Risk-MaPP: Managing the Risk of Cross Contamination

By Stephanie Wilkins
at PharmaConsult US

Risk-Based Manufacture of Pharmaceutical Products – Risk-MaPP – enables manufacturers to justify scientifically that the risk of cross contamination is under control and below acceptable limits in multi-product facilities.

The International Society for Pharmaceutical Engineering (ISPE) recently released Volume 7 of their Baseline® Guide series, *Risk-Based Manufacture of Pharmaceutical Products, A Guide to Managing Risks Associated with Cross Contamination*, also known as Risk-MaPP. In general, Risk-MaPP provides a scientific, risk-based approach – based on ICH Q9 – to manage the risk of cross contamination in order to achieve and maintain an appropriate balance between product quality and operator safety.

ICH Q9 defines risk as the combination of the probability of occurrence of harm and the severity of that harm. In the context of Risk-MaPP, risk is a function of the hazard of the compound (severity) and the exposure to the hazard (occurrence of harm).

Regulatory agencies across the globe are citing manufacturers with multi-product facilities for not having a risk assessment on the risk of cross contamination, or that the risk assessment that has been done is not scientifically based. Risk-MaPP provides a scientific methodology that manufacturers can follow not only for risk assessment but also for risk management of cross contamination.

David Cockburn of the European Medicines Agency (EMA, formerly EMEA) stated in October 2010 at the DC session of the Risk-MaPP launch that this guide has made a practical reality of the EMEA 2005 *Dedicated Manufacturing Facilities in the Manufacture of Certain Medicinal Products* concept paper. The EMA has been working on the revised text for EU GMP clauses 3.6, 5.18 and 5.19 with regard to cross contamination and the need for dedicated facilities since 2005. Their latest update on the revised text suggests that toxicological input is necessary when using a risk management approach to manufacturing products in a multi-product facility.

BACKGROUND

The cornerstone of the Risk-MaPP approach is the use of Acceptable Daily Exposure (ADE) to understand the hazard and set safe levels. This limit is based on science and quantitative data, and is set by a qualified toxicologist. The ADE of a substance is defined as the dose that is unlikely to cause an adverse effect if an individual is exposed to it by any route, at or below this dose every day for a lifetime. By the definition, the risk would be acceptable if the results of cleaning data and cross contamination data indicated that the levels are below the ADE. The ADE is typically expressed in milligrams per day.

Cleaning limits should be assessed against the ADE to ensure they are protective of patient health. Many companies use 1/1000th of a low clinical dose (LCD), 10ppm or the LD_{50} to calculate the maximum allowable carry-over (MAC). There are instances were these methods are protective of patient health, but there are important instances, especially when handling high hazard compounds, where these limits are not protective. The only way to really assess if the cleaning limits are protective is to calculate the safety threshold value (STV) based on the ADE. The STV is basically calculated in the same way as the MAC, but instead of using 1/1000th of an LCD, 10ppm or the LD_{50}, the ADE value is used. A company should not set their cleaning limits at the STV since any failure would then mean the product should be rejected. Statistical analysis should be used to set actual process limits. The distance between the STV and the process limit is the margin of safety provided by the process. By also setting alert limits, a company can be notified when the cleaning process is drifting out of its normal operating range so that increased attention can be given to ensure the process does not go out of control.

Another important aspect of Risk-MaPP outlines the modes of exposure that can lead to cross contamination. These modes are mix-up, retention, mechanical transfer and airborne transfer. It should be noted that these modes are different to those for operator protection which are inhalation, dermal, ingestion, intravenous and mucosal membranes. This distinction brings out the point that, when assessing risk, the target population needs to be clearly understood so that the proper mode of exposure is

analysed. The need to balance industrial hygiene issues and GMP issues is a big part of the Risk-MaPP approach. The use of a holistic team approach that includes representation from all the stakeholder groups helps to maintain the balance so that, while reducing the risk for one stakeholder group, risk is not increased for any other group.

SCENARIOS

During the ISPE Risk-MaPP launch sessions in Brussels and Singapore, Catherine Lefebvre of AFSSAPS (Agence Française de Sécurité Sanitaire des Produits de Santé) presented several scenarios where manufacturers had incorrectly applied risk management to justify the use of multi-product facilities. Below are some of these scenarios, followed by a description of how the use of Risk-MaPP could have helped the manufacturer properly justify their case.

Scenario One

A manufacturer has the information available to develop an ADE or similar health-based limit and, because cleaning can be validated, the manufacturer has concluded that they can safely manufacture in a multi-product facility.

While being able to clean to the appropriate limits is a significant factor in determining if a product can be safely handled in a multi-product facility, it is only one of the factors to be considered. If risk is a function of the hazard (the compound) and the exposure to that compound, then all exposure routes need to be addressed. A key feature of the Risk-MaPP guide is the logic diagram, which takes a team through the issues to consider when determining if a compound can be safely handled in a facility. After confirming that there are no regulatory requirements for the product to be handled in a dedicated facility (such as in the case of penicillin for the FDA), the next step is to obtain the health-based criteria. Once this criterion is understood, evaluating if cleaning can be done is the next step and – as in this case – if the cleaning limits can be met, then the potential for mix up, mechanical transfer and airborne transfer also need to be evaluated. So long as all the exposure routes can be safely controlled so that the health-based limit is not exceeded, the product should be able to be handled safely in the shared facility.

Scenario Two

A manufacturer has a self-contained facility, separated from the rest of the plant, and has therefore concluded in their quantitative risk management (QRM) plan for the whole plant that all class V products can be handled in this self-contained facility.

This manufacturer is basically setting up this self-contained facility as a multi-product facility for all class V products and therefore should have a QRM plan for the facility to show that the risk of cross-contamination is below acceptable limits. Again, the logic diagram should be used to guide a team through the issues that should be considered to determine if the products can safely be handled in this shared self-contained facility.

Scenario Three

The use of a quality risk management tool, such as failure modes and effects analysis (FMEA), is a scientific approach.

A quality risk management tool – no matter which one is selected – is just a tool; the data that is used to justify the inputs to the tool is what makes the analysis scientific. For example, setting health-based limits such as the ADE or the STV for cleaning, and evaluating these limits against the historical or expected data brings the science to the analysis. In addition, reviewing other data collected – such as adverse events, data logs, trend data and so on – support the inputs to the tool and the credibility of the inputs.

CONCLUSION

While Risk-MaPP is not a regulatory requirement, it is a valuable tool that can show whether a manufacturer is controlling the risk of cross contamination. As Edwin Melendez of the US FDA stated during the DC session of the Risk-MaPP launch, the ISPE Guide helps make the current practice – as referenced by the 'c' in the cGMPs – available to all manufacturers. By using the methodology in Risk-MaPP, manufacturers large and small, innovator or generic, client or CMO can scientifically justify that the risk of cross contamination is under control and below acceptable limits in their multi-product facilities.

Stephanie Wilkins, PE, Lean Six Sigma Green Belt, has over 27 years of professional experience in project management, engineering and validation solutions for the pharmaceutical/biotech industry including research, development, pilot plant and manufacturing facilities. She is President of PharmaConsult US, Inc, which provides cross contamination and containment consulting to the pharmaceutical industry. Stephanie is the Co-Chair of the ISPE Risk-MaPP Baseline® Guide Task Team and was a member of the ISPE International Board of Directors. She is also a reviewer of articles to be placed in the ISPE Pharmaceutical Engineering journal, and has contributed articles, given lectures and organised courses for the ISPE. Stephanie graduated from the Pennsylvania State University (PA, US) with a Bachelor of Architectural Engineering. Email: stephanie.wilkins@pharmaconsultus.com