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Process Validation – Examples of Deficiencies

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1. Poor controls in place for the identification of CPPs

- No procedure addressed the identification of Critical Process Parameters for manufacturing processes, and it was not documented from where these would be obtained when writing PV protocols

- In the PV of the Capsule X manufacturing process, blending parameters were determined to be critical, but the *homogeneity-of-mix* test was not classified as critical in the PV protocol, and this was not justified.

- In the PV exercise on the Y Tray Drying Process, no rationale was documented for why vacuum pressure and time were not considered CPPs
  - Only Temperature was considered a CPP in this process
  - But the process was required to be run under full vacuum over at least 16 hours

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2. Poor linkages between risk assessment activities and PV protocols

- No assessment was made of the validation status of the various controls in manufacturing process X that had been identified in Risk Assessment Y as being important from a risk mitigation perspective

- In relation to filling process Z, a HACCP exercise identified that a higher level of localised environmental monitoring was required when Intervention A was being made
  - But while this was deemed a *Critical Control Point* in the HACCP assessment, the higher level of localised environmental monitoring had not been put in place
  - And no validation exercise or other justification supported this decision

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3. Insufficient extent of PV testing performed

- The extent of testing performed to validate three process changes (sieved API, different grade of stearic acid and revised blending time) made to address Content Uniformity OOS issues with Process X was not justified:
  - A significantly reduced level of Content Uniformity testing had been applied during the 2nd and 3rd PV batches
  - It was Content Uniformity problems that had led to the process changes

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4. Lack of good science when defining PV acceptance criteria

- The PV protocol for the above Tablet X process provided no criteria for the maximum number of sticking events that could be accepted during the validation exercise to judge the process changes successful
  - This was important because the earlier Content Uniformity problems had been linked with a high number of tablet sticking events during compression
- This protocol also provided no criteria for the *% Agglomeration* test on the screened API lots used in the validation study
  - The reason for the *For Information* specification was not documented
  - This was important because the earlier Content Uniformity problems had also been linked with API agglomeration issues

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5. Poor critical evaluation of PV data

- During the validation of the API X manufacturing process performed to support the introduction of a new lot number of the Master Cell Bank:
  - The criterion that the HPLC impurity profile of the fermentation broth be equivalent to that obtained with three control batches had not been met
    - A new potential impurity peak was observed in 1 of the 3 validation batches, but the company had failed to detect this and it was erroneously concluded that the validation acceptance criteria had been met
  - The two other PV batches had significantly higher impurity levels than that control batches, but this fact was not adequately considered when assessing the results of the validation exercise

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6. Lack of good science used in designing PV protocols

- During the validation of the API fermentation process X to support the introduction of a new lot number of the Master Cell Bank:
  - No consideration had been given to the need to run a Photo Diode Array (PDA) UV scan during the chromatography to determine if there were any impurities present that absorbed at wavelengths other than 225nm
  - This was important as a new impurity was seen in validation batch 1
- During the PV on the process for API X, neither microbial nor endotoxin issues were addressed when determining batch homogeneity profiles
  - This was important given the high water content in the finished dried API, and given that this API was to be used in formulating a sterile drug product

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7. Insufficient sampling activities

- All potential worst case situations had not been addressed in the sampling plan for the validation of the Powder X process
  - The final sachets from the batch were not considered when sampling the product

- In the validation of an extended hold time (from 36 to 96 hours) for the X Tablets undercoat solution, no rationale for compositing the samples for microbiological testing was provided

- The sampling regime for Content Uniformity was different for each of the two batches studied and this was not justified:
  - For PV Batch X, 30 samples were taken (beginning and end of compression) For PV Batch Y, only 10 samples were taken

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8. Lack of review of validation status following the receipt of important new data

- Immediately following the PV of several strengths of Tablet X:
  - 8 batches had to be rejected for a number of different reasons (low assay blends, low assay and non-uniform tablet cores, low hardness)
    - 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
- The process for the 2mg Tablet strength had not been validated in almost 5 years
  - And no assessment was made during that time of whether any re-validation work is required
  - X change controls and Y process deviations had occurred during that period

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9. Actual manufacturing processes not supported by PV data

- During the 2010 PV work performed on the autoclave sterilisation cycle used with Process X:
  - The 15 minute sterilisation cycle that was permitted in the batch record had not been validated

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10. Poor use of concurrent validation

- In the most recent PV for Process Y, no summary report had been generated which assessed the reproducibility of the process
    - This was a concurrent validation exercise with three separate reports drawn up and each batch had been concurrently released

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Questions / Discussion?

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