Saudi Pharmaceutical Journal 26 (2018) 71–74

Contents lists available at ScienceDirect

Saudi Pharmaceutical Journal

journal homepage: www.sciencedirect.com

Original article

Advancing pharmaceuticals and patient safety in Saudi Arabia: A 2030 vision initiative

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ARTICLE INFO

Article history:
Received 11 June 2017
Accepted 18 October 2017
Available online 21 October 2017

ABSTRACT

Low-quality medicines deliver sub-optimal clinical outcomes and waste precious health resources. It is important to ensure that public funds are spent on healthcare technologies that meet national regulatory bodies such as the Saudi Food and Drug Authority (SFDA), quality standards for safety, efficacy, and quality. Medicines quality is a complicated combination of pre-market regulatory specifications, appropriate sourcing of ingredients (active pharmaceutical ingredient (API), excipients, etc.), manufacturing processes, healthcare ecosystem communications, and regular and robust pharmacovigilance practices. A recent conference in Riyadh, sponsored by King Saud University, sought to discuss these issues and develop specific policy recommendations for the Saudi 2030 Vision plan. This and other efforts will require more and more creative educational programs for physicians, pharmacists, hospitals, and patients, and, most importantly evolving regulations on quality standards and oversight by Saudi health authorities.

1. Background

The increasing prevalence of low-quality medicines has become a global public health issue because of the dangerous therapeutic consequences associated with their use (Ten Ham, 2003). Low-quality medicines are either counterfeit or substandard products. The risks are high and global. Common examples are the growing number of counterfeit and substandard essential medicines such as antimicrobials (Kyriacos et al., 2008; Wondemagegnehu, 2011). That are expired, degraded because of improper storage or distribution. This unfortunate reality makes evolving quality guidelines and inspection protocols more urgent than ever. For example, new guidelines for industrial sampling have been developed to assess the quality of pharmaceutical products via inspection of random samples. However, since only small samples can be collected, the true prevalence of the low-quality medicines usually fails to be adequately determined (Reinke, 1991; Newton et al., 2009).

Substandard medicines also include drugs that are registered in a single country and approved by a local regulatory authority. However, these drugs often lack recognized levels of quality specification and often lack evidence of clinical safety and efficacy. Not surprisingly, many fail to provide the expected clinical outcome in patients. Several published articles have demonstrated poor patient outcomes when for instance cancer patients and patients on anti-psychotropic medications were switched from innovator drug to copy drugs which turned out to be of substandard quality or has decreased tolerability requiring close monitoring

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Peer review under responsibility of King Saud University.

Production and hosting by Elsevier

https://doi.org/10.1016/j.jsps.2017.10.011
1319-0164/

throughout brand-generic or generic-generic transition (Andermann et al., 2007; Desmarais et al., 2011).

According to Johnston and Holt in the British Journal of Clinical Pharmacology, "any formulation of a medication may be regarded as substandard if it has either too much or too little of the API compared with the formulation specifications (Johnston and Holt, 2014). Official national pharmacopoeias, such as the British Pharmacopoeia (BP) and United States Pharmacopeia (USP), publish the quality standards for medicinal substances and preparations manufactured or sold in the country". The information given specifies the acceptable limits for the amount of the API that should be present in a given formulation. However, many examples from a range of drug classes have been published of over/under-concentration of APIs in marketed drugs (Medina et al., 2016).

Inappropriate packaging can affect formulation content in certain storage conditions. For example, a study of generic versions of the antihypertensive medicine ramipril tablets found that, on initial inspection, quarter the sample inspected did not meet the label specifications for drug content. After three months of storage in temperature and relative humid-stressed conditions, further samples failed to meet the content specifications (Johnston and Holt, 2014; Medina et al., 2016). In other cases, a product may contain no API or the drug content may be completely different to that stated on the label. This may occur through deliberate falsification, but as the examples below demonstrate, accidental mislabeling which may also occur:

- One batch of the antibiotic (rifampicin) was mislabelled and bottles contained clonazepam (Health Canada, 2009).
- One lot of minocycline was mislabelled as amlodipine (Canada, 2013).
- One lot of finasteride was labelled as containing citalopram (Food and Drug Administration, 2011).
- Zopiclone was substituted for furosemide in a possible packaging mix-up (L'Agence nationale de sécurité du médicament et des produits de santé, 2017).

Moreover, Johnston and Holt has summarized that "in many other cases, contamination has clearly occurred due to poor manufacturing and/or quality-control processes, or unsuitable packaging. Contaminants have included the following: particulate matter in injectable cefotaxime; small glass particles in bottles of generic atorvastatin; tablet degradation products in docetaxel, streptokinase and clopidogrel; and potentially genotoxic impurities in batches of nelfinavir due to incomplete removal of ethanol following the cleaning of manufacturing equipment (Johnston and Holt, 2014). In addition to the official recall notices and studies published in peer-reviewed journals, there are numerous examples in the press of contamination in marketed drugs, such as the incidents described below" (Johnston and Holt, 2014).

- Paclitaxel formulation produced in India was found to contain excessive endotoxin levels and was withdrawn from the market (Herald, 2009).
- Batches of Tylenol, Motrin, Rolaids and Benadryl were recalled in the USA due to the presence of 2,4,6-tribromoanisole (Kavilanz, 2010).
- Generic formulations of clopidogrel marketed in India and Europe were found to contain methyl chloride, which can cause hepatic, renal and nervous system damage (Zoler, 2010).
- Methyldopa tablets produced in Cyprus were banned by the Tanzania Food and Drugs Authority as it was found that drug identification labels could be detached easily from the packaging, and there was 'vivid fungal growth' on the tablets (Ernest, 2011).

National regulatory bodies in Saudi Arabia such as the (SFDA) are responsible for assuring the safety, efficacy, and quality of food, drugs and medical devices for human and veterinary use. There is limited data on the size of medications quality in Saudi Arabia and the size of such problem. The list of essential medicines from the World Health Organization (WHO) is also considered essential in primary health care in Saudi Arabia. Yet, unfortunately, many medications from this list are among the most widely substandard and counterfeited (Caudron et al., 2008). For example, one study conducted in Saudi Arabia showed that amoxicillin has already been identified as substandard (Bin Abdulhak et al., 2011). Consequently, one of the central aims of advancing pharmaceuticals and patient care in Saudi Arabia is the "safe use" of quality medications (Comission, 2012).

One initiative of the Saudi 2030 vision plan should be to advance patient care through a more robust, safety/quality-centered culture together with a more collegial relationship between local and international drug manufacturers and Saudi regulatory authorities. Such an enhanced working relationship would result in a higher quality care to the public (Saudi, 2030). This concept of aggressive attention to better patient care through greater attention to quality and safety is only now emerging in developed and less developed countries.

2. Aim and Objectives of the scientific Meeting and workshop

To discuss regulatory science concepts related to advancing both the quality of medications and patient care in Saudi Arabia.

- Understand the complexity of the topic of drug quality and its importance relative to patient outcomes and as part of overall clinical practice
- Gain knowledge related to the many different aspects of quality, from drug manufacturing through registration, and improving both patient outcomes and pharmacovigilance reporting.

3. Methods

In November 2016, international experts in healthcare innovation and regulatory science joined Saudi academics and government representatives in Riyadh for a two-day conference, "Advancing Quality of Medications and Advancing Patient Care." Participants included representatives from government, academia and drug companies. Expert speakers shared their ideas with the audience with interactive discussions after each presentation and were recorded. Recommendations to advance the quality of healthcare and improve patient safety are summarized in the result section.

4. Results and discussion

Over two days, 30 experts from Riyadh region attended and enriched the discussion (Table 1).

Table 1
Baseline information of attendees (n = 30).

Characteristics	N, (%)
Gender	
Male	20 (66.7)
Area of experience[*]	
Academics	20 (66.7)
Regulators	2 (6.7)
Health Care Practitioners	13 (43.3)
Research centers	3 (10.0%)

[*] Total does not equal 100%.

The major theme of the colloquium was the importance of medicines quality. Aristotle said, "Quality is not an act, it is a habit." Habits are learned and improved through iterative learning and experience. Nowhere is this more evidently manifested than through the many and variable methodologies for medicines licensing and pharmacovigilance practices. Can there be a floor and a ceiling for drug safety and quality? Should we allow some drug manufacturers to have lower standards than others based on local situations? Can a substandard medicine ever be considered "safe and effective?"

There was general agreement that lower levels of quality for lower cost items aren't acceptable. The bad news is that there are gaps and asymmetries in how "quality" is both defined (through the licensing process) and maintained (via pharmacovigilance practices).

The general consensus of conference attendees was that Saudi 21st century pharmacovigilance practices must take into consideration the realities of Saudi national regulatory staff levels, training programs, and existing regulatory authority, and the general state of awareness of physicians, pharmacists (both hospital and commercial), and patients.

Regulatory transparency in Saudi Arabia was another topic that was robustly debated. Should there be "reference regulatory systems" as there are reference nations for pricing decisions although still controversial? And how would this impact the concept of regulatory reciprocity? The congress also discussed the virtues of embracing a philosophy of multi-variant inputs and the potential leapfrog impact of technologies such as artificial intelligence that result in shortening the reporting-to-action continuum, assisting in the decreasing the overall costs and inefficiency of the Kingdom's healthcare system.

There was general agreement that a key way to enhance both the quality of medicines and health outcomes is to continuously upgrade existing registration guidelines, and design and implement collaborative programs to enhance communications between regulatory agencies and physicians, hospitals, pharmacists, and patients to drive more timely post-marketing reports of both adverse events and substandard pharmaceutical outcomes.

Presentations and discussions ranged over many topics but focused specifically on a few key points:

- There is an urgent need to focus on the process of drug manufacturing and the required multiple quality checks required to be in place
- When patients have access to more effective medications, their overall health improves, even as their overall medical expenses go down. That, in turn, reduces national health-care spending and boosts the economy. Value must be measured in patient outcomes.
- Healthcare innovation saves lives, saves money, promotes economic growth, and provides hope.
- If we do not support the development of new medicines through strident quality specifications, timely licensing and fair pricing based on acceptable pricing system, innovation will be stopped in its tracks – and that is not an acceptable public health outcome.
- Regulators can be partners in innovation three ways: Through robust oversight, through active collaboration, and, most importantly, by being an innovation enabler.

The conference adopted the following recommendations:

- National regulatory bodies in Saudi Arabia such as the SFAD should conduct its own bioequivalence studies rather than relying on those provided by other generic and biosimilar drug manufacturers.
- Bioequivalence information should be provided in the generic and biosimilar drug leaflets.
- Frequent and risk-based bioequivalence studies to assess the quality of marketed either generic or brand medications is important and needs future regulations to assure the quality of post-marketed medications.
- National regulatory bodies should work with industry, academia and other stakeholders to develop better regulations and increase the transparency of manufacturing quality standards.
- The value of pharmaceutical regulations to the Saudi public and health care providers is still not sufficiently enforced through public media campaigns and scientific conferences.
- There is a lack of national standards regarding therapeutic switching of generic and biosimilar medicines in the Kingdome of Saudi Arabia (KSA).
- Current rules or regulations by the National regulatory bodies need to ensure the integrity of the generic and biosimilar drugs supply chain in KSA similarly to innovative medicines.
- Patients should be provided with information written in layman's terms about the bioequivalence of generic drugs so that they can be more informed healthcare consumers.
- There should be greater cooperation between the different entities of the KSA Ministry of health as well as between the Ministry of Health and regulatory agencies to create educational outreach programs aimed at the public and the health care providers alike to educate them about pharmaceutical quality issues and how they can affect quality of care.
- Both regulatory agencies and the Ministry of Health should work together on more comprehensive and transparent regulations that govern therapeutic switching between brands, generics and biosimilars for each health condition.
- Medication leaflets have not taken into consideration the limited health literacy level of most patients in KSA. Therefore, an interdisciplinary committee of health professionals and researchers should be formed to review medication leaflets before they are released to the public.
- The Saudi generic drugs approval process should be reformed to take into more careful consideration the issue of quality.
- A clear and transparent mechanism for patients and health care providers to report quality issues of generic and biosimilar medicines (when switching from one to another) should be established.
- There is a need for a national health outcomes research center to conduct observational studies about the quality of medications in general and generic and biosimilar drugs in particular.
- A Saudi fast-track approval process for new medications should be established.

5. Conclusion

Working together to raise the quality of medicines in Saudi Arabia and will create a sound foundations to address a multitude of regulatory dilemmas such accelerated approval pathways, the manufacturing of biosimilars, the control of API and excipient quality, more robust pharmacovigilance reporting, and a more aggressive battle against counterfeiting. These and other efforts will require more and more creative educational programs for physicians, pharmacists, hospitals, and patients, and, most importantly evolving regulations on quality standards and oversight by Saudi health authorities.

Disclosure

The workshop was supported unconditionally by Novartis Saudi Arabia. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Acknowledgment

We would like to acknowledge the Deanship of Research Chairs, King Saud University, Riyadh, Saudi Arabia.

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