

Emerging Concern of the Impact of Temperature Excursions on the Quality of Medicines Along the Supply Chain in Malaysia

Mathews A*, Dash Gouri Kumar

Faculty of Pharmacy and Health Sciences, Universiti Kuala Lumpur Royal College of Medicine Perak, 30450 Ipoh, Malaysia.

ABSTRACT

The pertinent quality assurance question to be addressed within the pharmaceutical supply chain starting from the finished product in a manufacturing facility to the time a patient receives the medicine, is how much of the potency has been lost due to the effect of temperature excursions. The product may be shipped (by sea, land or air) to various storage distributor facilities within the country. The distributor then may supply directly or indirectly via wholesalers to clinics, pharmacies and hospitals. Most non-cold chain medicines would need a storage temperature of below 25°C but day-time temperatures in Malaysia exceed this temperature throughout the day. Although temperatures in main storage facilities are monitored and documented, concerns arise during shipments in non-air-conditioned metal containers across sea channels which can last weeks and temperatures are expected to soar. The official pharmacopoeias note the need for caution when medicines are exposed to temperature excursions. There is a need for research to be carried out to determine the extent of degradation of medicines along the supply chain.

Key words: Temperature excursions, supply chain, degradation of medicines

INTRODUCTION

The complexity of the pharmaceutical supply chain requires an understanding of the interdependency between the related processes and product characteristics¹. In the Malaysian context, there are foreign multinational companies and local pharmaceutical manufacturers. Multinational companies import their products from overseas via sea and air channels. Cold-chain products needing freezer or refrigerated storage conditions are transported by air in special heat-resistant boxes with specified number of ice-packs arranged in a particular configuration to ensure that the temperature range is maintained throughout the journey which must be completed within a specified time-frame. Non-cold chain products needing storage temperature of below 25°C are imported into the country with not too much emphasis on the temperature requirement along the supply chain and they are transported in non-refrigerated metal containers. These containers may pass through different temperature zones from very cold to very hot climates. The assumption for this is that non-cold chain products have undergone accelerated stability testing and the temperature excursions along the supply chain should not affect the potency of the products. Once in the country, the products are stored in temperature-regulated environment. The emphasis on the need for temperature mapping, back-up power systems, continuous temperature monitoring, communication escalation in times of power failure and documentation may vary from distributor to distributor. The quality standard in multinational distributor's and well established

local manufacturer's storage centers can be considered to be very similar.

Once in Malaysia, the product may be transferred via many different channels before eventually reaching the patient. The product may be transferred to the main distributor which has sub-distributor centers throughout the country bearing in mind that Malaysia comprises of two land masses separated by more than one thousand kilometer of sea necessitating the transportation of pharmaceuticals using sea channels. The product may then be sold to wholesalers. The product is then supplied in non-temperature regulated but air-conditioned vehicles to the pharmacy, clinic, health center and hospital where it may be stored for varying periods before eventually being supplied to the patient. The day-time temperatures are constantly above 32°C throughout the year. The product will be exposed to temperature excursions all along the pharmaceutical supply chain. A major concern of the pharmaceutical industry and health authorities is to ensure that the medicines that are delivered to patients are without loss of therapeutic effectiveness. Selling of substandard and counterfeit drugs has been an issue ever since an early herbalist assistant noted that one pile of dry herbs looks much like another². There is some awareness in the literature that non-cold chain products exposed to temperature excursions can cause degradation of the active component of the drug thus affecting its effectiveness. The distribution network for medicinal products is increasingly complex and involves many players. Multinational companies are strict in ensuring that their

products kept at distributor warehouses are as per storage conditions required and storage temperature is monitored around the clock. The standard operating procedure in one multinational distributor company noted that any exposure to temperatures outside the range for more than two hours for non-cold chain products would result in a halt to operations until the Quality Assurance Department of the multinational company gives the approval to release the products³.

Temperature excursion is defined in the WHO Guidance as "an excursion event in which the time- temperature sensitive pharmaceutical product is exposed to temperatures outside the range prescribed for storage and/or transport⁴. The mean kinetic temperature (MKT) is a currently accepted parameter which provides the notion that the product quality is intact even when temperature excursions occur. The United States Pharmacopoeia USP 33 – NF⁵ states that provided the mean kinetic temperature remains in the allowed range, transient spikes of up-to 40°C are permitted as long as they do not exceed twenty-four hours. MKT, as defined by the United States Pharmacopoeia, is a single calculated temperature at which the total amount of degradation over a particular period is equal to the sum of the individual degradations that would occur at various temperatures. Pharmaceutical dosage forms are researched, formulated with shelf-life studies before being manufactured, stored and transported throughout the world to reach the patient with the intention of ensuring the expected quality has been maintained. This is provided that the stated conditions of storage such as temperature, humidity, light and even vibrations are adhered to throughout the pharmaceutical supply chain. In line with the emerging concern of the effect of temperature excursions along the supply chain, Ammann⁶ noted that stability studies are needed to define the handling and transport conditions of temperature-sensitive pharmaceutical products. Temperature is the main focus for testing because almost all pharmaceutical products are sensitive to temperature and transport in controlled conditions is not always reliable. A stability strategy plan need to be developed linking time of exposure to different temperatures. Conducting stability tests on temperature excursions are difficult because it is not possible to predict when the next excursion will take place and hence the need to simulate real-life situations. From the stability studies, mathematical modeling, safety margin, stability program and distribution stability studies, a stability knowledge in the form of a chart with time of temperature excursion on the x-axis and time of exposure on the y-axis. If a product has been exposed to a time period at a particular temperature, the chart can be used as a referral for the supply chain personnel to decide on the impact on the quality of the medicine. In view of supply chain conditions being different from country to county, the stability studies need to be country-focused. Information on packaging only indicate the required storage condition such as below 25°C but with no information relating to the fact that it is invariable that the product will be exposed to temperatures above this during the distribution process. The current trend, especially amongst the multinational

pharmaceutical companies, is to define conditions for stability testing for global marketing. For this, the companies are orientating their protocols to a single set of conditions that cover extreme environmental conditions. The specific changes for global testing include increase in duration of accelerated testing period from six to twelve months and the conduct of additional tests at 50°C for three months⁷. With the accelerated stability testing at higher temperature and longer periods, extending to 12 months it should cover all periods when temperature excursions occur along the supply chain. This should address the caution statement by the United States Pharmacopoeia that temperature excursions may affect the potency of medicines. It also indicates that this type of stability testing may not currently be the norm yet in the pharmaceutical industry. Storage conditions in tropical countries pose a big challenge in ensuring storage conditions are met throughout the supply chain. The quality defining gap is transportation between storage facilities which may practice Good Distribution Practice (GDP)⁸. Medicines may be transported across seas in non-temperature regulated metal containers, fully exposed to the elements. Temperatures in the containers according to one study exceeded 53°C⁹. It is not infrequent that delays during transport can put product quality at risk when temperature control cannot be maintained causing temperature excursions¹⁰. Current research is insufficient to clarify the extent of poor drug quality. In practice, drug quality is dependent on the overlapping effects of poor manufacturing standards, criminal counterfeiting, adulteration with inactive or toxic fillers, relabeling of time-expired drugs and degradation during storage². A study is on-going to determine whether or not temperature excursions to pharmaceutical products transported in non-temperature regulated metal containers across the South-China Sea has impacted the content of active ingredients. In Malaysia, GDP as stated in the Malaysian National Pharmaceutical Control Bureau Guidelines⁸ is defined as "the measures that need to be considered in the storage, transportation and distribution of any registered product / notified cosmetic and its related materials such that the nature and quality intended is preserved when it reaches the consumer"¹⁰. European Union Good Distribution Practice¹¹ states that it is of key importance that the quality and the integrity of the medicinal products are maintained during the entire supply chain from the manufacturer to the patient. There is growing focus on GDP by the Malaysian authorities⁸ to ensure the product moving along the whole of the supply chain adheres to the temperature requirement. The Malaysian National Pharmaceutical Control Bureau in its Good Distribution Practice Guidelines⁸ further elaborates that products should be stored and transported in accordance with procedures in such a way that the identity of the products is not lost. The products should not contaminate and is not contaminated by other products. Adequate precautions should be taken to ensure that temperature and relative humidity conditions are maintained. Vehicles and equipment used to distribute or transport the products should be suitable for their use and appropriately equipped to prevent exposure of the

products to conditions that could affect their stability. If special storage conditions such as temperature are required during transit it should be checked, monitored and recorded and records maintained for a specified period of time. Most medicinal products are sensitive to temperature and despite the product research and development team's efforts, they have to be stored continuously within limited temperature range until their expiry date⁴. Drugs that have been stored in poor conditions can degrade faster than do those stored adequately and might have reduced active pharmaceutical ingredients and increased toxicity¹². Hunt *et al.*¹³ in their stimuli report to the revision process of the United States Pharmacopoeia provide a brief overview of drug product stability studies and practices with a focus on temperature control during storage and distribution. They noted that recent stability studies support redefining controlled room temperature by broadening the permitted range when appropriate for specific products from 20° - 25°C to 2°- 30°C. The WHO International Pharmacopoeia Guidelines¹⁴ notes that in tropical climates degradation is likely to occur in a humid atmosphere and that decomposition is faster at elevated temperatures. The longer the time and the higher the temperature exposure to the out-of-range conditions, the higher the amount of degradation products⁴. For substances and dosage forms that deteriorate easily under adverse storage conditions (such as in tropical climates), a warning should be given indicating degradation is likely to occur in humid atmosphere and that decomposition is faster at elevated temperatures¹⁴. Temperature ranges permitted during pharmaceutical product distribution, as well as the labeled storage conditions, are inseparably linked to stability data for each product.

In a study carried out in South-East Asia, out of 1437 samples of anti-malarial drugs, 35% failed chemical analysis¹⁵. Products sensitive to high temperatures can deteriorate by receiving thermal energy that will decrease the active ingredient content through transformation of degraded components (oxidative, hydrolyzed), some of them with possible toxic properties. In the current manufacturing environment, products can be shipped and distributed across different climatic zones¹⁰. A WHO study¹⁶ in Sub-Saharan Africa noted that 27% of anti-malarial drugs tested failed chemical assay analysis. Poor-quality medicines were found in 48.3% of providers at all levels of the supply chain for anti-malarial drugs¹⁷. Insufficient amounts of active pharmaceutical ingredients endanger patient safety and may contribute to the development of drug resistance¹⁷. A United States Pharmacopoeia survey¹⁸ on the quality of selected anti-malarial medicines in three African countries revealed that 32% of samples failed chemical assay analysis.

Transportation of medicines from Peninsular Malaysia to the State of Sabah, located on the island of Borneo is carried out using non-temperature regulated metal containers across the South-China Sea. Medicines can be stored in such containers for weeks before arriving at the temperature-controlled distribution centre in Sabah. There is no study carried out on the effect on the quality of medicines transported in such a manner. The concern is

that with the exposed containers the temperatures inside the containers are expected to soar. Sub-quality medicines especially those used in managing long term disease conditions would have profound impact on the therapeutic outcome. Poor quality anti-malarial drugs lead to drug resistance and inadequate treatment which post an urgent threat to vulnerable populations and jeopardize progress and investments in combating malaria. Concurrent interventions and a multi-faceted approach are needed to define and eliminate criminal production, distribution, and poor manufacturing of anti-malarial drugs¹⁵. Manufacturers should clearly understand what the consequences of temperature excursions are during products storage and transport from their manufacturing site to patients. They should evaluate if the available stability data are insufficient to address the potential temperature excursions⁴. Quality risk management is being discussed in the literature as one of the most important tasks when it comes to the pharmaceutical industry because medicines are produced and whose quality is directly related to the patient's health. A risk analysis and evaluation tool from risk communication, initiation which includes risk assessment, risk control, risk review to risk management constitutes the quality risk management process¹⁹. A temperature excursion study program comprising of the determination of global product characteristics, assessing the risks of the distribution channels in relation with product characteristics resulting in the building of stability knowledge, running a risk analysis and evaluating the results. Transport channels depend on the destinations, on the amount and type of products and on the company's distribution strategies as well as the determination of environmental deleterious conditions. Time and temperature should be balanced and conclusions to demonstrate when and how long products keep their properties taking into consideration the repetition of excursions during the life of a product and the consequence of such repeated excursions⁴. Medicines are tested to assess the effects of temperature, moisture, oxygen and light, are packaged and stored to ensure they remain stable and effective over their shelf life. This is provided that the storage conditions are adhered to throughout the supply chain. There is now growing concern in the pharmaceutical industry the need to ensure that the pharmaceutical product when it reaches the patient is as intended by the manufacturer and there is no loss of therapeutic properties. It is estimated that it takes about three to six months before the finished product reaches a patient taking into consideration the storage period of one month at the manufacturer's warehouse, one month on transportation, another one to two months at the distributor's warehouse and another one to two months at the sub-distributor warehouse, pharmacy, hospital and clinic. During these three to six months, the products may be exposed to temperature excursions. Pharmaceutical products undergo stability program during the manufacturing phase to determine its stability till the expiry date. Simulation studies are carried out to determine the behaviour of the drug substance under accelerated storage temperature conditions. Standard

pharmacopoeias such as the European, US and UK now state that there is the possibility of active ingredient deterioration if the product is exposed to temperature excursions. Pharmaceutical products with storage condition of less than 25°C would mean storage within temperature-controlled environment in equatorial countries throughout the year and for countries with seasons, the high temperature excursions exceeding even 40°C during summer would mean the necessity of the provision of temperature-controlled environment. There are gaps in the long pharmaceutical supply chain from the manufacturer to the patient where the temperature will exceed 25°C. The gaps include the mode of transportation from the manufacturer's warehouse to the different countries. The products could be transported by non-temperature regulated sea containers and to varying periods of exposure to temperature excursions. These periods in some cases may exceed the USP recommended allowance for up to 30°C and that the kinetic temperature remains in the allowed range, transient spikes up to 40°C are permitted as long as they do not exceed twenty-four hours. This brings up the question whether the drugs are exposed to periods more than twenty-four hours and this is possible if the time taken for a non-temperature regulated metal container needing travel time more than 72 hours for example in the case of Malaysia from Port Klang to the Kota Kinabalu Port on the island of Borneo. Studies have shown that temperatures can soar to more than 50°C within these metal containers⁹. The focus of the multinational companies is in making sure that their products are being stored at the required temperatures when in the main distributor's warehouse with around the clock temperature monitoring and power back-up systems. In addition, it is a requirement that clearance be obtained from their Quality Assurance Department if temperature is outside the set limits for more than two hours for products needing a less than 25°C storage condition. Products are distributed to community pharmacies, hospitals, clinics using air-conditioned vans and with the outside temperature exceeding 32°C, the products in all probability will be exposed to temperatures exceeding the required temperature for more than two hours during the delivery cycle. How much degradation occurs is the question in hand. This concern is not only for tropical countries but also temperate and cool-climate countries where temperatures in summer can exceed 40°C for days at a stretch. Other than the main distributors where storage conditions are optimal, gaps which can contribute towards temperature excursions include stores in wholesalers, outsourced transportation including delivery vans, rural location of health clinics, storage facilities in community pharmacies, hospitals, clinics where emphasis for the need for around the clock proper storage temperature are less regulated. There is emerging focus on quality risk management in the pharmaceutical industry which includes the supply chain and all this point to the fact that products can be exposed to temperature excursions and this may affect the potency of medicines. In Malaysia, it is estimated about 35% of hypertensive patients²⁰ and about 60% of diabetic patients²¹ do not achieve their therapeutic

end-points. Overall resistance to common antimalarial drugs continue to be very high²². The question yet to be answered is whether or not the degradation of the active components in these medicines has a contributory factor.

CONCLUSION

There is growing concern in the pharmaceutical world regarding the exposure of pharmaceutical products to temperature excursions along the supply chain and the impact on the active ingredient and consequently on the therapeutic efficacy of the product. Although there is greater emphasis on storage requirements at main storage centers, there are gaps along the supply chain which need to be addressed. Sending products by temperature-regulated metal containers across sea channels will increase supply chain costs. Question yet to be answered is what percentage of the non-achievement of the therapeutic end-points is due to the degradation of the active ingredient due to improper storage. Patients are also dispensed medicines up to three months and there is the question how these medicines are stored in their homes. The medicines could be stored in refrigerators (2-8°C) or in the room temperature (where day-time temperature invariably exceeds 25°C). Again the question is of how much degradation, if any, had occurred. Studies show that there is poor quality antimalarial drugs in South-east Asia and Sub-Saharan Africa. However, the cause of the poor quality is not well ascertained, whether it is due to exposure to temperature excursions along the supply chain causing the degradation of the active ingredient, due to counterfeit products or due to non-adherence to Good Manufacturing Practices (GMP). Research is being carried out in Malaysia to establish whether the gaps in storage outside the recommended temperature storage conditions have impacted the potency of the drug. Examples of anti-diabetic and anti-malarial drugs are selected for this study in view of the high prevalence of diabetes and malaria in Malaysia. Depending on the result of the study, further in depth-study can be carried out to determine the supply-chain gaps contributing to the deficit in quality of drugs in the country. The problem statement in this review article is that since there is transportation of medicines by non-temperature regulated metal containers in Malaysia, there is concern whether or not the quality of medicines have been affected. The onus of maintaining quality of the product should be the responsibility of the supply chain function and not the manufacturer who has correctly stated that if a product is stored at the recommended temperature it will last till the stated expiry date on the packaging. The manufacturer is also not in control of the movement of the product once it leaves the manufacturing facility.

REFERENCES

1. Lucas TI, Bishara RH, Seevers RH. A stability program for the distribution of drug products. *Pharmaceutical Technology* 2004; S.1: 68-73.
2. Seear M. Pharmaceutical quality: an urgent and unresolved issue. *The Lancet* 2012; 12(6): 428-429.

3. Communication escalation process for out-of-temperature situation. DKSH SOP CDC 31 Rev.1. 2 Jan 2013
4. Ammann C. Handling temperature excursions and the role of stability data. *Journal of Pharmaceutical and Biopharmaceutical Contract Services* [Internet]. 2013 [cited 25 September 2013]. Available from <http://www.pharmoutsourcing.com/Featured-Articles/146648-Handling-Temperature-Excursions-and-the-Role-of-Stability-Data/>.
5. USP 33-NF 28. General Notices and Requirements 10.30 Storage Temperature and Humidity. 2011 [cited 1 May 2011]; Available from http://www.usp.org/sites/default/files/usp_pdf/EN/USPNF/USP34-NF29General%20Notices.pdf
6. Ammann C. Stability studies needed to define the handling and transport conditions of sensitive pharmaceutical or biotechnological products. *AAPS Pharm Sci Tech* 2011; 12(4): 1264-1275.
7. Bajaj S, Singla D, Sakhuja N. Stability testing of pharmaceutical products. *Journal of Applied Pharmaceutical Science* 2012; 1(3): 129-138.
8. National Pharmaceutical Control Bureau. Guidelines on Good Distribution Practice (GDP). 2013 [cited 2013]. Available from <http://portal.bpfk.gov.my/index.cfm?menuid=90&q=Good%20Distribution%20Practice>
9. Premtitikul P. A study on a few typical shipments and the effect on Temperature and Relative Humidity [Internet] 2012 [cited 24 September 2012]; Available from <http://wordpress.interdrythailand.com/index.php/ocean-container-temperature-and-humidity-study/#ixzz3bybJWFFR>
10. Panzade P. Transportation Stability Studies: Temperature Excursions Management? [Internet]. 2014 [cited 19 November 2014]; Available from <https://www.linkedin.com/pulse/20141119100809-22013644-transportation-stability-studies-temperature-excursions-management>.
11. Official Journal of the European Union. Guidelines on Good Distribution Practice of medicinal products for human use. [Internet] 2013 [cited 23 November 2013]. Available from http://ec.europa.eu/health/human-use/good_distribution_practice/index_en.htm.
12. Abu Reid I, El-Samani S, Hag Omer A, et al. Stability of drugs in tropics. A study in Sudan. *International Journal of Pharmaceutics* 1990; 4, 6-10.
13. Hunt DG, Chandler C, Ulrich DA, Poska R, Montero A. USP Controlled Room Temperature Range Expansion - Stimuli to Revision Process. *International Pharmacopoeia* 4th Ed; *International Pharmacopoeia Guidelines* 2014; USP 33–NF 28 Reissue R-11. 2014. 10.30.60.
14. WHO International Pharmacopoeia Guidelines. 2014 [cited 2014]. Available from <http://www.who.int/medicines/publications/pharmacopoeia/en/>
15. Nayyar GML, Breman JG, Newton PN, Herrington J. Poor Quality anti-malarial drugs in Southeast Asia and Sub-Saharan Africa. *The Lancet* 2012; 12 (6): 488 – 496.
16. WHO - Survey of the quality of selected anti-malarial medicines circulating in six countries of Sub-Saharan Africa. 2011 [cited January 2011]; Available from http://www.who.int/medicines/publications/WHO_Q_AMSA_report.pdf
17. Hetzel MW, Page-Sharp M, Bala N, Pulford J, Betuela I, Davis TM, Lavu EK. Quality of antimalarial drugs and antibiotics in Papua New Guinea: a survey of the health facility supply chain. *EK-PLoS ONE* 2014; 9 (5): e96810.
18. United States Pharmacopoeia. Survey of the quality of selected antimalarial medicines circulating in Madagascar, Senegal, and Uganda [cited November 2009]; Available from http://www.usaid.gov/our_work/global_health/hs/publications/qamsa_report_1109.pdf
19. Das A, Kadwey P, Mishra JK, Moorkoth S. Quality Risk Management (QRM) in Pharmaceutical Industry: Tools and Methodology. *International Journal of Pharmaceutical Quality Assurance* 2014; 5(3), 13-21.
20. Malaysian Society of Hypertension, Ministry of Health, Malaysia, Academy of Medicine, Malaysia. Management of hypertension 4th Ed. [Internet]. 2013 [cited 2013]; Available from http://www.moh.gov.my/attachments/CPG_Management_of_Hypertension_4th_Edition.
21. Ahmad NS, Islahudin F, Thomas P. Factors associated with good glycemic control among patients with type 2 diabetes mellitus. *Journal of Diabetes Investigation* 2013; 5(5): 563-569.
22. Ministry of Health Malaysia. A study on overall resistance to antimalarial drugs. 1993 [cited 2013]; Available from www.moh.gov.my/.../554756755a584a69615852686.