Stability	Distribution Control Management	Performance Management	Supplier Chain Partner Management	Qualification/ Validation	Continuous Improvement	Import/ Export Compliance
Storage Temperature	Qualification and Training of Personnel	Performance Measurement and Reporting	Partner Selection	Ambient Temperature Profiles	Industry Trends	Customs Release
Shipping Temperatures	Premises and Equipment	Self Inspections	Quality Audit	Passive Shipping Systems	Regulatory Trends	Documentation Control
Stability Testing to Support Distribution	Material Handling	Management Review Meetings	Quality Agreements	Active Shipping	Requalification	Product Tracking
	Storage and Inventory Control		Business Review Meetings	Facility Qualification		
	Transportation			Warehouse Management System Validation		
	Product Disposition and Distribution			Distribution Validation Master Plans		
	Product Protection					
	Returns Management					
	Exception Management					

Literature Review: DISTRIBUTION SYSTEM OF PHARMACEUTICAL PRODUCTS IN SAUDI ARABIA

Submitted By

Submitted To

Subject

Date

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I. INTRODUCTION

The Kingdom of Saudi Arabia has been acknowledged in the international setting for their efforts to adopt to the globally implemented standards on pharmaceutical drug distribution systems. Saudi Arabia has notably excelled in their strict regulation and standards of temperature handling of pharmaceutical products all throughout its distribution chain. The following review of literatures has gathered several studies, and has reviewed relevant policies in pursuit of examining: (1) the Saudi Arabian pharmaceutical sector and their distribution standards; (2) the Saudi Arabian distribution model in line with globally recommended standards; and (3) the monitoring and regulation of storage systems within their Saudi Arabian pharmaceutical sector.

II. SAUDI ARABIAN PHARMACEUTICALS & DISTRIBUTION STANDARDS

The pharmaceutical product distribution standards implemented in the Kingdom of Saudi Arabia follows the WHO prescribed practices that are also being implemented in more than 35 countries. In the following discussions, this paper covers (a) a brief overview of the pharmaceutical sector of Saudi Arabia focusing on sectorial, financial,

workforce and infrastructure, and policy domains, (b) Good Distribution Practice, and (c) Good Storage Practice.

a. The Saudi Arabian Pharmaceuticals Sector

Overview of the Sector

The Kingdom of Saudi Arabia operates one of the largest pharmaceutical markets in the Middle East. According to the 2013 report of the *Gulf Cooperation Council* (GCC), out of the US$ 8.5 billion market size of the Middle East, Saudi Arabia accounted to 59.4% (i.e. equivalent to US$ 5.1 billion as of 2012) of the Gulf's overall pharmaceutical industry size with the UAE as the second largest at 18.3%; although, compared to global standards, the pharmaceutical sector in the member countries of GCC can still be described as an emerging industry due to several limitations, such as the need for focus on developing indigenous production, shortage of skilled manpower, and limited funding on related research and development (GCC, 2013). Formerly, the Ministry of Health (MOH) handled the pharmaceutical regulatory processes in Saudi Arabia; however, in July 2009, the authority was transferred to the Saudi Food and Drug Authority (SFDA) (est. March 2003) including the authority to license and distribute pharmaceutical products, to establish manufacturing facilities (Winfield, et al., 2009).

Overview of Sector Finances

According to the report of the SFDA in collaboration with the World Health Organisation (WHO) (2012), the total annual health expenditure of the country in 2009 reached US$ 19.3 billion with a per capita expense of US$714. In the total population of more than 27 million, 69% is covered by the public health service, public health

insurance, or social insurance, while approximately 31% is under private health coverage (SFDA, 2012). Of the total health expenditure, the Kingdom of Saudi Arabia spends more or less 18% on pharmaceutical-related expenses (SFDA, 2012). Considering the market size covered by Saudi Arabian pharmaceutical sector, approximately 35% of its purchase are conducted by the government that enables the thriving of the market through provisions of free medical and healthcare services (GCC, 2013). The greater share of these expenses are driven not only by the demand, but mainly by the larger procurement for imported pharmaceutical products, and fair share in size of local manufacturing (GCC, 2013). Meanwhile, 51.9% of total pharmaceutical expenses stems from private health expenditure (The World Bank, 2009). Due to the market size embedded in the sector based on the financial angle. GCC (2013) in collaboration with the WHO has placed stricter measures towards the implementation of their GMP, GDP, and GSP in order to prevent the recoil of costs, especially considering the size of importation activities on-going in the pharmaceutical sector (WHO, 2003).

Consequences of Maldistribution

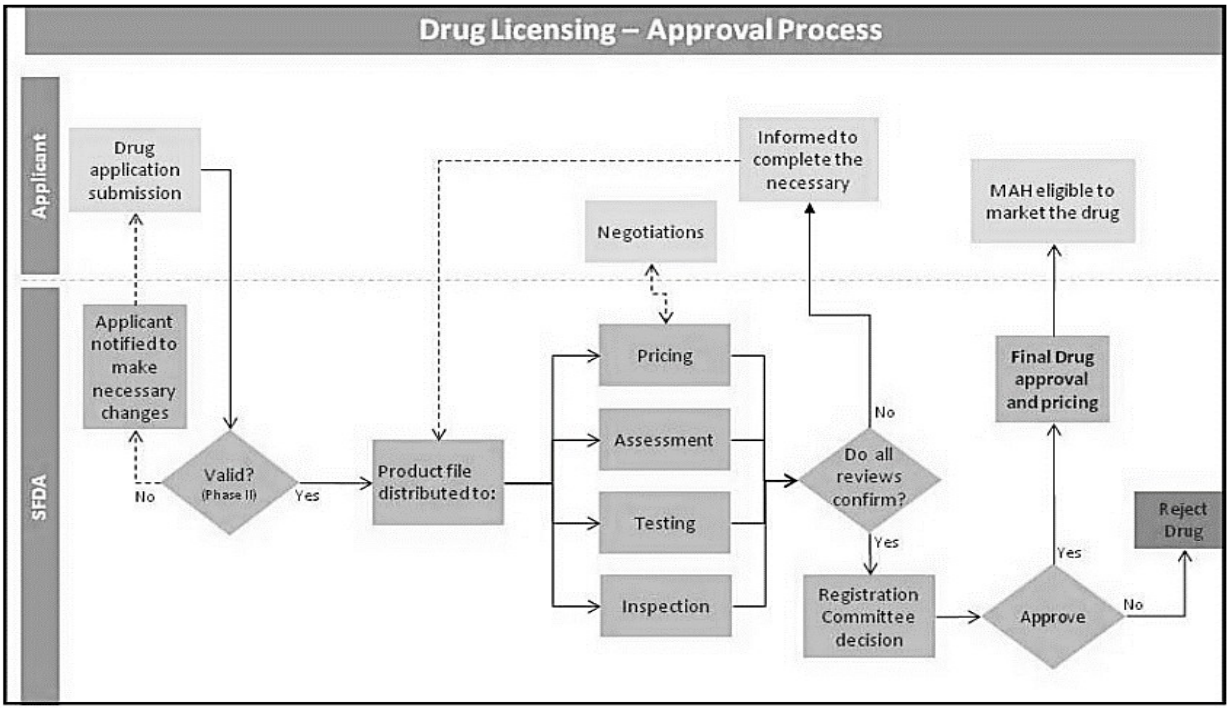
Distribution of drug plays a key element in securing drug safe consumption for its end users. Due to the demand characteristics of Saudi Arabian pharmaceutical sector wherein the highly patronised are the imported products, the consequences to maldistribution become the critical concern of the regulatory body. According to MOH (2010), licensed pharmacists from both private and public sectors sums to 14,928, and from this number, only 3,537 can serves the public sector. Both the regulatory and professional bodies are in their initial phases of handling the market size of the Saudi Arabian pharmaceutical sector. Accordingly, this accounts to 5.5 licensed pharmacists

per 10,000 population, while 1.3 per 10,000 population in the public sector (MOH, 2010). In terms of infrastructure, Saudi Arabia operates more than 6,000 licensed pharmacies as of 2010 (MOH, 2010). Considering the inadequate front-line quality control of the professional body in the retail end-point, this condition places the end-chain in potential consequences of maldistribution: (1) temperature surges outside the recommended drug profile leading to compromised drug quality; (2) decrease in the potent life span of drugs possibly impacting the product cost, supply chain, and end-user welfare; (3) weak points in the distribution processes can allow illegally imported, stolen, and substandard medicines to enter the supply chain; and (4) health-related side-effects may arise due to compromised drug quality (Bishara, 2006; Tantash, 2012). Unfortunately, as of 2012, SFDA announced that the government still does not have a specific strategic plan for pharmaceutical human resource development (SFDA, 2012); although, SFDA has focused its attention on supply chain infrastructure in pursuit of preventing these consequences.

Quality Assurance in Distribution & Policy Framework

Focusing on the infrastructure development, SFDA ensures the quality of pharmaceutical product distribution by adopting global standards into its supply chain. The *National Health Policy* (NHP) was updated in 2010 to enforce the coverage of the *National Medicines Policy* (NMP) prescribed by the WHO. According to WHO (2003), the NMP involves the national commitment to a goal and a guide for action in pursuit of promoting the equity and sustainability of both public and private pharmaceutical sectors. NMP resulted in the promotion of medicine accessibility and ease of distribution (Cameron, et al., 2009), as well as in enforcing safe and effective storage standards

(Hassalia, et al., 2013). According to SFDA (2012), Saudi Arabia's NMP covers the selection of essential medicines, medicine financing, pricing, procurement, distribution and regulation, drug safety policies (i.e. pharmacovigilance), institution of the rational use of medicines, and human resource development in the health sector. SFDA policy framework on drug licensing and approval holds significant impact as to whether or not a pharmaceutical product can be distributed within the supply chain (see Fig. 1). In pursuit of securing the distribution process, SFDA proceeds in the regulation of the distribution processes monitoring whether the policies concerning trade and distributions are being complied, and whether drug companies are being consistent with



their approved presented metrics and performance presented during licensing and approval (Al-Saggabi, 2009). Additionally, SFDA examines the drug application along with the requirements ensuring whether the product corresponded with the specifications of the *Good Manufacturing Practice* (GMP) guidelines (Issa, et al., 2009). Once approved, SFDA secures the distribution process following two fundamentally established standards: (1) Good Distribution Practice; and (2) Good Storage Practice‘

b. Good Distribution Practice’

WHO (2010) has issued a global standards on ‘Good Distribution Practice’ (GDP) for pharmaceutical products that constitutes six general principles: (1) all parties

involved in the distribution of supply chain is responsible for ensuring the quality of products, and for maintaining the integrity of distribution process from the manufacturing site to the entity responsible for dispensing and providing of products to patients or relevant agents; (2) the principles of GDP should be incorporated in the national legislation and guidelines for the pharmaceutical distribution processes with at least establishing the minimum standards; (3) the principles of GDP shall apply to forward and backward distribution chains (e.g. product recalls); (4) principles of GDP should be complied even in the case of products donation; (5) all entities involved in the distribution process must diligently comply to the principles of GDP; and (6) there should be collaboration between all parties including the governments, customs agencies, law enforcement agencies, regulatory authorities, manufacturers, distributors, and entities responsible for the supply chain.

While the standards of GDP apply to more than 35 countries, Saudi Arabia impose its added distribution standards (i.e. temperature-controlled transport) apart from the general regulates stipulated under WHO and FDA/EU GDP (Kauer, 2013). GDP regulations implemented by SFDA covers from (a) importation, particularly in port handling and customs clearance, (b) storage building policies (e.g. Environmental Control of Ancillary Areas, power supply, loading and receiving bays, Goods Assemble and Quarantine Areas), (c) temperature-controlled storage, (d) materials handling, (e) transport and delivery, (f) labelling, (g) stock management, and (h) general record-keeping, and temperature and humidity records monitoring (SFDA, 2013).

c. Good Storage Practice

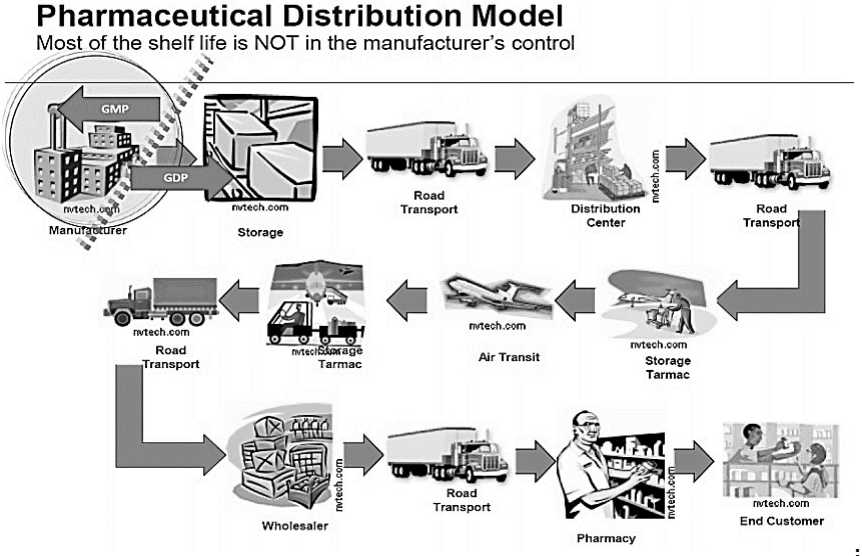
WHO (2003) specified generally applicable ‘Good Storage Practice’ (GSP) principles covering (a) the personnel management and pre-requisites for posts at storage premises and facilities, (b) storage policies on premises and facilities, (c) storage condition criteria (e.g. labelling criteria and stability testing criteria), and (d) monitoring storage condition proceedings and requirements (e.g. records-keeping, labelling, receipt provisions, stock rotation and control, returned goods management, dispatch and transport, and product recall). Meanwhile, in SFDA, greater focus has been given in the (1) storage buildings, (2) temperature-controlled storage, (3) labelling, and (4) stock management proceedings (SFDA, 2013). A key highlight of Saudi Arabian storage practice is the highly incorporated temperature controlled storage from point source until retail stocking of pharmaceutical products (Khojah, et al., 2013).

III. THE SAUDI ARABIAN GDP MODEL: EXAMINING THE DISTRIBUTION

Having examined the different areas of Saudi pharmaceutical sector, this section covers the (a) distribution model followed within the sector, and (b) the GMP-GDP applications of Saudi Arabia in these distribution processes.

a. The Distribution Model

Saudi Arabia hosts the largest manufacturing segment in the Gulf with approximately 15 to 20 pharmaceutical manufacturers operating, and with domestic production accounting to 15% of the national pharmaceutical supply (GCC, 2013). GDP



implementation in Saudi Arabia follows the WHO-prescribed model also followed by 35 different countries including the United States, the United Kingdom, Canada, Argentina, Brazil, Denmark, European Union, China, Australia, and India (Kauer, 2013). The distribution model follows the philosophy of the combined GMP and GDP implementation – '*from point source to recipient*' (Al-Essa, et al., 2012). According to GCC, a vast majority of pharmaceutical manufacturing plants can be located in Saudi Arabia, such as the operations under the Saudi Arabia-based *Saudi Pharmaceutical Industries and Medical Appliances Corporation* (SPIMACO), Banaja Holdings and Tamer Group, Jamjoom Pharma, Tabuk Pharmaceutical Manufacturing, and Jazeera Pharmaceutical industries (GCC, 2013). Through the drug licensing and approval mechanisms, SFDA is able to secure readiness of pharmaceutical products before being incorporated within the supply chain (Al-Essa, et al., 2012). As illustrated in figure 2, the distribution model processes include: (a) starts from warehouse storage of manufactured products; (b) transport of goods to distribution centres; (c) transport to airfreights; (d) transport to wholesalers; and (e) transport to pharmacy until end customer consumption. However,

given the distribution model, SFDA adds stricter policies on distribution, handling, and transportation criteria within their supply chain.

b. Inspection and Regulation of GMP-GDP Execution

SFDA distribution system covers two primary key areas: (1) importation, (2) material handling, and (3) transport and delivery. Distribution policies on import management is one of the key focal points of SFDA distribution model as its pharmaceutical sector mainly relies on importation activities. Given the size of the Saudi Arabian pharmaceutical sector, the size of its imported drugs is significantly higher than its exportation activity (i.e. respectively, US$ 3,352.9 million versus $235.2 million as of 2010) (GCC, 2013). Thus, importation GDP regulations of SFDA cover: (a) port handling, and (b) customs clearance. First, SFDA secures that the 'Port of Entry' of imported pharmaceutical products is equipped with temperature-controlled storage environments and material handling mechanisms to comply with the necessary level of protection and minimise the risk of product damage. Second, SFDA secures immediate offloading and transport of products to prescribed and approved storage locations upon arrival of shipment. Third, pharmaceutical product shipments are cleared through pre-clearance procedure carried out by SFDA via clearing agent or freight forwarder in collaboration with customs to ensure rapid clearance and to prevent temperature excursions risking the shipment quality (SFDA, 2012; Al Khouri, 2000).

c. The GDP Checklist

Having examined the policy frameworks of GDP and its relationship with the execution of GMP and GSP, SFDA intersects the executions of these frameworks using

a GDP Checklist that covers: (1) General questions regarding the QMS; (2) Personnel; (3) Premises and equipment; (4) Documentation; (5) Outsourced and activities; (6) incoming goods; (7) warehousing; (8) picking; (9) dispatch; (10) transportation; and (11) complaints, returned products and recalls (Dietz, 2013). The checklist is designed to support the preparation and execution of GDP covering the product life cycle stages from manufacturing to delivery to end-users. Accordingly, the life cycle phase of a finished pharmaceutical product is characterised by storage and transportation activities collectively referred to as 'Good Distribution Practices' (Dietz, 2013). The checklist elements guide the inspection of GDP compliance in pursuit of securing the correct and efficient execution of GDP framework. The policy elements of the checklist are explained further in the following sections.

d. Ideal Model of Inspectors Carrying Out GDP

The inspection model utilised in the execution of GDP compromises seven areas: (1) stability; (2) distribution control management; (3) performance management; (4) supplier chain partner management; (5) qualification validation; (6) continuous improvement; and lastly, (7) import/export compliance (SFDA, 2012; WHO, 2010; WHO, 2003). These components can be referred to as the pillars of inspecting GDP execution (see Fig. 3). First, stability pertains to the inspection of storage temperature, shipping temperature, and stability testing to support the distribution. Second, inspectors proceed in determining distribution control management components, particularly the qualification and training of personnel, premises and equipment, material handling, storage and inventory control, transportation; product disposition and distribution, product protection, returns management, and exception management. Next, the

inspectors proceed for inspecting the performance management elements, particularly

Stability	Distribution Control Management	Performance Management	Supplier Chain Partner Management	Qualification/ Validation	Continuous Improvement	Import/ Export Compliance
Storage Temperature Shipping Temperatures Stability Testing to Support Distribution	Qualification and Training of Personnel Premises and Equipment Material Handling Storage and Inventory Control Transportation Product Disposition and Distribution Product Protection Returns Management Exception Management	Performance Measurement and Reporting Self Inspections Management Review Meetings	Partner Selection Quality Audit Quality Agreements Business Review Meetings	Ambient Temperature Profiles Passive Shipping Systems Active Shipping Facility Qualification Warehouse Management System Validation Distribution Validation Master Plans	Industry Trends Regulatory Trends Requalification	Customs Release Documentation Control Product Tracking

the performance measurement and reporting guidelines, self-inspections and tools used by the company, and the management review meetings held. Supplier chain partner management is also inspected in order for the regulating body to determine the partner selection procedures employed by the drug company, quality audit guidelines employed, quality agreements made, and relevant business review meetings.

The last three steps in inspecting GDP are the most crucial pointers as these determine the compliance degree of the manufacturing and distributing entity. The inspector proceeds in examining compliance in the following areas: qualification and validation of ambient temperature profiles, passive and active shipping systems, facility qualification, warehouse management and system validation, and distribution validation master plans. Next, the inspector determines presence of continuous improvement employed by the company based on industry trend innovations, regulatory trends, and requalification. Lastly, the inspector examines the company's import and export compliance via customs release, documentation control, and product tracking (WHO, 2003; WHO, 2010).

e. GDP Policy Being Inspected

Current policies of SFDA were consequent to the growing importation requirements of pharmaceutical market, the expanded role of the government in the supply chain of pharmaceutical products (e.g. medical reimbursements, and procurement), expanding retail distributorship activities, and growing patronisation of the consumer markets for products of patented drug manufacturers (i.e. importation activities) (Alsultan, 2011). According to GCC (2013): (1) the Government established the *National Unified Procurement Company* for Medical Supplies in 2007 to host as the

national exclusive supplier of medicines and medical appliances to government institutions in the aim of eliminating procurement inefficiencies and reducing prices (Alkhenizan, 2014); (2) Retail distribution accounts a significant share as it is comprised with close to 4,000 pharmacies that enables 88% of the total market in Saudi Arabia (Alsultan, 2011); and (3) most of local manufacturing concentrates on export markets for multinational branded drugs (e.g. GlaxoSmithKline, Daiichi Sankyo Co., and Astellas Pharma), and only less than 20% of pharmaceutical manufacturing are attributed to generic drug production (i.e. patented drug distribution dominates the Gulf's pharmaceutical market compared to generics handled by domestic manufacturers with only 5%-6% market share (Tantash, 2012)).

For these reasons, SFDA has enforced their standards and policies on products manufacturing (GMP), and handling and distribution (GDP) to govern mainly the importation activities, foreign manufacturers, and encourage quality over locally produced generic brands in terms of quality guarantees (Tantash, 2012; Alkhenizan, 2014). Thus, material handling, and transport and delivery policies employed in the distribution process employ high degree of GDP adaptations. SFDA Transport and Delivery (2013) policies of pharmaceutical products constitute: (a) product stability profiling; (b) transport route profiling and qualification; (c) calibration and verification of transport monitoring devices; (d) shipping container standards and packing; (e) products handling during packing and transport, (f) cleaning road vehicles and transport containers, and (g) transport of returned and recalled products.

Product Stability Profiling: Stability testing is the medium used for determining the expiration date and optimum storage conditions for pharmaceutical products in time

under the influence of a variety of environmental factors, particularly temperature, humidity, and light (Khoja, 2011). During this stage, transport and deliver storage features are checked according to the indicated stability profiles of each pharmaceutical product batch in order to prevent product degradation brought by poor storage conditions. Each batch is sorted and loaded only to transport vehicles that meet the stability standards indicated in each drug stability profile (SFDA, 2012).

Transport Route Profiling & Qualification: Aside from vehicle conditions, transport route profile is also done to ensure that pharmaceutical products can be safely transported within the transport temperature profile indicated for each product. Route qualification criteria include: (a) selection of route based on the permissible range of potential ambient temperature and humidity conditions throughout the year; and (b) using of recommended methods (e.g. weather data, laboratory and field tests) to determine the minimal variations of environmental risk factors encountered within route options (Al-Essa, et al., 2012; Khoja, 2011).

Calibration & Verification of Transport Monitoring Devices: GDP of WHO (2010) mandated the need for calibration of equipment used for monitoring of storage conditions at defined intervals. Thus, SFDA strictly imposes the need to calibrate transport temperature control devices, monitoring devices, humidity monitoring devices, and transport alarm equipment against a certified and traceable reference standard at least once a year to ensure the delivery of products within the transport temperature profiled indicated for each product (SFDA, 2013).

Products Handling During Packing and Transport: SFDA mandates the following policies when handling of pharmaceutical products during packing and transport: (a)

take precautionary measures against spillage or breakage, contamination, and cross-contamination; (b) determine the products to recipients with the most suitable modes of transportation available that can minimise delivery time; and (c) ensure that recipients receiving the products are well-instructed on the correct storage of the product prior to use (Kauer, 2013; WHO, 2003). Additionally, the selected the modes of products handling during packing and transport must secure the integrity of stability and packaging, and prevent any more of contamination (SFDA, 2013; Khojah, et al., 2013).

Cleaning Road Vehicles and Transport Containers: SFDA (2013) mandates regularly scheduled cleaning and decontamination programme for all road vehicles and reusable shipping containers used in the distribution process of pharmaceutical products. All entities participating in the transport must comply with the following policies: (a) internal surfaces of load compartments must be cleaned on scheduled intervals and after use; (b) prevent any means that may result to the accumulation of contaminants (e.g. dust, dirt, waste) in the load compartments, and in reusable shipping containers; (c) prevent any means that may result to accumulation of frost and ice especially in cold environments (e.g. refrigerated vehicles); and (d) frequently collect waste in assigned closed containers and organise for safe disposal (Al Khouri, 2000; WHO, 2003; Shafaat, et al., 2013).

Transport of Returned and Recalled Products: In the case of transporting returned and/or recalled pharmaceutical products, SFDA also implements a backward application of GDP. As per mandates, SFDA (2013) imposes the following for the transport of returned products: (a) sender and recipient must collaborate in securing that the products being returned are still within indicated temperature range during transport;

(b) ambient temperature profile must be accounted over the duration of transport; and (c) secure the quarantine of pending returned products in temperature-controlled storage. On the other hand, for product recalls, SFDA (2013) imposes the need to: (a) secure proper and legible indication of products for disposal as either 'recalled' or 'withdrawn'; and (b) transport back from the recipient all products for recall, and ensure quarantine of recalled products under secure conditions, especially when in pending final decision for disposal (Khojah, et al., 2013).

IV. ISSUES ARISING WITH DISTRIBUTION SYSTEM: STABILITY, CALIBRATION & TEMPERATURE CONTROL

The following section examines the monitoring protocols, regulations, and inspection routines concerning temperature and storage systems. The following discussion covers (a) the cold chain implementation in Saudi Arabia, and (b) their practices for inspection and regulation of temperature systems in line with GDP and GSP.

a. The Cold Chain Implementation in Saudi Arabia

In January 2013, the Saudi Arabian health minister announced the intent to include plans on improving healthcare services and meeting the health requirements of the citizens within the health budget of SAR 54.4 billion for 2013 (GCC, 2013). Temperature monitoring is one of the key highlighting features of Saudi Arabia's own adaptation of GDP, and has been one of the many most improved areas in the Saudi health care infrastructure and facilities. The SFDA highly acknowledges the risks introduced by environmental factors, particularly temperature along with humidity and

light, into pharmaceutical product quality chain (Al-Essa, et al., 2012; GCC, 2013). Saudi Arabian pharmaceutical market relies heavily on importation in order to replenish their supply chain that suggests the importance of securing temperature integrity during transit (Alsultan, 2011). Additionally, pharmaceutical consumers have always preferred patented products (i.e. obtained mostly from foreign suppliers) than domestically produced generic rendering the need for strict guidelines in securing the safety and quality security of pharmaceutical products during transport and delivery (SFDA, 2012). WHO has recognised and incorporated the temperature management in the supply chain, which the agency referred to as the '*Pharmaceutical Cold Chain*' (WHO, 2010). Cold chain refers to the system of transporting and storing pharmaceutical products following the prescribed temperature between 2 degrees Celsius and 8 degrees Celsius as per the MOH and the WHO (WHO, 2010). Currently regulatory trends focused upon by WHO in the GDP-cold chain implementation included the: (a) appointment of the responsibility for cold chain management into the manufacturers; (b) increase of oversight, management, and control of environmental conditions in the entire supply chain (i.e. from manufacturer to consumer), especially in temperature sensitive drugs; (c) increased importance of temperature control and monitoring in mitigating and identifying risks during cold chain transport; and (d) patient safety related to product quality during transportation and storage as a heightened prioritisation (Bishara, 2006).

Cold chain implementation (i.e. related to temperature and stability requirements) varies depending on the stability profile of the products being transported (Bishara, 2006). For instance in vaccine management, cold chain begins: (a) first in the construction of prescribed refrigerator or freezer in the vaccine manufacturing plant to

allow storage suited for maintaining appropriate temperature control; (b) second, the vaccines along with the appliance is mediated from the vaccine distributor to the provider's premises (e.g. immunisation clinic); and finally, (c) vaccine administration with respect to consistent temperature monitoring takes place (Mugharbel & Al Wakeel, 2009). Additionally, selected storage container must also comply with the standards of GDP and GSP. In Saudi Arabia, a *vaccine vial monitor* (VVM) is used to aid health workers in determining whether a vaccine has been damaged by heat, or has lost its potency and efficacy due to temperature variation (Mugharbel & Al Wakeel, 2009). However, in light of the growing international and national recognition on the importance of cold chain, there is still a big compliance gap between the governmental health institutions and privatised hospitals. Mugharbel & Al Wakeel (2009) conducted a cross-sectional study using stratified random sampling technique from a sample size comprised of 10 governmental primary health care centres or governmental health facilities (GHF) out of the 20 centres present and operating within Dammam area, and five out of 17 *private health clinics* (PHC) also within the area scope. The latter authors were able to determine interesting findings: (a) while 100% maintained proper vaccine temperature in all GHF clinics, only less than 20% of PHC were able to comply to MOH and WHO criteria on vaccine temperature storage; (b) knowledge of vaccine management in terms of temperature highly differs between GHF with 100% of staff assessed were knowledgeable, while only 20 to 40% of PHC were knowledgeable ($p \leq 0.05$); and lastly, (c) vaccine vials present on the refrigerator shelves at the time of assessment were appropriate for 100% of GHF, while 40% only for PHC (Mugharbel & Al Wakeel, 2009).

b. Inspection and Regulation of Temperature Systems

Temperature monitoring guidelines enforced, implemented, and regulated by SFDA starts from GMP to GDP execution even covering importation procedures (e.g. temperature configuration in temporary storage at '*port of entry*' facilities), storage building standards, materials handling, vehicle and route selections, and shipping container selections (SFDA, 2013). Temperature monitoring and regulation of related standards have been recognised as the primary concerns in the GDP-GSP executions of SFDA within their distribution system of pharmaceutical products. The following the policies inspected by the SFDA inspectors focusing on temperature-related management issues and concerns:

Temperature Storage at Port of Entry: Importation requires the offloading of pharmaceutical shipments from the wharf or airport to safe and suitable temperature-controlled designated storage areas. During drug licensing and approval, SFDA (2013) regulates the temperature control protocols followed by the manufacturer to ensure that products delivered from port of entry are free from environmental contamination before it can be transferred to designated local storage facilities (Bishara, 2006). Additionally, the port of entry carriers and transport vehicles follow GDP protocols by securing appropriate temperature-controlled environments when transporting products from wharf/airport to designated storage facilities (Kauer, 2013).

Storage Building Inspection and GSP Accreditation: In line with GSP execution, storage building construction or procurement requirements imposed by SFDA focus on ensuring the presence of appropriate materials and technologies in housing the storage requirements of pharmaceutical products. Thus, SFDA (2013) requires that: (a) storage

buildings are purposely designed or well-adapted in storing of pharmaceutical products; (b) the buildings are designed to suit the prevailing climate taking the efficient use of passive heating, cooling, and ventilation into considerations; (c) the buildings are designed and equipped to allow minimum utility consumptions (e.g. fuel and electricity usage); (d) materials used for building construction are easy to maintain, and convenient for long-term use; and (e) the building is designed to minimise hiding and nesting areas for pests. Aside from construction standards, SFDA also regulates: (1) *accommodation and layout* – SFDA inspects and ensures the layout allotment for storage areas, goods assembly, receiving and dispatch bays, and office area (GCC, 2013); (2) *loading and receiving bays* – SFDA inspects the layout provisions for loading and receiving bays taking into consideration receiving-dispatch traffic, protection of goods from direct contaminant exposure (e.g. most especially the sunlight and other potential sources of temperature extremes) (Shafaat, et al., 2013; Bishara, 2006); and (3) *power supply* – SFDA inspects power networks to secure (3.1) the capacity of the facility to manage combined start-up load for all connected temperature-controlling and temperature-monitoring appliance, (3.2) a recommended allowance to main power supply consumption, (3.3) availability of automatic main failure start-up and automatic shutdown during power restoration, (3.4) adequate fuel tank capacity for prolonged power outage, and (3.5.) regular intervals of UPS and generator testing with complied records keeping proceedings (SFDA, 2013; Mugharbel & Al Wakeel, 2009; Khoja, 2011).

Critical Temperature-Controlled Areas: Another building requirements inspected and regulated by SFDA include (a) the standards for goods assembly and quarantine

areas, and (b) the environmental control of ancillary areas. In terms of goods assembly, SFDA ensures that the storage buildings would allow sufficient space to receive, assemble and pack pharmaceutical products relevant to the expected load per dispatch (Kauer, 2013). Additionally, assembly areas must be under temperature-controlled condition with temperature criteria of below 25 degrees Celsius for the assembly of products with no less than two hours in temperature requirement of 2-8 degrees Celsius (SFDA, 2013). In an ideal setting, SFDA recommends that the assembly area should be close to the 2-8 degrees Celsius normally mandated for temperature-controlled storage area (Bishara, 2006). Meanwhile, quarantine area provides a designated space for the isolation of returned, recalled, and/or withdrawn stocks under pending decision of disposal or re-stocking (Bishara, 2006). For the quarantine area requirements, SFDA inspects if the materials present in the quarantine areas are clearly identified with their corresponding temperature control status for items returned for re-stocking, recalled for testing, and awaiting for disposal (SFDA, 2013). On the other hand, SFDA also maintains strict regulation of environmental control of ancillary areas where pharmaceutical products are temporarily held during arrival, assembly, or dispatch (WHO, 2010). In these ancillary areas, SFDA inspects if: (a) the ancillary areas are able to maintain required temperature range, and humidity range specified according to stability profile of products being handled; (b) the ancillary areas are protected from undue exposure of direct sunlight and extreme weather conditions, and other potential contaminants (e.g. dust, dirt, and waste accumulation); (c) the ancillary areas are adequately ventilated, lit to enable sound operations, and controlled and monitored with

adequate records keeping instrumentations during actual operations (SFDA, 2013; Khoja, 2011).

Requirements for Temperature-Controlled Storage & Vehicles: Temperature-controlled storage constitutes temperature-controlled rooms, cold rooms, freezer rooms, refrigerators, and freezers that should all be compliance to the following SFDA requirements: (1) SFDA requires that all temperature-controlled rooms, cold rooms, and freezer rooms should be – (1.1) capable of sustaining the recommended temperature range indicated by the system set points over the full annual ambient temperature range experienced at the storage location; (1.2) equipped with *auto-defrost mechanism* with minimal effect on temperature during defrost cycle, and *low temperature protection circuit* in cold climates confronted by risks of breaching low temperature set points (i.e. applicable for products that are damaged by exposure to temperature lower than their minimum stability temperature requirement); (1.3) connected to a UPS or alternative power supply in case of power outage; (1.4) able to provide separate controlled storage rooms for controlled and hazardous products; and (1.5) equipped with calibrated continuous temperature monitoring system with sensors capable of monitoring and alerting for temperature extremes, continuous humidity monitoring devices capable of detecting humidity extremes, and alarms for notifying temperature excursions, and/or refrigeration failure (SFDA, 2013; WHO, 2003; Khoja, 2011); (2) SFDA also requires that all refrigerators and freezers should be – (2.1) equipped with calibrated temperature monitoring devices relevant to the level of risk presented by drug stability profile; (2.2) capable maintaining recommended temperature range; and (2.3) fitted with appropriate access control system (SFDA, 2013; WHO, 2003); and (3) SFDA also regulates and

inspects compliance for temperature-controlled transport requirements – (3.1) inspects the compliance of air transport to *service level agreement* (SLA) particularly in maintaining load temperatures within transport temperature profile for each product; and (3.2) temperature-controlled vehicles must be able to comply with temperature range compliance, presence of required installed devices (e.g. low temperature protection circuit, and humidity monitoring system accurate to ± 0.5 °C for temperature and ± 5% RH for humidity), capable of temperature recording system with minimum recording frequency of six times per hour for each sensor position (SFDA, 2013; WHO, 2010).

Shipping Container Standards and Packing: SFDA specified their policies on selection of shipping containers: (1) selected shipping containers must comply with the national and international standards with respect to the product type, selected transport route, and mode of transportation; (2) selected shipping containers must ensure that all personnel and the general public are protected from hazards potentially resulting from spillage, leakage or excessive internal pressure; (3) shipping containers used must be able to protect the product against potential mechanical damage and influence of ambient temperature that will be encountered during transportation and delivery; and (4) containers used must be closed in a manner suggestive of tampering proof (SFDA, 2013; Al-Essa, et al., 2012; Al Khouri, 2000; Shafaat, et al., 2013).

Meanwhile specific policies are mandated when using uninsulated and insulated passive containers, as well as active containers. When using uninsulated containers and active containers, SFDA advises to: (a) transport uninsulated containers in a qualified temperature-controlled environment (e.g. actively or passively temperature-controlled vehicular environment); and (b) secure the capability of the transport system

in maintaining the temperature of the product within the indicated storage conditions (Khojah, et al., 2013). On the other hand, when using insulated passive containers including any and all necessary ancillary packaging (e.g. bubble wrap, dry ice, phase changing materials), insulated passive containers must: (a) ensure that the packaging system used complies with the container qualification standards (e.g. inclusion of full details of packaging assembly, thermal conditioning regime, indication of minimum and maximum shipping volume, correct placement of temperature monitors, and features safe weight and thermal mass accommodation (Shafaat, et al., 2013; SFDA, 2013).

c. Examining the Weaknesses of GDP Checklist

Having examined the elements of GDP, it is evident that GDP has focused significantly in the areas concerning personnel, premises and equipment, documentation, condition criteria of incoming goods, warehousing policies and standards, picking, dispatch, transportation, and the handling of returned products and recalls. However, as per the SFDA execution of the GDP framework, their inspection policies have: (a) distinct lack of strict monitoring activities in relation to their outsourcing activities other than the GMP as GDP pre-requisites (i.e. this can be attributed to the heaving drug importation leaving manufacturers to proceed with their internal outsourcing standards); (b) personnel criteria have not been well absorbed in the SFDA GDP execution, particularly in terms of continuous workforce training and quality of workforce-infrastructure handling; and (c) GDP policies have only focused the distribution inspection on the mid-line processes, such as storage and distribution, despite the ultimate pursuit of ensuring drug quality throughout the life stages of the

finished products (i.e. front-line inspection, such as retail distribution, lacks in the framework).

V. SYNTHESIS OF REVIEW OF LITERATURE

The pharmaceutical sector of the Kingdom of Saudi Arabia has adopted the policies and standards imposed by WHO under GMP, GDP, and GSP; however, the national execution has given stronger emphasis on their temperature regulation and monitoring protocols, which are mainly carried out by the SFDA. Accordingly, the execution of GMP starts during the drug licensing and approval proceedings until the manufacturing of finished pharmaceutical products. From this point onward, GDP-related protocols are regulated and continuously inspected by the SFDA in pursuit of securing the compliance of all related entities from each point of distribution process. From GMP to GDP execution, the SFDA covers the inspection of importation, material handling, and transport and delivery. Meanwhile, in-between GDP and GSP execution, SFDA monitors the compliance for cold chain implementation with emphasis on compliance to temperature controlling protocols and requisites. Lastly, SFDA monitors and regulates temperature systems present in the storage at port of entry, designated storage buildings, critical temperature-controlled areas, temperature controlled storage and vehicles, and shipping container standards and packing.

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