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# Commercial Manufacturing - Qualification & Validation-related GMP Deficiencies and Other Lifecycle Considerations

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# Topics for today…

- Key Lifecycle considerations as products move into Commercial Manufacturing
- Qualification, Validation & Change Management – Deficiency examples
  - Equipment & Facility Qualification
  - Supplier Qualification
  - Process Validation
  - Cleaning Validation
  - Change Management
- Some thoughts on Risk Review - A Key Lifecycle Activity often overlooked
  - Tips for ensuring such reviews add value

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# Key Lifecycle Activities

- Many references in ICH Q10 to the Lifecycle approach
  - The start of commercial manufacturing in the lifecycle of products is the focus of this talk

- Several important activities come into play at this stage:
  - The Qualification of Equipment & Facilities
  - The Qualification of Suppliers of Critical Starting Materials
  - The Validation of Commercial Manufacturing Processes
  - The Validation of Cleaning Processes
  - Managing Changes to the Initial Commercial Processes
  - Performing Quality Risk Management Activities - for a multitude of reasons
    - Process Improvement Initiatives
    - New Supplier Approvals
    - Change Control proposals
    - Deviations
    - Stability OOSs

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# Key Lifecycle Activities

- But serious deficiencies in all of these areas continue to be identified during Regulatory Inspections
  - This talk presents examples of some of those deficiencies

- The PQS model described in ICH Q10, coupled with the concepts of Q9 and Q8(R2), presents practical opportunities for companies to avoid such deficiencies.... How?
  - Q10 places an emphasis on key activities that, if applied correctly, can not only enhance the quality of medicines, they will drive innovation and continual improvement in the manufacturing processes producing those medicines, and they afford the potential for more risk-based regulatory approaches

  - The ICH Q10 model focuses on four key elements:
    - Process Performance and Product Quality Monitoring
    - CAPA Activities
    - The Management of Changes
    - The Management Review of Process Performance and Product Quality Monitoring

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# *Qualification & Validation Activities*

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# Qualification & Validation Considerations

- ICH Q10 states that the goals of commercial manufacturing activities include
  - achieving product realisation
  - establishing and maintaining a state of control
  - facilitating continual improvement

- Q10 states that the pharmaceutical quality system should assure that the desired product quality is routinely met, suitable process performance is achieved, the set of controls are appropriate, improvement opportunities are identified and evaluated, and the body of knowledge is continually expanded.

- Qualification & Validation activities are central to each of these areas
  - Q&V are important in establishing and maintaining a state of control, allowing for meaningful Process Performance and Product Quality Monitoring
  - Q&V support the implementation of continual improvement in equipment and manufacturing processes and lead to increased process knowledge

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# Inspecting Qualification & Validation Activities

- Controls and procedures relating to Qualification and Validation are reviewed closely during regulatory inspections

- Inspectors may spend a large proportion of an inspection in this area
  - During a five day general GMP inspection, one day or more may be spent on Q&V
  - Selected Q&V activities are also likely be reviewed when Inspectors are reviewing Change Controls & Deviation Reports

- Many deficiencies are identified in these areas
  - In the EU, they can often be classified as Major or Critical
  - An inadequate state of control is usually the common factor in such deficiencies
  - A lack of assurance in the continued suitability and capability of processes is the result
  - Sometimes recalls can result, and batch release must sometimes cease until the issues have been corrected

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# Deficiencies in Qualification & Validation

- Deficient Qualification and Validation Practices and Controls can demonstrate an ineffective PQS at a site
  - In the ICH Q10 environment, the effectiveness of the PQS is probably a pre-requisite to obtaining any kind of regulatory flexibility
  - See Annex 1 of ICH Q10 for details
- Many of the Critical GMP deficiencies which we have issued have related to deficient Qualification and Validation practices and controls
  - In one Critical Deficiency issued by the IMB, of the 105 individual points making up the deficiency, about 50 of those related to Q&V!
- A comprehensive, well resourced, risk-based and scientifically designed Q&V programme at a site, coupled with good change control, facilitates compliance in many ways
  - ➢ This will usually lead to satisfactory GMP inspections
  - ➢ Patients and animal well-being is protected

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# Equipment & Facility Qualification

## A major source of GMP deficiencies

- Poorly designed and understood HVAC systems & containment controls
- Deficient equipment qualification protocols
  - e.g. Lack of effective risk assessments
  - e.g. The complexity and criticality of equipment and systems are often not taken into account when designing qualification protocols
- Deficient approaches to periodic reviews of qualification status
  - e.g. Especially in relation to the Change Control history

- Often qualification activities are not sufficiently science or risk-based, and they can present risks to product quality

  - ***ICH Q10:*** *QRM is integral to an effective pharmaceutical quality system. It can provide a proactive approach to identifying, scientifically evaluating and controlling potential risks to quality.*

- See following slides for examples of deficiencies in this area

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# Qualification Deficiencies – Protocol designs

In a 2009 requalification of Tray Dryer X:

- No rationale was documented in the qualification protocol for running the dryer under pressurised conditions and for only over 6 hours, given that the routine drying processes were performed under full vacuum and for significantly longer periods of time (16 hours).
- No rationale was documented for the decision not to take all temperature data points into account when averaging the results, and only hourly results were taken and averaged.

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# Qualification Deficiencies – Protocol designs

- During the 2009 qualification of the interface between the QC LIMS system and the Electronic Batch Record system used by Production
  - No rationale was provided in the qualification protocol for the absence of any worst case condition testing or for any risk-based testing requirements.
    - For example, no challenge-type tests had been performed to ensure that the interface was working correctly when QC test results and batch disposition data were transferred from LIMS to the electronic batch record system and it was unclear whether these tests were required given the design of the system.

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# Qualification Deficiencies – Protocol designs

- In relation to the qualification of a particle size instrument:
  - The statement in the qualification protocol that there were no critical components or instruments in the analyser was not scientifically justified
    - Key components, such as the vacuum pump, the dry powder feeding unit and the stirrer mechanism (for liquid samples), were critical to the running of the analyser in order to obtain valid and reproducible results.
  - No testing was performed in the qualification exercise to check the correct functioning of the above key components of the instrument.
  - The testing performed during the qualification did not ensure that the typical use ranges of some key parameters were checked
    - The parameters for air pressure and material feed rate that were selected during the qualification exercise did not reflect routine use

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# Qualification Deficiencies - HVAC

- There were inadequate controls in place to minimise the potential for contamination and cross-contamination. For example:

  - Differential pressures were one of the primary means for containment throughout the facility, but there was no evidence that any operational qualification or calibration tests had been performed on the *Magnehelic* gauges for Building 1 of the plant, prior to production operations starting there

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# Qualification Deficiencies – Periodic Review

- In the 2010 review of the qualification status of Packaging Line 2:
  - The extent of change made to the line since the 2004 qualification had not been adequately assessed to determine whether any additional qualification was required
  - (A significant number of changes to the equipment had occurred in this time.)

- As of 2011, no periodic review of the qualification status of the IBC Washer in Production Building 2 had been performed
  - This equipment had last been qualified in 2001 and was in extensive use since then.

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# Qualification Deficiencies – Suppliers

- Nitrogen gas was extensively used in several processes, but the Nitrogen utility had not been qualified in any way to demonstrate its fitness for use...
  - And no testing of Nitrogen was being performed
  - In addition, the supplier of Nitrogen gas had not been evaluated by the company

- The majority of API starting material suppliers had not been qualified. Also:
  - No technical agreements were in place with any supplier
  - A significant amount of reduced testing was in place for almost all APIs

- The procedure in place for the approval of critical starting material suppliers did not require any trials or other production-related tests to be performed on the material before

- During the 2009 qualification audit of Company X (an API supplier), there was no documented evidence that the management of deviations and change controls were included within the scope of the audit.

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# Process Validation

**Process Validation is also a major source of deficiencies:**

- The number of batches included in the validation study was not justified
- The extent of testing performed is too low to demonstrate an adequately robust and capable process
- Little evidence that risk factors were designed into the validation protocol and no clear link between the protocol and any risk assessment exercise
  - This can result in a failure to identify all the important variables in the validation protocol
  - Sometimes the obvious ones are omitted
    - See EU GMP Annex 15… "*scope and extent of validation….*"
- Lack of any critical evaluation of the validation test results
  - See following slides for examples of deficiencies in this area

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# Process Validation Deficiencies

- The extent of validation testing performed to validate three process changes made to address content uniformity OOS issues (using sieved API, using a different grade of stearic acid and using revised blending time) was not formally justified
  - A significantly reduced level of Content Uniformity testing had been applied during the 2nd and 3rd batches and it was Content Uniformity problems that had led to the process changes.
  - There was no clear justification provided for the validation strategy that was adopted
  - Also, the protocol for this exercise provided no predefined criteria for the % Agglomeration test performed on the screened API lots used in the validation study
    - This was important because the Content Uniformity problems had been linked with API agglomeration issues.

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# Process Validation Deficiencies

- In 2010, following recent process validation studies performed on several strengths of X Tablets:
  - Seven batches manufactured between July and September 2010 had to be rejected for a number of different reasons
    - low assay blends
    - low tablet assay results
    - non-uniform tablet cores
    - low hardness results
  - But no assessment had been made of the validation status of the process given this high number of rejected batches within such a short timeframe.
    - ***This is an example of a poor use of knowledge management and process monitoring***

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# Process Validation Deficiencies

- The SOP on Process Validation did not address where CPPs were to be obtained from
  - The regulatory documentation referred to in the Validation SOP as the source of the CPPs generally did not identify which parameters were to be considered Critical and which ones were to be considered Key.

- In the 2010 validation protocol for a rework process on failed batches of API X:
  - The CPPs that were applied to this validation study did not reflect all of the parameters that were important in reducing the impurity of interest to acceptable levels
  - The absence of certain parameters from the CPP listing was not justified, such as the volume of IPA applied following centrifugation –
    - This was important in ensuring that the residual mother liquor in the filtered cake was adequately removed

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- ***Note:*** sometimes, it is not clear within companies where information on CQAs and CPPs for particular processes is documented

  - This illustrates deficient controls in relation to Knowledge Management

  - ***ICH Q10:*** ***Product and process knowledge should be managed from development through the commercial life of the product up to and including product discontinuation.***

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# Cleaning Validation

**When inspecting cleaning validation activities:**

- Sometimes cleaning procedures do not match what was validated
- Sometimes cleaning procedures for small but critical pieces of equipment are not validated
- Sometimes the calculated max. carryover limits have no scientific basis
- Sometimes analytical methods for rinse or swab samples are not validated
  - Especially important for LOD and LOQ
    - See following slides for examples of deficiencies in this area

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# Cleaning Validation Deficiencies

- In relation to cleaning validation:
  - There was no scientific basis for the selection of the carryover limit applied during cleaning validation activities, and neither batch sizes, material solubility, potency, toxicity nor pharmacological activity had been taken into account when determining such limits.
  - All of the cleaning validation samples taken to date were analysed using a TLC test method which had not been validated
    - and no Limit of Detection had been determined for the method.
  - The cleaning processes for small items of product contact equipment such as scoops and other utensils had not been validated
    - and items of this nature which had been cleaned were observed in production areas without being bagged or labelled as clean.

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# Cleaning Validation Deficiencies

- In the tablet plant, controls in relation to equipment cleaning were considered inadequate for the following reasons:
  - In the compression tooling room, the practice of cleaning different punch and die sets in the sonicating bath using the same cleaning fluid for up to ten punch and die sets was considered unacceptable, as it presented a significant risk of product cross contamination
  - No validation had been carried out on this cleaning method to ensure that product residue levels were acceptable after cleaning.
    - ***This is an example of a deficient use of science and risk-based approaches to cleaning and cleaning validation***

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# Change Management

**Change Management, being one of the four key elements of an ICH Q10 Quality Management System, has an important place within the lifecycle of a product**

- Many deficiencies are still identified in this area
  - Often, the risks presented by proposed changes are sometimes not identified or well managed
  - Quality Risk Management should be used to assess the potential impact of changes, this prevents Mis-classifying the change as minor
- See the following slide for an example of a deficiency in this area

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# Change Management Deficiency

- With respect to the change of blender in the Product X Capsules manufacturing process (from a Matcon IBC blender to a drum blender) following the deviation with Batch Y:
  - There was no assessment made of whether any process validation study was required to support the change, and this was not justified given the significant change in blending equipment that this change represented
  - There was no assessment made of whether any cleaning validation study was required to support the change, and this was not justified given the significant change in blending equipment that this change represented
  - There was no assessment made of whether the blending parameters used for the IBC blender were suitable for the drum blender (e.g. time, rotational speed, etc.)
  - There was no assessment made of there was any regulatory impact associated with the change.
- ***An example of a deficient use of science and risk-based approaches to Change Control***

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# *Risk Review – a key lifecycle activity*

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# Risk Review – a lifecycle process

**Risk Review is one of the key components of QRM as per ICH Q9**

***It is also a useful performance indicator in ICH Q10 when monitoring the effectiveness of processes within the Quality System***

- ICH Q9: Quality risk management is a systematic process for the assessment, control, communication and review of risks to the quality of the drug (medicinal) product across the product lifecycle.

**ICH Q9 - Risk Review**

- The output/results of the risk management process should be reviewed to take into account new knowledge and experience.

  - ***Problem :*** Risk Review is an activity that a lot of companies seem to struggle with

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# Risk Review - Some issues that arise during inspections

- When should the Risk Review be performed?
- What items should be reviewed?
- Is the Risk Review a new QRM exercise?
- Does every QRM exercise need to have a formal Risk Review performed?
- How many such Risk Reviews should be performed?

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# Tips for Performing Risk Reviews

**Tip:** It is useful to separate the Risk Review process into two distinct stages and to complete the first stage at the end of the original QRM exercise

- The first stage is to plan for the Risk Review during the QRM exercise
  - Identify and Document the specific items that should be reviewed, if any
  - Set a date by which the review should be carried out
  - Unplanned Risk Reviews are also triggered by unexpected events during the product lifecycle

- The second stage is to actually carry out the planned Risk Review
  - It may be a different set of people performing the review and they will need somewhere to start..... Stage 1 helps with this

- **Tip:** Put a real-time mechanism in place for individuals to make recommendations in relation to items they feel should be reviewed during the Risk Review stage for the process that was risk assessed in the original QRM exercise
  - ***This also helps ensure important knowledge about a potential risk is captured and not lost***

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# Tips for Performing Risk Reviews

**Tip:** Ensure the team is clear on the purpose of the Risk Review

- The Review is not a brand new QRM exercise on the same process/item
  - Its purpose is usually to evaluate the previous QRM exercise and its conclusions in light of the passage of time, taking into account process changes, new information and any new knowledge or experience gained
- It also lets one evaluate how well the previous QRM exercise reflects the current situation
  - This is so that one can determine whether the outcomes and conclusions from the previous exercise are still valid, or if they need modifying
  - This can be regarded as a continuous improvement exercise
- Risk Reviews can be a revisit of some or all elements of the previous QRM exercise
  - It is an opportunity to review, and to study in detail, any concerns or uncertainties that were experienced during the previous QRM exercise
  - For example…

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# Tips for Performing Risk Reviews

- For example:
  - The probability of occurrence of a specific cause of a Failure Mode was in dispute during the original QRM exercise
    - An average probability of occurrence rating was assigned
    - This means that the Risk that was estimated for that Failure Mode was in doubt
  - Experimental studies have been performed since the original QRM exercise and they present a more accurate estimate of the probability of occurrence
    - It will be beneficial to repeat that part of the QRM exercise during the Risk Review, taking this new knowledge into account
    - This allows one to obtain a more reliable probability of occurrence, and thus a more reliable risk estimate, for the Failure Mode

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# Tips for Performing Risk Reviews

**Tip:** Identify meaningful items to be reviewed during the Risk Review

- In addition to the items indicated by ICH Q9 that might impact the original quality risk management decision
  - *The results of product reviews, inspections, audits, change controls*
  - *Root causes from failure investigations, recalls, etc.*
- It is also useful to formally require the original QRM team to make formal recommendations to the Risk Review team for them to review specific aspects of the original QRM exercise at this time also
- For example, recommendations can relate to reviewing:
  - Specific Failure Modes that were discussed during the original QRM exercise but that were not considered important at the time
  - Specific Risks that were the subject of significant uncertainty or disagreement during the QRM exercise

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# Tips for Performing Risk Reviews

**Tip:** Other items that may usefully be reviewed during the Risk Review

- The Failure Modes that were risk-assessed during the previous QRM exercise should be reviewed
  - This allows one to determine how relevant those potential Failure Modes still are, and whether any new potential Failure Modes, not considered last time, should now be risk assessed

- For example, if the previous QRM exercise was performed on a new process, there may have been very little data to draw upon when identifying potential Failure Modes
  - *The passage of time now allows such info to be generated*
  - *The Risk Review step allows one to make use of experience, learning and knowledge gained over time (ICH Q10 – Knowledge Management)*
  - *Important new Failure Modes might be apparent that were not originally envisaged and which should be risk assessed now*

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# Tips for Performing Risk Reviews

**Tip:** Other items that may usefully be reviewed during the Risk Review cont'd

- Assess whether all of the key risk-mitigating controls identified during the original QRM exercise are still within their validated or qualified state
    - Also, assess the performance of the risk control measures that were implemented following the original QRM exercise
- Identify any required risk-mitigating controls that were not actually implemented
- Importantly, assess whether any of the risk control measures implemented following the previous QRM exercise led to any new Failure Modes or problems being introduced
- Compile, evaluate and interpret new trend data for the process (e.g. Control Chart data, CpK data, etc.) so that the original decisions about potential Failure Modes and their probabilities can be re-assessed

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# Questions & Discussion

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