

Case Study



Joint Risk Assessment During Technical Transfer

A framework for donor and recipient companies to jointly analyze and document the technical and business risks associated with a technical transfer

Every technical (tech) transfer is different, with companies taking different paths toward reaching their goal. Each one presents a unique set of challenges. These challenges are most often technical, but at times they may also be business related. However all donors (the outsourcing partner) and recipients (the contract manufacturer) have the same overall goal – to achieve a quick, efficient transfer of process and knowledge that meets all necessary quality and regulatory requirements.

To help drive the tech transfer of partner products, Alkermes sought to develop a risk assessment framework that involved both the donor company and the Alkermes transfer team in jointly assessing the tech transfer risks. This framework would address not just the usual technical challenges but also, where appropriate, the business challenges. This case study provides an overview of the implementation of this framework in a recent real-world tech transfer.

Background

A large pharmaceutical company wished to outsource to Alkermes the commercial manufacture of a solid oral dose product, which had been in commercial production for over five years. Alkermes had previous experience in the core technologies and processes involved. This was the donor's first major tech transfer to Alkermes.

The Challenge

The donor's desire was to minimize regulatory changes, which meant the donor equipment train would need to be replicated wherever possible. This required the purchase, installation and qualification of new equipment at the Alkermes Athlone, Ireland site. Some of this equipment was at a working scale new to Alkermes. Existing Alkermes equipment was to be employed for one core unit operation. This required a process scale change from the donor site. A lean approach to the tech transfer was agreed i.e., only one active engineering batch was to be manufactured prior to process validation. Minimal development data or product history was shared with the recipient site.

The Approach – Joint Risk Assessment

The first round of risk assessment was performed based on the Partner's transfer plan and process knowledge at Alkermes. First the risks were identified via brainstorming. The risks were then analyzed and evaluated via a risk ranking process and the use of Failure Mode, Effects and Criticality Analysis (FMECA). As part of this process, the joint team (of donor and recipient members) started to consider the controls that should be put in place or the additional data and/or studies required to mitigate the risks identified.

To reduce the time associated with working risks through the full FMECA process, Alkermes introduced a sub-process between risk ranking and the FMECA stage – referred to as the "silver bullet" step. Here, unanimous agreement of both teams can render the risk acceptable based on existing knowledge. It is important that the justification for applying the silver bullet step be thoroughly documented.

It was agreed that all risks identified must be closed out by one of the following means prior to proceeding to process validation:

- Donor and Alkermes deem the risks to be acceptable.
- Donor and Alkermes deem additional data is required. Donor to provide/facilitate data gathering.
- Donor and Alkermes deem additional data is required. Donor has existing supporting data. Donor declares the risk is acceptable.
- Alkermes deems the risk is unacceptable. Donor prepared to accept risk.
- Donor and Alkermes deem the risk to be unacceptable. Further work is required to close out.

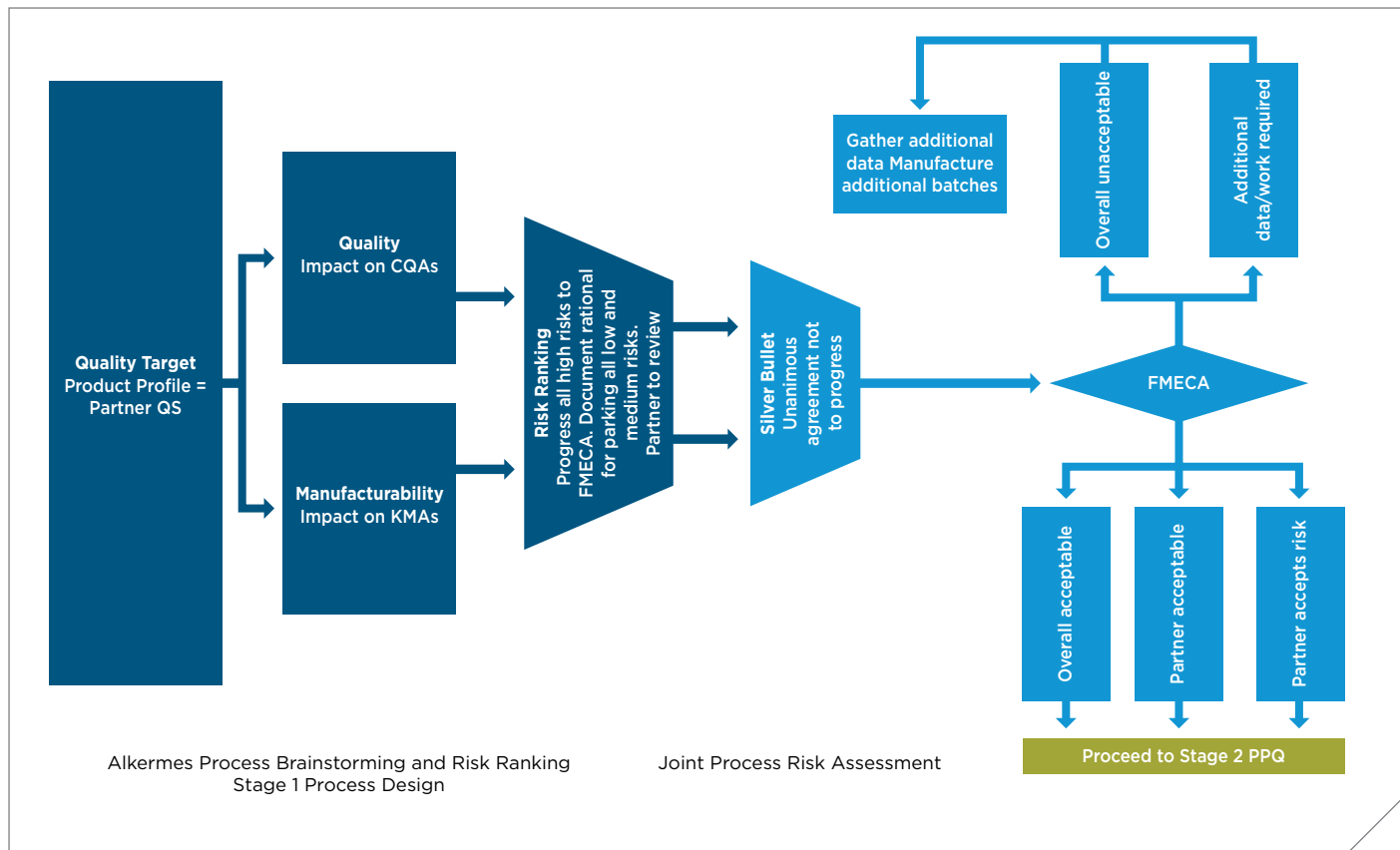


Figure 1. Risk assessment approach adopted by Alkermes in a tech transfer process.

Abbreviations: QS = Quality Systems, CQA = Critical Quality Attribute, KMA= Key Manufacturing Attribute, FMECA= Failure Mode Effects and Criticality Analysis, PPQ = Process Performance Qualification

Such decision paths are sometimes required due to the disparity in the process history knowledge between the donor and recipient sites. The key here is that the risk is considered, documented and responsibility for the risk is clearly agreed upon while allowing an efficient closure of the process via a simple declaration by the donor. Such decisions must always be made with the quality of the product and safety of patients as the primary consideration, regardless of the source of the process history knowledge (Figure 1).

Risks Identified

250 risks were identified at the initial brainstorming session and presented to the donor. Of these, 195 were deemed to be high-risk as they directly impacted a Critical Quality Attribute (CQA) at the end of the risk ranking process.

On completion of the risk ranking and silver bullet process with the donor company, 70 risks retained a high-risk designation and were progressed to FMECA. These risks included the risks associated with the single active engineering batch approach as requested by the donor. The FMECA process identified that engineering studies were required. This included a short placebo manufacturing campaign to support the lean active engineering campaign.

The risk assessment was revisited and updated at the end of the placebo engineering trials i.e., before the active engineering demonstration batch and again on completion of the demonstration batch. At this point, zero technical and five business risks remained identified as high-risk. All quality risks had been mitigated via the additional engineering studies and controls identified through the various iterations of the risk assessment. The remaining business risks were all deemed acceptable by the donor as they related to historical process data readily available to the donor but not shared with the Alkermes team. The five business risks were assessed, and it was agreed and documented that none of the business risks had any quality or patient safety impacts (Figure 2). On this basis, it was agreed to progress to validation – Stage 2 Process Performance Qualification (PPQ).

Conclusion – Successful Risk Assessment Completion

The time committed to jointly risk-assessing the process played a lead role in the efficient and successful tech transfer and validation of this product. The framework helped focus both parties throughout the tech transfer and was revisited many times to assist in technical decision-making. The work put into the risk assessment also fed directly into the development of the validation strategy for the product in question.

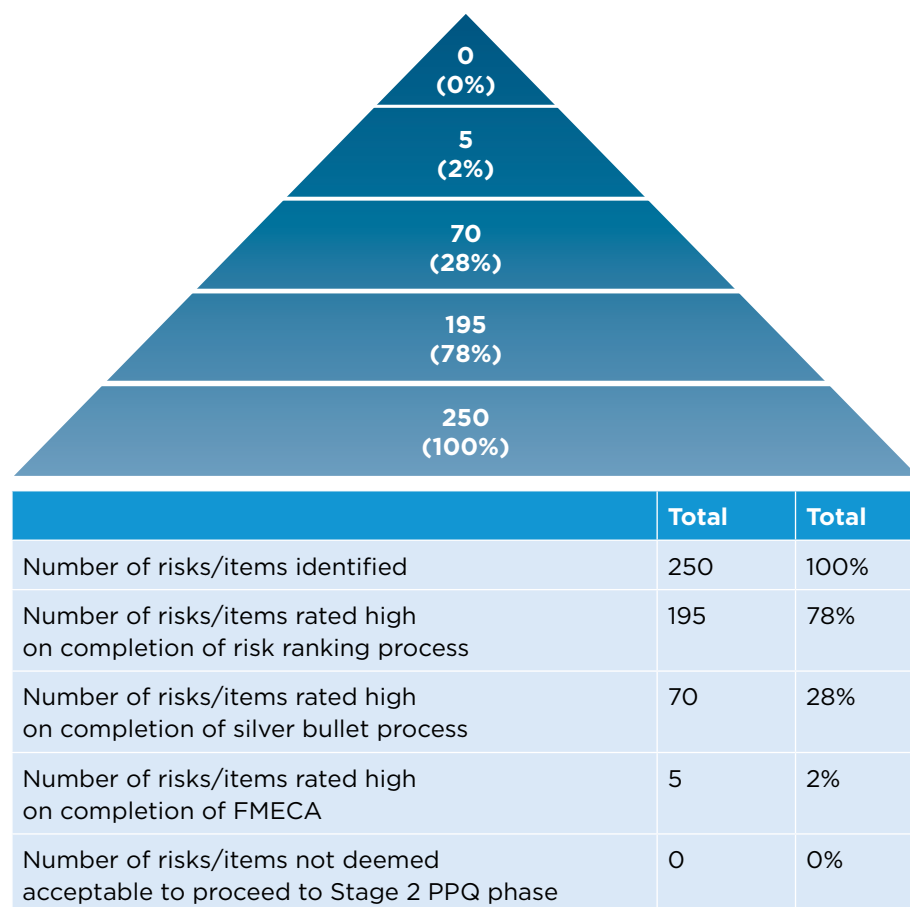
The framework was demonstrated to meet the user requirements suggested early in its development – it supported both parties in meeting their ICH obligations on risk assessment in tech transfers and confirmed the effectiveness of Alkermes' Quality Risk Management (QRM) approach. The transfer was deemed to be efficient, and the framework was found to be easy to use.

The tech transfer was deemed to be a success by both parties.

“All quality risks had been mitigated via the additional engineering studies and controls identified through the various iterations of the risk assessment.”

Lessons Learned

- Donor companies find it very reassuring to have a fully documented set of risks and responsibilities.
- By agreeing on the mechanism and areas of responsibility up-front, issues encountered during transfer can be speedily resolved.
- Alkermes' experience as this process evolved, is that improved up-front detailing of the assumptions that lie behind the risk assessment can reduce the number of risks that are dealt with via the silver bullet mechanism and thereby reduce the time associated with their assessment.
- Involving stakeholders on both sides from the outset is invaluable. The process and any differences in the processes between the donor and recipient sites are well understood long before the critical process qualification stage. This can make the review and approval of validation protocols, master batch records and change controls much more efficient.
- Dedicating time to the risk assessment is key – the first time a new process, piece of equipment or a commercial partner is involved in a risk assessment is time-consuming. Subsequent transfers can leverage the risk assessments developed in previous transfers. Eventually, a library of risk assessments covering all key unit operations is built.



Note – numbers rounded here for illustration purposes

Figure 2. Risk ranking process.



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