Quality Risk Management Issues

Neale Baldwin
Senior GMP Inspector
Manufacturing Quality Branch
Overview

1. QRM Inspection Examples
2. Key Issues Identified
3. TGA Expectations
4. Improvement opportunities
   - Process/Product Definition
   - CQA/CPP
5. Risk management
Issues identified at inspection

- In a number of examples of Change Controls reviewed, not all risks were identified, assessed or appropriate risk mitigation strategies implemented to ensure that the product would meet all critical quality attributes.

- Although the company had a current Quality Risk Management procedure in place, it was not clear how this was adopted in relevant parts of the Quality Management system, for example,
  - The change control risk assessment process was not based on the methods identified in the QRM SOP.
  - The impact assessment process defined in the Deviation management process was not aligned with the QRM processes identified in the company’s QRM procedure.
  - It was not clear where the QRM processes described in the QRM SOP were used as there was no examples provided to demonstrate its application.

- The risks of cross contamination was not fully addressed to ensure that residues would not contaminate subsequent batches other than from direct, product-contact equipment (i.e.. Did not consider cross-contamination from the area where multiple products were manufactured)
Issues identified at inspection

• For an API manufacturer, the company had assessed all product implicating risks as low as the likelihood of detection was high due to further processing steps (not within their control) was expected to detect any non-compliant product.

• There was no training associated with the application of Quality Risk Management processes and subsequently, risk assessments reviewed were either incomplete or inconsistently utilised

• The company had a risk register, however, there was limited examples recorded despite a number of completed risk assessments observed in multiple PQS processes.
Summary of Issues identified

Lack of integration of the QRM Policy/Procedure into the PQS

It is all good and well to have a well defined QRM Procedure, but if it is not clear how it is used or integrated in the PQS and it is not able to be explained at inspection then it would be reasonable to expect that it is not being used appropriately!

Particularly for OOS/OOT, Deviation, Change Control, Customer Complaints
Issues identified at inspection

- Poor definition of when to apply risk management processes
- Poor training with respect to use of risk management processes
- Incomplete identification, assessment and control of risk
- Inappropriate application of risk mitigation strategies
- Inappropriate acceptance of risk
- Incongruent application of risk management tools
- Lack of awareness of risk processes and their outcomes
- Poor assessment of effectiveness of risk mitigation strategies employed
- Complicated Risk Assessment processes that appear to be incorrectly applied and often not actioned
Lack of clear integration of Quality Risk Management Principles within relevant Pharmaceutical Quality System Processes

Lack of oversight/escalation of Quality Risks and there appropriate, timely mitigation
ICH Q9

Quality Risk Management (QRM) is a systematic process for the assessment, control, communication & review of risks to quality of the drug product across the product lifecycle

– The evaluation of the risk to quality should be based on scientific knowledge & ultimately link to the protection of the patient

– The level of effort, formality & documentation of the quality risk management process should be commensurate with the level of risk
TGA expectations

Written Policy (or Procedure)

- Identify that company’s approach to QRM
- Where in the PQS are these principles applied
- What methods are to be used (i.e. formal or informal)
- How Risk Assessments and their outcomes are documented & managed
- How these are communicated
- How mitigation strategies are applied
- How the effectiveness of mitigation strategies are assessed
TGA expectations cont.

Demonstrated implementation of QRM into PQS

- Linkage/consistency of PQS procedures where QRM is described to the QRM SOP/Policy
- Prospective risk assessment versus Impact assessment (and where/when used)
- Formal methods defined and where/when these are used
- Where and when informal processes are applicable (and how these should be recorded)
- Training of staff in QRM approach including formal processes
- Risk register (if/where applicable)
- Consistent use of QRM available in relevant PQS records
- Use in prospective activities (i.e. Change Control, Validation, etc.)
- Use in retrospective activities (i.e. OOS, Deviation, Customer Complaints)
For validated manufacturing processes

How can risk be assessed if the manufacturing process is not defined and critical aspects are identified?
Product/Process Definition

Critical Quality Attributes (CQA)
A physical, chemical, biological, or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality (ICH Q8)

Critical Process Parameter (CPP)
A process parameter whose variability has an impact on a CQA and therefore should be monitored or controlled to ensure the process produces the desired quality. (ICH Q8)
ANNEX 15
QUALIFICATION AND VALIDATION

Principle - It is a GMP requirement that manufacturers control the critical aspects of their particular operations through qualification and validation over the life cycle of the product and process.

Clause 5.7 - Process validation should establish whether all quality attributes and process parameters, which are considered important for ensuring the validated state and acceptable product quality, can be consistently met by the process. The basis by which process parameters and quality attributes were identified as being critical or non-critical should be clearly documented, taking into account the results of any risk assessment activities.
Process/Product Definition

Product Design/Development should aim to provide:

– Definition of Finished Dosage Form Specifications (or API)
– Key Manufacturing/Process stages
– Key in process Critical Quality Attributes
– Key in-process Critical Process Parameters
– Key Raw/Starting Material Parameters

➢ Process/Product Understanding identifies critical/non-critical activities for QRM
Risk Interpretation

Identified critical/non-critical activities assists in RA:
- Process/Product changes/Issues
- Equipment changes/issues
- Facility changes/issues
- Raw/starting material changes/issues
- Testing changes/issues
- Validation
Summary

MAKE SURE THE QRM POLICY/SOP IS INTEGRATED AND USED

NOT JUST A NICE DOCUMENT!