Process Validation – Examples of Deficiencies

Kevin O’Donnell, Ph.D.
Market Compliance Manager

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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.
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.
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 2\textsuperscript{nd} and 3\textsuperscript{rd} PV batches

  • It was Content Uniformity problems that had led to the process changes
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 \textit{% Agglomeration} test on the screened API lots used in the validation study

  • The reason for the \textit{For Information} specification was not documented

  • This was important because the earlier Content Uniformity problems had also been linked with API agglomeration issues
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
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
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
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
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.
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
Questions / Discussion?