Challenges of Implementation of FDA Guideline on Process Validation

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- The items presented here reflect those of the presenter and not of Genzyme

Main Challenges

- The FDA Guidance make sense
- There are four main challenges
  - Technical Transfer of older products
  - Knowledge Accumulation
  - Stage 3 Continued Process Verification
  - Statistical Sampling

Technical Transfer of Older Products

- Companies have developed in depth Technical Transfer processes for new products
- Thoroughly investigate the new processes
- What about older ones that have to move to make room for the new processes?
- Most companies have a single tech transfer process

Technical Transfer of Older Products

- “It is essential that activities and studies resulting in process understanding be documented. Documentation should reflect the basis for decisions made about the process. For example, manufacturers should document the variables studied for a unit operation and the rationale for those variables identified as significant.”
- “Process knowledge and understanding is the basis for establishing an approach to process control for each unit operation and the process overall.”

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Technical Transfer of Older Products

- Difficulty comes from:
  - Development may not have been done well for older products
  - Maintenance of the Knowledge Data base
  - Interest in sending site giving information to receiving site

Technical Transfer of Older Products - Solutions

- Development may not have been done well for older products
  - Redevelop the process at the receiving site
  - In depth analysis of the existing process thorough documenting the process
  - Having technical person from the receiving site “live” at the sending site and focus activities on learning about the process

Technical Transfer of Older Products - Solutions

- Maintenance of the Knowledge Data base
  - Build it from
    - Batch records
    - Investigations
    - Annual product reviews
  - Begin developing as production continues

- Interest in sending site giving information to receiving site
  - Utilize a team comprised of technical individuals from both sites
  - Minimize “fear” at sending site

Knowledge Accumulation

- “Documentation is important so that knowledge gained about a product and process is accessible and comprehensible to others involved in each stage of the lifecycle. Information transparency and accessibility are fundamental tenets of the scientific method. They are also essential to enabling organizational units responsible and accountable for the process to make informed, science-based decisions that ultimately support the release of a product to commerce.”

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Knowledge Accumulation

- Difficulty comes from:
  - Multisite/multinational companies
  - Maintenance of the database
  - Multiple contributors

Knowledge Accumulation Solutions

- Creation of a Centralized Repository
  - Web based on intranet
  - Must be searchable
  - Must have common terminologies
- Keep it up to date
  - Process engineers responsible for gathering data and adding to the database
  - Include links to APRs
  - Include links to investigations
- Allow for multiple contributors (different sites same products)
- Still a challenge

Stage 3 Continued Process Verification

- “An ongoing program to collect and analyze product and process data that relate to product quality must be established (§ 211.180(e)). The data collected should include relevant process trends and quality of incoming materials or components, in-process material, and finished products. The data should be statistically trended and reviewed by trained personnel.“
- “We recommend continued monitoring and sampling of process parameters and quality attributes at the level established during the process qualification stage until sufficient data are available to generate significant variability estimates.“

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Stage 3 Continued Process Verification

- Difficulty comes from:
  - Deciding where to document the program
  - Continued sampling at the PQ levels

Stage 3 Continued Process Verification Solutions

- Deciding where to document program
  - Utilize current Annual Product Review program
  - Enhanced Annual Product Review program
    - More emphasis on equipment changes
    - Review of sample result variability
    - Ensure thorough statistical evaluation and not just of finished product release data

Stage 3 Continued Process Verification Solutions

- Continued Sampling at Performance Qualification Levels
  - Pre-plan the activity (protocol) before PQ/PV runs
  - Allow for changes in the number of batches (more or less)
  - Staff the lab
  - Plan for longer release times
  - “Revalidation” Activities
    - Time driven – Revert to standard sampling with rationale
    - Change driven – Same approach as for “new” process but may be less

Statistical Sampling

- “In most cases, PPQ will have a higher level of sampling, additional testing, and greater scrutiny of process performance than would be typical of routine commercial production. The level of monitoring and testing should be sufficient to confirm uniform product quality throughout the batch. The increased level of scrutiny, testing, and sampling should continue through the process verification stage as appropriate, to establish levels and frequency of routine sampling and monitoring for the particular product and process. Considerations for the duration of the heightened sampling and monitoring period could include, but are not limited to, volume of production, process complexity, level of process understanding, and experience with similar products and processes.”

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Statistical Sampling

- Difficulty comes from:
  - What are the expectations – no guidance

Statistical Sampling Solutions

- Establish was confidence level your company wants (greater the confidence (e.g. 95%) means more samples
- Establish the number of batches (3?)
- Be wary of using statistical techniques from other industries that sample/test differently
- Enhance your knowledge at small scale
  - Utilize “PAT” techniques
  - Utilize indicator tests for a component
  - Utilize other similar product information (ensure the rationale)
    - “Previous credible experience with sufficiently similar products and processes can also be helpful.”

Questions

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