QUALITY RISK MANAGEMENT IMPLEMENTATION FOR A MEDICINAL PRODUCTS WHOLESALE DEALER

Adrian Busuttil, Anthony Serracino-Inglott
Department of Pharmacy, Faculty of Medicine and Surgery, University of Malta, Msida

Corresponding Author: Adrian Busuttil
E-mail: busuttila@gmail.com

ABSTRACT

OBJECTIVES The aims of this study were to compile a model of a Quality Management System (QMS) for distribution of medicines, identify the risks in distribution to the quality of medicinal products from a Maltese wholesale dealer's perspective and evaluate these risks using Quality Risk Management (QRM) methodology. The ultimate objective was to indicate whether risks are being well managed and to propose appropriate corrective and preventive actions (CAPA).

METHOD A set of model Standard Operating Procedures (SOPs) which describe the current wholesale dealer's operations was compiled. These SOPs were written in simple English to facilitate comprehensiveness by the employees. The various steps in the distribution of medicinal products by a wholesaler and the risks in each step were identified and a flowchart was compiled. A QRM assessment was carried out, taking into consideration current risk management activities described in SOPs. No further action was recommended for risks which were deemed as acceptable, however appropriate CAPA was recommended for risks deemed as being unacceptable.

KEY FINDINGS Out of 70 identified risks during QRM evaluation, 65 risks were deemed acceptable, while 5 were deemed not acceptable. Areas exhibiting unacceptable risks were 'Returns of medicinal products' (1 risk) and 'Temperature monitoring and control during shipment from supplier' (4 risks).

CONCLUSION CAPA was proposed to change the profile of unacceptable risks. A model QRM SOP was compiled to be used by Maltese wholesale dealers in setting up a QRM system and to help in fulfilling regulatory obligations.

KEYWORDS Quality Management System, Quality Risk Management, Standard Operating Procedure, Corrective and preventive action, Medicinal products, Wholesale distribution

INTRODUCTION

In an effort to modernise the regulation of pharmaceutical technology and quality through international collaboration via International Conference on Harmonisation (ICH), the EU has adopted and implemented guidelines to the use of Quality Risk Management (QRM) in pharmaceutical manufacturing. These guidelines available in ICHQ9[1] have been adopted in Annex 20[2] of the Eudralex Volume 4 Good Manufacturing (GMP) Guidelines. QRM methodology has been successfully implemented in pharmaceutical manufacturing.

The need for updated Good Distribution Practice (GDP) guidelines was felt since the GDP guidelines in place have been published in 1994.[3] Following consultation with stakeholders, the European Commission published revised GDP guidelines on March 7, 2013.[4] These new guidelines direct medicinal product wholesale dealers (MPWD) to start implementing a QRM system as per QRM methodology already used in the pharmaceutical manufacturing industry to improve risk management relating to the quality of medicinal products in the legal supply chain.

This study aimed to compile a model Quality Management System (QMS) for an established MPWD, to identify and assess risks and ultimately propose appropriate Corrective and Preventive Actions (CAPA) for unacceptable risks in the distribution chain. This project also aimed to compile a model SOP to be used for QRM application by a MPWD.

METHOD

DESIGN OF MODEL QMS

The design of a model QMS for MPWD XYZ Ltd was undertaken with the scope of describing the current procedures required to ensure that distribution of medicinal products is in line with current European and Maltese legislation and current GDP guidelines.

SOP Number	Version	Name of SOP
01	01	SOP Policies and Procedures
02	01	Storage Procedures
03	01	Sale and Supply Procedures
04	01	Returns and Complaints Procedures
05	01	Recalls Procedure
06	01	Internal Audits Procedure
07	01	Verification of Supplier and Customer Status
08	01	Training
09	01	Purchase and Receipt Procedures
10	01	RP Responsibilities
11	01	Change Control and Process Deviation Procedures
12	01	Cold Chain Integrity Procedures for Verified Suppliers
13	01	Return to Supplier / Disposal of Pharmaceuticals
14	01	Stock Taking and Expired / Damaged Pharmaceuticals Handling Procedure

Table 1 – A list of compiled Model Standard Operating Procedures

These SOPs were written in simple and concise English and aim to list all the procedures carried out by a MPWD for the supply of medicinal products and to remain fully compliant with current Maltese/EU legislation and GDP guidelines. List of compiled SOPs is available in Table 1.

IDENTIFICATION OF RISKS

The main steps involved in the distribution chain from when a product is ordered from supplier until delivery to an authorised client were identified. Steps were classified as being within the MPWD's control or not. Risks within each step were identified by asking the question; 'What can go wrong?'

RISK ANALYSIS

Failure Mode Effects and Criticality Analysis (FME(C)A) was chosen as the risk assessment tool since it is recommended as a main QRM tool by ICHQ9 and Annex 20 of GMP, due to its wide use in pharmaceutical QRM[5,6] and due to its relatively ease of use.[7]

An Excel sheet was compiled with the risk description and with current risk management actions according to the QMS model. On the basis of risk and current risk management actions, a score of 1-5 was assigned for each of three factors namely severity (S), probability (P) and detectability (D). Scores were assigned as follows: the higher the severity the higher the score, the higher

the probability the higher the score and the higher the detectability the lower the score. The Risk Probability Number (RPN) was then calculated per risk by multiplying the scores of severity (S), probability (P) and detectability (D) according to the equation: RPN = S x P x D. All details were added in an Excel sheet.

RISK ACCEPTABILITY

According to the developed model, the higher the score given for severity and probability, and the lower the score given for detectability, the higher the risk. Risks were classified into two categories: 'Acceptable' risks and 'Not acceptable' risks. The lowest possible RPN mathematically is 1, while the highest possible RPN is 125. A risk with an RPN above 20 was deemed as not acceptable to ascertain a higher degree of safety.

RESULTS

In total, 16 main steps were identified and a flowchart was compiled (Figure 1) illustrating the processes involved in the flow of medicinal products at a MPWD from supplier procurement to final client delivery.

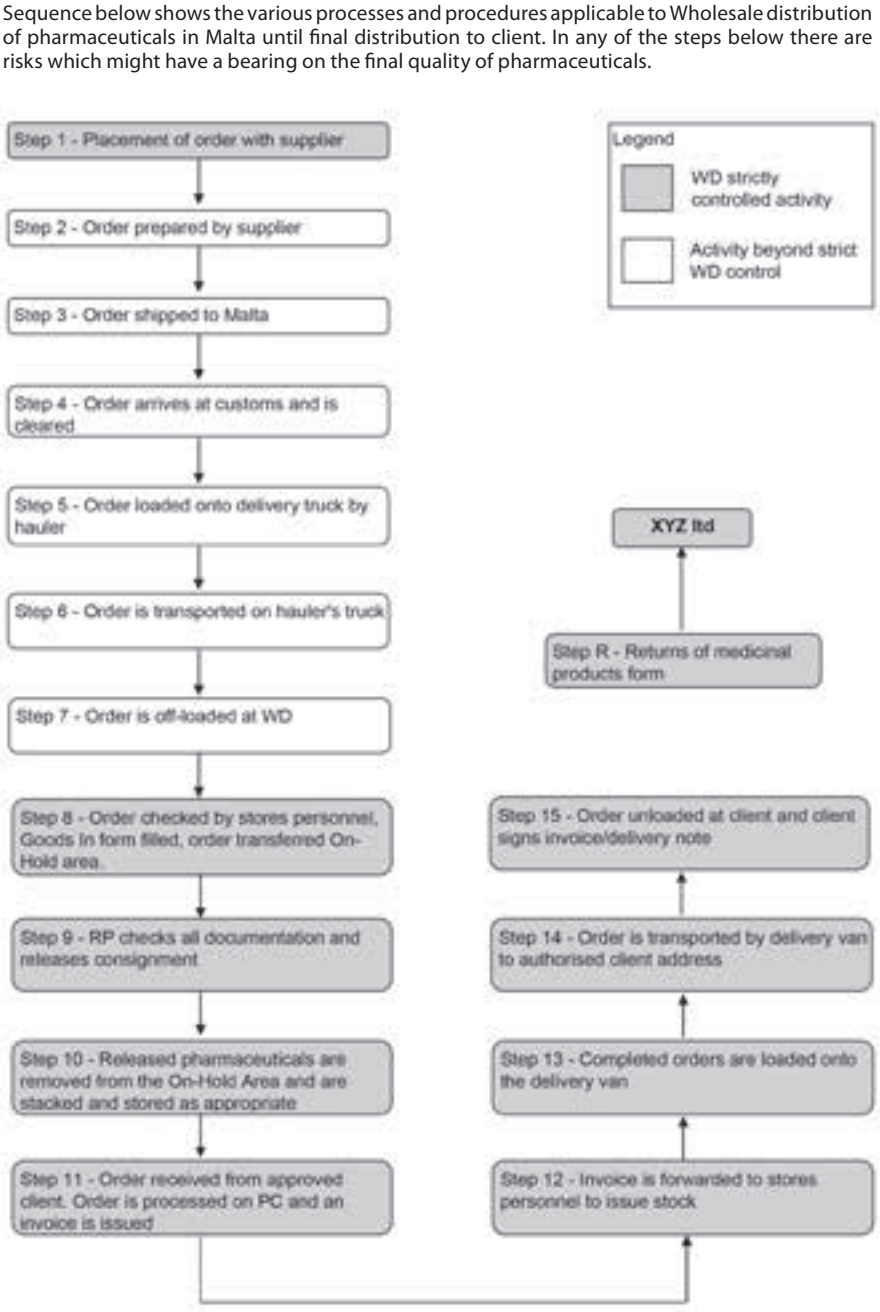

Figure 1: The various steps involved in the Distribution of Pharmaceuticals

The two areas which exhibited 'Non-acceptable' risks were 'Temperature conditions during transit' and 'Return of Pharmaceuticals'.

Seventy risks were identified and added to the flowchart in Figure 1. Using FME(C)A methodology evaluation, 65 risks were classified as 'Acceptable' (RPN ≤ 20) and 5 risks were classified as 'Not Acceptable' (RPN>20). From the 'Not-Acceptable' risks (n=5), 4 were related to temperature excursions when pharmaceuticals are transported by supplier without temperature data-logger and 1 risk is related to acceptance of returns from clients without temperature records present.

CAPA was proposed for all unacceptable risks (Table 2).

QUALITY RISK MANAGEMENT SOP

A model wholesale QRM SOP was compiled to facilitate re-evaluation of the QMS using QRM methodology by the MPWD.

DISCUSSION

MODEL STANDARD OPERATING PROCEDURES

The model SOPs drafted are based on actual SOPs in use by Maltese wholesale dealers which in turn are based on GDP guidelines. The scope of these procedures is to enable the MPWD to have as much control as possible on all operations which take place and which can impact the quality of medicinal products. Some of the procedures compiled in this study, which are still very essential for the proper functioning of a MPWD go beyond strict GDP requirements, for example pharmaceutical waste disposal.

QRM EXERCISE

The results produced by the FME(C)A evaluation showed that the vast majority of risk factors identified were being appropriately managed with current risk management actions and the latent risk is acceptable (RPN = or < 20). Since the model SOPs and operations are modelled around real wholesale dealer's operations rather than being just theoretical, this might explain why the majority of RPNs scored 20 or below. The two areas which exhibited 'Non-acceptable' risks were 'Temperature conditions during transit' and 'Return of Pharmaceuticals'. These two areas have also been identified as being problematic by the European Commission and the new GDP Guidelines aim to regulate these areas more thoroughly.

Risk Description	RPN Score	Risk Acceptability	Proposed risk minimisation and / or risk management CAPA actions
Temperature excursion during transit for room temperature pharmaceuticals (store below 25 °C) **without** data logger in place during winter	30	Not Acceptable	It is recommended that supplier includes a data logger with shipment. This will highly increase detectability and this risk can be managed as per same risk **with** data logger.
Temperature excursion during transit for room temperature pharmaceuticals (store below 25 °C) **without** data logger in place during summer	60	Not Acceptable	
Temperature excursion during transit for cold-chain pharmaceuticals (store at 2-8 °C) **without** data logger in place during summer	75	Not Acceptable	
Temperature excursion during transit for cold-chain pharmaceuticals (store at 2-8 °C) **without** data logger in place during winter	60	Not Acceptable	
Unexpired pharmaceuticals accepted into good stock that were kept in unacceptable temperature conditions at client	48	Not Acceptable	It is recommended that unless temperature records can be easily accessible and verifiable, returns of all pharmaceuticals are **not** accepted.

Table 2: Description of 'Not Acceptable Risks' and Proposed CAPA

This study shows how theoretical guidelines and recommendations of risk management as per Annex 20 and ICH Q9 can be combined with the real world scenario resulting in a comprehensive risk assessment taking into consideration the risks at each step of the distribution chain for the MPWD.

Transportation of medicinal products from the EU supplier to the Maltese wholesale dealer consists of consignments that are typically bulkier than orders supplied by the MPWD to the individual pharmacy. The shipping time to receive such a consignment is also significantly higher than the time required by the local MPWD to deliver to an authorised client such as a pharmacy. On this basis alone, the risk of temperature excursions in consignments in transit to Malta is higher. It is therefore reasonable to assume that more effort to control temperature and detect excursions should be necessary for the shipment with higher risk rather than the local deliveries. Proposed CAPA is to change commercial and technical agreement with suppliers to include temperature data loggers in consignments shipped to Maltese MPWD. The increased detectability will decrease the RPN scores to an acceptable level as per risks of temperature excursions with data loggers included.

In the current SOP model, returned medicinal products (room temperature pharmaceuticals only) are accepted provided that the pharmacist signs a form declaring appropriate storage. However, one cannot guarantee that such storage conditions where kept, since temperature records are not verified. It is suggested to amend the SOP to refrain from accepting any returns unless verified with temperature data that storage conditions at the client have been optimal.

QRM IN PRACTICE FOR A MPWD

Various examples and guidance documents were found in the literature about the use of QRM in pharmaceutical manufacturing. However, no specific information was available regarding the implementation of a QRM system for a MPWD. This study shows how theoretical guidelines and recommendations of risk management as per Annex 20 and ICH Q9 can be combined with the real world scenario resulting in a comprehensive risk assessment taking into consideration the risks at each step of the distribution chain for the MPWD. The compiled QRM SOP can be adapted by a MPWD to evaluate its QMS. Such a project needs to be constantly updated with new data to truly reflect risks or cater for new risks as required.

CONCLUSION

When implemented, the QMS and QRM systems developed in this study can help the MPWD to ensure that all distribution operations are under control and thus be in a better position to safeguard the quality of medicinal products. Through compliance with legislation and GDP guidelines, the MPWD will ensure better patient care through the availability of high quality medicinal products.

References

1. ICH Expert Working group. International conference on harmonisation of technical requirements for registration of pharmaceuticals for human use: Quality risk management Q9; 2005 Nov 9 [cited 2014 Jan 21] Available from: URL: www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q9/Step4/Q9_Guideline.pdf.
2. Working Party on Control of Medicines and Inspections. EudraLex The Rules Governing Medicinal Products in the European Union Volume 4 EU Guidelines to Good Manufacturing Practice Medicinal Products for Human and Veterinary Use - Annex 20 Quality Risk Management. European Commission; 2008 Feb 14 [cited 2014 Jan 21] Available from: URL: http://ec.europa.eu/health/files/eudralex/vol-4/pdfs-en/2008_02_12_gmp_annex20_en.pdf.
3. Guidelines on Good Distribution Practice of Medicinal Products for Human Use (94/C 63/03). OJ C 63 (1994 Mar 1) p. 3-7 [cited 2014 Jan 21]. Available from: URL: http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:C:1994:063:0004:0007:EN:PDF.
4. Guidelines of 7th March 2013 on Good Distribution Practice of Medicinal Products for Human Use (2013/C 68/01). OJ C 68 (2013 Mar 7) p. 1-14 [cited 2014 Jan 21]. Available from: URL: http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:C:2013:068:0001:0014:EN:PDF.
5. Frank T, Brooks S, Creekmore R, Hasselbalch B, MurrayK, Oben K etal. Quality Risk Management Principles and Industry Case Studies. Risk Management working group. The Pharmaceutical Quality Research Institute Manufacturing Technology Committee;2008.
6. Gregg Claycamp H. ICH Q9: Quality Risk Management. Presented at CDER Advisory Committee for Pharmaceutical Sciences (ACPS); 2006 Oct 5-6; Rockville MD (USA) [cited 2014 Jan 21] Powerpoint presentation available from: URL: www.fda.gov/ohrms/dockets/ac/06/slides/2006-4241s1_3.ppt.
7. Kuczek. T. Analyse Opportunity Part 1 – Failure Mode Effects Analysis (FMEA). Indiana (US): Purdue University. [cited 2014 Jan 21] Powerpoint presentation Available from: URL: www.stat.purdue.edu/~kuczek/stat513/IT%20381_Chap_7.ppt.