Risk Management in Biologics Technology Transfer

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*PDA J Pharm Sci and Tech* 2016, 70 596-599
Access the most recent version at doi:10.5731/pdajpst.2016.006718
ABSTRACT: Technology transfer of biological products is a complex process that is important for product commercialization. To achieve a successful technology transfer, the risks that arise from changes throughout the project must be managed. Iterative risk analysis and mitigation tools can be used to both evaluate and reduce risk. The technology transfer stage gate model is used as an example tool to help manage risks derived from both designed process change and unplanned changes that arise due to unforeseen circumstances. The strategy of risk assessment for a change can be tailored to the type of change. In addition, a cross-functional team and centralized documentation helps maximize risk management efficiency to achieve a successful technology transfer.

KEYWORDS: Risk management, Technology transfer, Biopharmaceutical processes.

1. Introduction

Risk management is an integral part of biologic processes technology transfer in industrial biologics manufacturing. Within a technology transfer project, multiple categories of risks are often discussed. Table I categorizes some typical risks encountered throughout a technology transfer.

The focus of this article will be on the management of comparability risks; manufacturing process, equipment, utilities, facility, and project risks are beyond the scope of this article. Comparability risks are differentiated from project risks, even though comparability failure will almost always result in a project timeline delay.

The circumstances of each technology transfer are almost always different, and so there should always be an evaluation of how to best use technology transfer management tools. As an example, this article will describe leveraging the Stage Gate Model for Technology Transfer to systematically assess and manage risks. Risks to comparability can be assessed iteratively at different stages and sub-stages throughout technology transfer. Figure 1 shows a stage gate model for technology transfer (see “Overview of Best Practices for Biopharmaceutical Technology Transfers” for more details).

Change is inherent (purposeful or otherwise) to technology transfers and often leads to comparability risks. This article discusses two types of changes: known changes/differences and unanticipated changes/differences. Assessments are performed on risks due to both known changes and unanticipated changes.

2. Known Changes

Known changes are often forced due to equipment or facility needs, such as scale-up of the manufacturing process or engineering constraints. Known changes may be unavoidable due to availability of identical raw materials, equipment, personnel, analytical instrumentation, or fundamental differences between the sending unit (SU) and receiving unit (RU) manufacturing utilities and facilities. Other known changes may be due to scale change or process improvement. Risk management for these types of changes can usually be easier to address because assessment of the changes can be performed upfront, when there is time to evaluate impact and plan for mitigations.

2.1. Assessment of Known Changes

Using the Stage Gate Model (Figure 2) example, there is an initial high-level risk assessment of the known differences between the SU and RU during the Process Transfer Initiation, Gap Analysis Sub-stage. Large differences are usually known at this stage of a tech-
nology transfer, thus a risk assessment can be initiated. Through this risk assessment, mitigation actions are identified and added to the project plans in the subsequent Process Transfer Planning Sub-stage. This risk assessment is then routinely updated throughout the entire project at subsequent stage gates to capture newly identified risks as well as update the remediation of previously captured risks.

Figure 3 is a sample flow chart of using the process description of the SU as the basis for risk assessing known changes. A draft of the RU process description can be first created based on the SU process description. Known changes at the RU can then be evaluated against the SU process description during a technical review to determine the risk. Also, if a product is manufactured at more than one facility, changes can be assessed not only against the defined SU, but all approved facilities’ manufacturing processes. Only accepted changes based on the risk would be incorporated into the RU process and included in the RU process description. Often, the RU will prefer to mitigate longer term risk of new processes by having these types of changes built in as optional, or reversible to an earlier proven state. However, this may not be possible if the change is regarded by the regulatory agency as a significant improvement over a previous process, so caution may be warranted in the action taken to mitigate risk of these types of changes.

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In the Process Transfer Stage (Figure 2), the risks derived from known changes (to process, equipment, facilities, etc.) can be assessed individually and holistically (aggregated) by system. It is preferable to perform these assessments before capital expenditure on equipment procurement or facility modifications.

### 2.1.1 Assessment of Individual Changes

Individual assessment of risk due to changes is often performed when design concepts for the facility, equipment, and process are first being developed during the Process Transfer, Planning Sub-stage. Once the design is finalized, the changes can be aggregated per system and the risk for the system can be holistically evaluated.

#### 2.1.2 Assessment of Aggregated Changes

Often there are multiple changes to an equipment system or process unit operation. In these cases it is often important to evaluate risk due to the interplay between the multiple changes to the one system. For example, a change in the thickness of a product preparation vessel wall and a change in the cooling medium (e.g., chilled water to ethylene glycol) used in the vessel jacket may be individually assessed to be low risk and not affect the process. However, when the changes are evaluated together, it may be realized that the difference in the wall thickness compounded with the different cooling medium could affect the temperature-controlling capabilities of the vessel and may have unintended impact to the product. As part of the known change risk assessment, the aggregated change risk assessment can be performed during the Process Transfer, Planning Sub-stage and throughout the subsequent stages of the technology transfer process.

<table>
<thead>
<tr>
<th>Risk Type</th>
<th>Description</th>
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<tbody>
<tr>
<td>Comparability</td>
<td>Leads to non-comparability of process or product between sending and receiving units</td>
</tr>
<tr>
<td>Manufacturing Process Risks</td>
<td>Risks to routine manufacturing, e.g., microbial contamination risks, operator error, etc.</td>
</tr>
<tr>
<td>Equipment, Utilities, and Facility Risks</td>
<td>Risks associated with equipment, utilities, or facilities failure</td>
</tr>
<tr>
<td>Project</td>
<td>Leads to delay in project timeline (often related to planning, resources, etc.)</td>
</tr>
</tbody>
</table>

### TABLE I

Types of Risks Associated with Technology Transfer
3. Unanticipated Changes

In addition to known changes, there will often be a number of unanticipated changes that occur. These unanticipated changes are usually small in scope due to the vigorous process of risk assessing known changes. Unanticipated changes may be discovered during Process Transfer Planning, Execution, or even Completion/GMP campaign Sub-stages and are risk-assessed as they arise. Unanticipated changes that are discovered during Startup, Shakedown, Engineering, or Process Performance Qualification runs of the Process Transfer Execution Stage may benefit from using qualified small-scale models (if available) to assess the risk.

3.1. Assessment of Unanticipated Changes

One strategy for commercial-to-commercial transfers is to risk-assess the unanticipated changes and then bundle the low-risk items into one change control evaluation. Changes that are discovered with higher risk are separated and assessed individually. A flow chart for this type of strategy is shown in Figure 4.

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**Figure 2**
Stage gate model with risk assessment.

**Figure 3**
Example flow for integration of planned changes to a process description.

**Figure 4**
Change control strategy for unanticipated changes.
4. Risk Management Structure and Organization

Organization of people and documentation is a critical aspect of risk management in technology transfer. Having an integrated technology transfer team structure allows all relevant functions to address and mitigate change in a timely manner and to escalate issues quickly. The example structure in Figure 5 allows cross-functional assessment of risk in a fairly rapid manner and provides links to the operations and quality groups for potential escalation of issues. As changes are not always predictable, the availability of cross-functional teams on a continuous basis is needed.

Risk assessment documents generally capture definition of risk and justification for controlling risk. Storing risk assessments in a centralized repository allows for efficient cross-functional cooperation because they are often initiated by process development or technical support groups and supported and approved by manufacturing and quality groups.

5. Conclusion

Risk management is an integral part of technology transfer that occurs throughout the technology transfer process. While larger changes are often well recognized and mitigated, smaller, unplanned changes can arise in a technology transfer and cause issues if there is not capacity to handle them. Evaluation, re-evaluation, addition of new risk, and documentation of change can be best managed by recognizing that it will happen and by having a cross-functional team and centralized documents in place to manage risk. Effective risk management will reduce the risk of a failure to produce comparable product during a technology transfer and help ensure success of the transfer.

Acknowledgements

The authors wish to acknowledge John Bowers (Merck) and other members of the BioPhorum Operations Group (BPOG) Technology Transfer workstream for their contributions to this article. Since its inception in 2004, the BioPhorum has become the open and trusted environment where senior leaders of the biopharma industry come together to openly share and discuss the emerging trends and challenges facing their industry. BioPhorum currently comprises more than 1200 active participants in six forums—Drug Substance, The Development Group, Fill Finish, The Technology Roadmap, BioPhorum IT Group, BioPhorum Supply Partners.
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