Roundtable Sessions 1 and 2 - New Analytical Technologies Being Implemented in GMP Product Testing and Manufacturing – Focus on Regulatory Challenges

Facilitator and Scribe: Scott J. Berger, Ph.D. , *Waters Corporation*

Abstract:

The decision to move newer technologies into a GMP environment is often a complex interplay of perceived benefits and challenges. These benefits can drive greater efficiency of analysis, address product or process attributes not accessible to traditional analysis methodologies or respond to regulatory scrutiny of older methods that are limited in capability or robustness. The perceived challenges of implementing new technologies may include the implementation and operational costs, changes required in staff training and expertise, concerns with robustness of the newer technology, regulatory inexperience with the new methodology, linking historical product experience to results generated using the new approach, and concerns of replicating methods at secondary manufacturing or quality sites across geographies.

Discussion Questions:

1) What are key drivers for implementing new technologies into GMP operations at your company?
2) Are there any new technologies you have successfully deployed as GMP assays? Key Experiences?
3) Are there any new technologies you have been unsuccessful in deploying as GMP assays? Why?
4) What is the process for moving assays from development (assumption) to GMP Operations?
   When does this occur in development/commercialization?
   Who leads? Who needs to be convinced? Who ultimately decides?
   When to engage regulators to discuss these plans?
   Do assays ever change between FIO (For Info Only Assays) and Product/Process Spec?
   Experiences with the regulators (Emerging Technology Teams and Reviewers).
5) Do you rely on vendor interactions as part of transitioning technologies to GMP operations and engaging with regulators?
6) How do you deal with regulatory expectations for method lifecycle management when deploying newer technologies (that have technology lifecycles of their own) into GMP use?

Notes:

Recent technologies that have overcome barriers to now be more common in GMP organizations.

- iCIEF: Now mature, took 3-5 years to transition from Dev to GMP once decision is made.
  - IEX is not working for many ADC's.
  - Replaced IEX in many organizations.
  - Robustness long term still not fully established.
- RAMAN (Chemometrics, Glucose, Lactate, Cell Density, Titer)
- HPLC to UPLC (UHPLC)
- 1D SDS-PAGE to CE-SDS

- Technology travels with molecules Development to Clinical to Commercial

- FDA Comment: Don't be scared if new technology finds extra peaks over the old one, just use historical samples to show that they were always there, and you should be fine.
- Some new assays get added to GMP list because of regulatory questions and can happen even on older approved products undergoing process changes (Technology/Analytical Lifecycle).
- FDA Comment: We approve new methods/technologies that have not been implemented by an organization for years because of the delayed approval times from other regulatory agencies.
    - When you do finally implement the new assays, note this in your annual report.
- Recognize that there are Business Drivers and Technical Drivers that drive adoption. The best technologies may fail to advance due to lack of business justification.
- Technologies that are on cusp of making GMP transition (Desired?)
    - Desire Near RT Sterility/Viral Burden Testing
        - Some western regulators are encouraging, some international resistance.
    - In Process Cell Analytics
    - Reactor monitoring / Cell Culture monitoring/ Flow A280
    - MAM Attribute Monitoring
        - Big Challenge is that Import testing is seen as a barrier to wider QC deployment, as many geographies would be stressed to replicate. Waivers can be made?
    - MALLS (Light Scattering) – Technique finding more acceptance. Online MALLS monitoring is not evidencing as good a performance.
    - Rapid Glycosylation methods desired as offline testing delivers next day results.
    - Cell Therapies would benefit from Flow Cytometry/Sorting approaches for GMP applications.
- Training of Regulators in any new technology is critical to wider acceptance.
    - Technology Vendors and Sponsor companies should be proactive in this process.
- Drivers for New Tech: Better Data, Faster Turnaround, Cheaper, Address short shelf life products (e.g. radiopharm).
- Clinical QC is a pilot for new technologies.
- Need to define purpose of technology. FIO vs Deviation Warning vs Decision Making Tool
- Challenges to New Tech
    - Outsourcing to a CXO not equipped to support (lag before ROI allows CXO CapEx)
    - Compendial methods are hard to ignore.
    - Regulatory scrutiny / Different agencies
    - Lack of industry driver to broadly support change (e.g. HCP)
    - Lack of Analytical People in Mfg/QC (e.g. MAM), Need to Upskill/Train Analysts
    - Automation of data analysis is efficient, but any manual interventions raise flags for reviewers/auditors (e.g. Peak Integration has long been this way)
    - SW validation can be treacherous – benefit of support of instruments by major CDS/SW vendors that have compliant-ready platforms.
- Best Practices: Extensive paralell operation of old and new tech/assays
    - Historical samples, stress samples
    - May extend into post-approval batches, if limited data historically (ROI concern)
    - Do as FIO until change approved to avoid risk of assay failure impacting batch release.
    - What if new assay (as FIO?) shows a true fail but old assay is ok – hold batch?
- Do Platform Methods discourage "out of box" thinking?