the total).
2. From the outcomes of the model, it was noted that there is a considerable difference between the top five and the bottom five risk probabilities across the different categories. The risk probability in the first ranked category of products was 21,400 times higher than in the lowest category, i.e. the model has the capacity to differentiate between different categories of medicines and to enable more precise decisions on what items to target for testing.
3. The top 52 categories represent approximately 80% of the probabilities in the model (i.e. by targeting these categories of medicines, 80% of potentially low quality products may be included).

The outcomes analysis shows considerable diversity in relation to the main statistical tests (correlation and significance).The summary statistics of the model show a moderate correlation between the anticipated risk related to categories of medicines and the possibility of detecting (at least one) low quality product in that group. The summary also shows that when the risk increases, there is a proportional increase in the detection of the product. Nonetheless, there are some limitations to this model (based on the statistics). First, the data related to the outcomes are very limited in number as only 404 results (outcomes) were used in the model. Never the less, the model also showed positive and relatively significant correlation factors, as indicated above. Using more data in the future derived from the routine testing process should confirm the significance of using this model. Second, the model gives the same weight for all factors under analysis (therapeutic groups, dosage forms, etc.) and does not consider their importance in relation to each other (relative weights). Incorporating such a feature would be an advanced step, enabling the model to be improved. This should be undertaken when more data are available.

Usefulness of the model and approach

The model provides a scientific approach for checking the quality of pharmaceuticals circulated on the market. The proposed scheme to expand the quality/efficacy checks of medicines has proven to be a useful strategy to ensure the availability of effective products that are of good quality. This is a relatively new approach and will help decision makers in resource-limited settings in developing countries, in which the challenges in making choices are widely recognized. Based on that, the usefulness of this proposed approach might be considered in relation to the following aspects: i) the detection rate, and ii) informed selection of medicines for quality checking.

Detection rate

The adverse events the model is designed to try to prevent were related to the failure to detect substandard drugs. Indeed, this outcomes aims to maximize the possibility of identifying such products. By applying this model in practice, it is potentially possible to detect 80% of low quality products by focusing on testing medicine categories that are associated with high risk levels. In Sudan as piloting setting, using this model, it was found that 11% of registered products might represent the main source of substandard medicines in the country. The development of this model represents a significant change in improving the efficiency of the system and it has helped the authorities to increase the detection rate of these low quality products. It is important to appreciate the role of active

surveillance in increasing the detection rate of these products. The expansion of any PMS system could fundamentally be built on this concept. Implementing more dynamic and active surveillance will enable greater interaction between different parts of the system and the availability of more information. The information system will become more able to signal potential problems and identify cases that may involve low quality products.

Informed selection of medicines for quality checking

The selection of products to be included in an annual testing programme should be based on rigorous criteria that maximize the outcomes of the testing and evaluation process. Based on this model, the following selection protocol was proposed to be applied by medicines regulatory authorities:

1. After determining the capacity of the authorized laboratories, the annual plan for testing should consider the ranking of different categories. The selection of products for inclusion in any annual plans will be related to those categories ranked highest on the list at the time at which the products are selected, usually in the preceding year. The selection mechanism may adopt one of two possible approaches: (a) starting to target the categories of products one by one depending on their rank, or (b) distributing the products in each month based on the weight of the categories (but again based on ranking).

2. If two categories are similar in terms of the expected risk probabilities, either an outranking technique or a swapping technique can be employed (both are well known statistical methods).

3. Products eligible for the selection process should be authorized at least two years prior to selection. This will ensure that the product has completed the distribution phase of its lifecycle and also that there is sufficient feedback from the system for its inclusion.

4. Consideration should be given to products authorized more than two years ago but which have never been tested. This indicates their market status (not actually marketed) and they might be excluded.

5. The selection process should consider different information gathered from a range of sources to inform the evaluation plans incorporating the following aspects:

– Experts' opinions should be considered including, for example, the regular meeting of regional inspectors plus the establishment of an advisory group for quality monitoring that gives advice on the main test parameters in the product specifications.

– Health priorities in the country based on routinely collected morbidity and mortality data.

– Bioequivalence information concerning the product.

– Market information concerning a product, including its distribution pattern.

– Health and safety information concerning the product that indicates its impact on public health.

– Quality problems experienced in other countries and disseminated by the relevant authorities.

– The classification of medicines, i.e. whether it is essential or not (based on the National Essential Medicines List).

– The status of the remaining shelf life of selected products and if this is known to affect the outcomes of testing/evaluation.

6. Sampling sites should be selected based on evidence concerning the structure of distribution channels in the country. This should consider climatic conditions, the equal share of sampling load between states, the availability of targeted products/batches, the size of the market, the clinical use of the product, etc.

7. Using feedback from health workers concerning their experience of the quality and efficacy of medicines has been proven to be an effective tool. This might provide a more in-depth understanding of the samples collected and other related and associated factors.

8. Information should be sent in advance to select sampling sites to confirm the availability and the market status of targeted products; this could be done using many sorts of data collection tool (most likely through questionnaires).

Improving the effectiveness of the system

The impact of substandard medicines on public health, the use of resources and the economic impact all drive the need for interventions and innovations. The model proposed, in this exploration work, provides a tool that helps in developing effective plans to mitigate this problem and to reduce its impact on public health. This approach is considered effective for many reasons as it will assist in allocating resources and in the prioritization of monitoring activities. In addition, the model will help create an optimal and cost-effective scheme for monitoring the quality/efficacy of pharmaceutical products.

To judge whether any system is effective or not, we should evaluate the system against its objectives and whether or not these are achieved. Although the linkages between the inputs and the model outcomes need to be studied further, the application of the model indicates the possibility of improving the PMS system in terms of the selection process and the detection rate of unsatisfactory products. It is strongly recommended that the results of applying this approach be observed after at least five years, as adequate data will then have been generated to develop greater predictability towards generating a tool that can obtain more certain results. The range of results and the outcomes anticipated from our findings can inform on the directions and trends of risks. When analysing the results of the findings and associated factors, this should be very helpful in gaining greater understanding of the system. This includes results concerning products that comply with specifications, products associated with minor issues, products found to be outside specification, and problems representing critical health risks.

CONCLUSION

The outcomes of the proposed approach will enable authorities to expand the input measures of their surveillance systems beyond considering quality to include also the efficacy of medicines. The model was tested for its usefulness and effectiveness and the results obtained show potential applications of the system in improving the post-marketing surveillance system. The concept of risk-based quality monitoring schemes of pharmaceutical products is not new, but more applications need to be considered by the authorities. The model should help medicines regulatory authorities in resource-limited settings to improve their post-marketing surveillance systems. The proposed system will help the relevant authorities respond effectively to concerns regarding the quality of medicines from different sources. Governments will appreciate its practical implications in ensuring the protection of public health and controlling increased public expenditure on medicines.

CONFLICT OF INTEREST

The authors declare no conflict of interest in this work.

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