Susan Schniepp, RCA Distinguished Fellow

Michelle Heiter, RCA Quality and Compliance Specialist

Developing a Quality Risk Management Plan and Global Supplier Qualifications

A well-written and well-implemented quality risk management plan is an integral and valuable element of an effective quality system. During the development and manufacturing of pharmaceutical products, the bottom line is that things can and will go wrong. The purpose of a quality risk management plan is to help ensure continued compliance with regulatory requirements, such as good manufacturing practices or good laboratory practices, when events occur during manufacturing that potentially impact patient safety and product quality. The International Council for Harmonization (ICH) Q9 states;

> *"Two primary principles of quality risk management are: the evaluation of the risk to quality should be based on scientific knowledge and ultimately link to the protection of the patient; and, the level of effort, formality, and documentation of the quality risk management process should be commensurate with the level of risk" (1).*

In developing your company's plan, you will need to consider all aspects of the operation that impact the product. Managing your company's risk with a well-defined plan may help reduce the activities associated with poor quality and inefficiencies associated with the product and the process, such as a reduction in deviations/investigations, scrap or wasted materials, customer complaints, and product yield.

The concept is to evaluate all aspects of the manufacturing process and identify areas of vulnerability. These vulnerabilities need to be assessed for their impact on the operation and the potential level of risk they pose. A well-written quality risk management plan is an ongoing process requiring rigorous documentation throughout the product life-cycle. It provides a solid rationale for how to improve efficiency and spend resources on the important activities to improve product quality rather than on low-risk activities that have little to no impact.

> **There are four basic elements that should be included in a quality risk management plan.**

Element One

The first element is to perform an analysis of the identified risk associated with the operations. For example, if your product is being produced using an older manufacturing line, there is a risk that the line will experience frequent breakdowns.

Element Two

The second step is to evaluate the risk in terms of its impact on your ability to supply a quality product. In this case, frequent shut downs can lead to product rejections, yield loss, and potential drug shortages.

Element Three

Once the risk has been identified and the impact evaluated, controls to mitigate the potential situation need to be identified and implemented. Some of the possible mitigation control strategies might include ensuring there are appropriate change parts for the line in inventory or plans to qualify the product production on a new more modern manufacturing line.

Element Four

The last key element needed is data input and management. The data evaluated should be able to indicate if and when you need to employ one of your control strategies. A simple illustration of this is if you see an increase in down time on the line or a steady decrease in yield. This data could be indicators that the manufacturing line is headed for a catastrophic failure and steps need to be taken to prevent a drug shortage situation.

Other Evaluation Areas

The above discussion is only an example of a risk assessment in one area of an operation. Other areas of the process need to be evaluated for potential vulnerabilities and risk. These areas include an evaluation of the reliability of raw material suppliers, stability and compliance of contractual suppliers (e.g., contract manufacturing organizations, contract test organizations), age and reliability of laboratory test equipment, etc. In other words, a solid, well-written and dynamic quality risk management plan will evaluate the overall organization, identify high risk vulnerabilities, identify strategies for mitigation of the high-risk vulnerabilities, and rely on data to perform continuous monitoring of the vulnerabilities. And, of course, the plan will provide the appropriate documentation and rationale for the decisions.

Implementing a quality risk management plan in an organization can also be challenging. It needs to be introduced and discussed with all applicable function personnel involved in the operations including, but not limited to, finance, manufacturing, regulatory affairs, purchasing, auditing, and senior management. The plan should be dynamic and should be modified as situations change.

Let's say you produce a product and you have a single-source supplier for one of your excipients. You have audited the supplier and have identified some significant gaps in their quality system. You identify this vulnerability in your quality risk management plan and indicate it is a high-risk item because of the lack of compliance of the excipient vendor. One of your mitigation strategies might be to qualify an alternate supplier for the excipient. Once you have qualified that alternate supplier, you need to update your plan to downgrade the risk because you have taken the appropriate steps to mitigate it and eliminate the identified vulnerability.

Qualifying a Secondary Supplier

When qualifying a secondary supplier you may want to consider choosing a supplier in a different geographic location than that of the original supplier. There may be geographical situations or circumstances that could affect the ability of the original supplier to supply the necessary material in a timely manner. This concept could also be applied not only to secondary suppliers of a raw material but also suppliers of the final pharmaceutical product.

When choosing a new supplier in a different geographical location it will be important to understand the capabilities of the new region. The following Table demonstrates some of the information you will want to assess. The chart identifies the Regulatory Agency in charge of the region you might be considering as well as identifying the estimated number of employees currently in the industry, the results of 2019 drug quality inspections (NAI, VAI and OIA) including data on Data Integrity issues tied to warning letter citations. The decision to qualify a new location is a difficult one but with the proper information it can be done as a part of a well defined and implemented Quality Risk Management Plan. Quality risk management plans are important because they help improve a company's ability to provide quality product to patients. They are contingency plans with identified actions that help to ensure a continuous supply of product to the market that meets the expectations of being safe, effective, and available. They are dynamic documents that require integration into and data inputs from all departments in order to be successfully implemented at a company, require integration into and data inputs from all departments in order to be successfully implemented at a company.

Table 1: Timeline and Labeling Requirements Vary by Country

			FY2019 Inspections for Drug Quality (11)			Data Integrity Issues Identified in Warning letters by Country		
Country	**Regulatory Agency**	**Exchange of Information with FDA**	**NAI**	**VAI**	**OAI**	**2017 (5)**	**2018 (5)**	**2019**
USA	Food and Drug Administration (FDA)	N/A	228	299	56	15	8	32 (6)*
Canada	Health Canada	Yes (9, 10)	24	37	2	2	1	1 (6a)
Mexico	Commission Federal para la Protection contra Riesgos Sanitarios (COFEPRIS)		1	3	20	1	1	1 (6a)
Puerto Rico	Food and Drug Administration (FDA)	N/A	2	10	1	0	0	0
Costa Rica	Ministerio de Salud		0	0	1	0	0	1 (6a)
Australia	Therapeutic Goods Administration (TGA)	Yes (8)	3	6	1	0	1	2 (6a)
Czech Republic	State Institute for Drug Control	Yes (7)	0	3	0	0	0	0
Hungary	National Institute of Pharmacy	Yes (7)	3	0	0	0	0	0
Poland	Office and Registration of Medicinal Products, Medicinal Devices and Biocidal Products	Yes (7)	0	0	0	0	0	0

Country	**Workforce Employee#**	**Wages and Salaries (USD million) (1)**	**Corporate Tax (3)**
USA	251,995(1)	13.21	21% (top)
Canada	29,802 (13)	1.29	15% (top)
Mexico	51,125(1)	2.17	30%
Puerto Rico	90,000 (4)	Not Available	38%
Costa Rica	3,500 (12)	0.49	30% (top)
Australia	15,565 (14)	1.11	30%
Czech Republic	10,083 (2)	0.18	19% (base)
Hungary	29,400 (2)	0.48	19% (base)
Poland	29,873 (2)	0.54	19% (base)

Resources

1. International Federation of Pharmaceutical Manufacturers and Associations, "The Pharmaceutical Industry and Global Health Facts and Figures 2017", Annex 3 Pharma Economic footprint 2014. - https://www.ifpma.org/wp-content/uploads/2017/02/IFPMA-Facts-And-Figures-2017.pdf

2. European Federation of Pharmaceutical Industries and Associations , " The Pharmaceutical Industry in Figures Key Data 2019, pg. 12 - https://efpia.eu/media/413006/the-pharmaceutical-industry-in-figures.pdf

3. 2020 Index of Freedom - Country Rankings - https://www.heritage.org/index/ranking

4. FDA; Securing the Future for Puerto Rico: Restoring the Island's Robust Medical Product Manufacturing Sector https://www.fda.gov/media/108975/download

5. "An Analysis of 2018 FDA Warning Letters Citing Data Integrity Failures" - https://www.pharmaceuticalonline.com/doc/an-analysis-of-fda-warning-letters-citing-data-integrity-failures-0001

6. 2019 Data Integrity issues linked to warning letters by country. Note USA has 32 with 20 of these for OTC products. - * Note: 20 of the 32 Warning letters were to OTC products with DI issues. - https://govzilla.com/wp-content/uploads/2020/04/FY2019-Drug-GMP-Warning-Letters.pdf

(6a) US Food and Drug Warning Letter 2019 - https://www.fda.gov/drugs/warning-letters-and-notice-violation-letters-pharmaceutical-companies/warning-letters-2019

7. Mutual Recognition Agreement (MRA) between FDA and European Union (EMA) allows drug inspectors to rely upon information from drug inspections conducted within each other's borders. FDA will conduct pre-approval inspection but less surveillance inspections. https://www.fda.gov/international-programs/international-arrangements/mutual-recognition-agreement-mra

8. FDA-Australia Cooperative Agreement regarding Exchange of Information on GMP Inspections of Human Pharmaceutical Facilities. https://www.fda.gov/international-programs/cooperative-arrangements/fda-australia-cooperative-agreement-regarding-exchange-information-gmp-inspections-human

9. USA FDA and Health Canada cooperate on regulatory activities. Continued discussions seeking opportunities for convergence of regulatory systems and developing work plans while respecting the sovereignty of each country to make independent regulatory decisions -https://www.canada.ca/en/health-canada/corporate/about-health-canada/legislation-guidelines/acts-regulations/canada-united-states-regulatory-cooperation-council/united-states-food-drug-administration-health-canada-regulatory-partnership-statement.html

10. Canada and EU have a Mutual Recognition Agreement (MRA) in effect - https://www.canada.ca/en/health-canada/services/drugs-health-products/compliance-enforcement/international/mutual-recognition-agreements/updates/mutual-recognition-agreement-canada-european-community.html#a3

11. FY2019 Summary of 483 citations for Drug Quality. https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/inspection-references/inspection-observations

12. Central American Group, "Pharmaceutical Manufacturing Costa Rica" - https://www.thecentralamericangroup.com/pharmaceutical-manufacturing-costa-rica/

13. Government of Canada Pharmaceutical Industry Profile - https://www.ic.gc.ca/eic/site/lsg-pdsv.nsf/eng/h_hn01703.html

14. Pharmaceutical Product Manufacturing in Australia industry statistics - https://www.ibisworld.com/au/industry/pharmaceutical-product-manufacturing/188/