Welcome to

CMC STRATEGY FORUM
ADVANCING BIOPHARMACEUTICAL DEVELOPMENT

July 18-19, 2016
Gaithersburg Marriott Hotel
Gaithersburg, MD USA
Validation Session

- Great talk on three validation stages of Process Design (understand source of variation and how to control them before locking the process), PPQ (where you look at type II risk, likelihood of releasing a lot that has failed attributes), CPV (where you look at Type I risk, likelihood of failing a good batch).
  - Control strategy driven by relative risk; Mitigation and control tied to level and type of risk
  - Importance of extended sampling to demonstrate homogeneity, understand source of variation and impact,
  - Various statistical approaches for trend analysis, for example use of tolerance interval, where the width is justified based on severity of risk
  - We heard setting CpKs after having at least 25-30 batch data
Validation Session

• We heard about setting specs tied to clinical experience, but that has the risk that CpK will never be greater than 1.
  - So we should be able to justify broader specs leveraging structure-function understanding, level of risk, type of attribute, etc.
  - A concern raised that if select specs based on manufacturing capability at one site where you don’t know source of variation at another site, that might constrain validation at a second site.
Legacy products session

• CPV:
  - Example from BMS on 3-level of data review: monthly at mfg level, end to end with cross functional life cycle teams deeper dive, and management level across products
  - Data visualization is king, helps you see if there are jumps to do further data analysis
  - Different trend analysis methods with specific application
  - Assay Variation Ratio (to assess contribution of assay variation to product data using RS)
  - Use of heat map for quick view of each site’s performance
• For DP monitoring, start with less (manageable parameters to investigate and build on it)
Legacy products session

- Interesting discussion on combo products, bringing legacy products to current GMP compliance
  - Start with Risk management plan
  - Design verification
- Scope of Work -HUGE
  - Starts with Stage 3 CPV
  - look at Quality System gaps
  - review history files, index them to build a story about design and controls
  - Biocompatibility
  - User-Needs requirement documents like QTPP of the combined system (in addition to device only package and product only package)
- Remediation activities
- Design verification traceability matrix
Numerous examples of deficiencies and 483s and what the regulators/inspectors look for

- Clear Message: Quality Unit needs to understand the process and product
- Quality Unit is your surveillance, they have to be involved in investigations
- Does the operator understand why they have to do certain things?
  - Managers/Management need to know what’s going on on the floor
- An SOP is not enough, it is the depth of understanding by operator, management, and Quality Unit
Legacy products session – Inspections/Compliance

• What are the recurring themes in inspections? What should sponsors prioritize?
  - QUALITY – how well are you investigating deviations? are you finding root cause? Are you extending the investigations to other products, other batches?
  - PRODUCT-PROCESS UNDERSTANDING
    - Is there adequate Quality Surveillance?
  - It’s not bad to have high number of deviations if you are tough on yourself (e.g. pulling a deviation on an alert limit), rather how well you address them
    - Lack of deviations is concerning!!!
Legacy products session

More discussion of specs:

• Case of removal of final testing with a lot of historical data, low risk, in-process analysis done, data reported by no specs (e.g. pH, osmolality, SDS-PAGE, etc)

• When can you stop having FIO –while FIO might be acceptable at IND for non-safety impacting attributes, you definitely need to put criteria by pivotal trials
  - The desire is to collect as much data (perhaps FIO) and then decide what to drop and what to put on release with acceptable criteria
Legacy products session

Barriers to process/assay improvement

- Takes 4 years to drop previous assay by the time of global approval
- Can we see a regulatory environment that enables faster implementation of assay improvements
- We heard in general companies are improving assays and processes to improve yield or decrease cost, etc
  - Good timing when you are making major changes, then in the context of new BLA you improve old items
- We heard biosimilars are pushing technology to improved processes and assays and formulations in some cases of legacy products.