



Establishing Process Independent Analytical Testing Strategies During Process Development

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Abstract

The diversity of worldwide supplier capabilities reflects importance of leveraging an analytical testing strategy early in a program as part of the manufacturer selection process for raw materials, intermediate and final products. This should include a fit for use assessment including an assessment of analytical controls to ensure overall product quality compliance and for historical data. At earlier clinical stages of development striking a balance between pricing, technical capability, experience, and project timelines is critical. Cost and timing are often primary selection criteria for contract manufacturing organizations. However, this does not preclude a critical assessment of the overall route of manufacture and the quality control methods of raw materials, intermediates, and final product. HPLC methods while commonly used, are specifically developed for the manufacturing process and intermediates that are produced. The integration of process independent methods such as NMR, MS ICP, and NIR as manufacturing process control and product release methods provides a means to establish release specifications that can detect impurities from unexpected sources. H-NMR recently was established as a technique to test Heparin active pharmaceutical ingredient. Due to cost and timing the manufacturing process and supplier network for Phase 1 and Phase 2 clinical supplies are often not scalable or commercially viable. Therefore, robust process and release analytical controls are critical to assess the overall purity and potency and process history. These controls provide a clear assessment of the formation and fate of process impurities, are critical to establish product integrity, and establish a basis for future process development. HPLC methods while very specific for the manufacturing process, require revision as the process changes. The development of a process independent analytical strategy is better suited to assess product quality and consistency as the manufacturing process evolves. The globalization of the manufacturing supply chain requires analytical procedures that supplement traditional process dependent analytical strategies with methods that are process independent. NMR, MS, ICP and NIR provide a means to fingerprint raw material, intermediates and final products. These data establish a historical foundation for programs that meet final regulatory approval as commercial products.

Introduction

FDA's emerging Quality by Design (QbD) guidelines provides the pharmaceutical industry with increased self-regulatory flexibility while maintaining tight quality standards. This is accomplished through the use of 1) a Design Space to establish the quality standards, 2) the use of Risk Assessment to define the quality standard working space and 3) the utility of Process Analytical Technology to monitor and adjust those standards. Pharmaceutical manufacturing is an inherently complex process made more so by diversity of therapeutic agents biological and chemical, natural and synthetic sources and a global economy. QbD concepts should be made early in the development process. Considerations of critical quality attributes of new drug products should include sources of raw materials and intermediates and container closure systems. Supply chain considerations should include QbD principles for the selection of raw material and intermediates vendors as well as the overall process for the manufacture of active pharmaceutical ingredients and drug product. The use of process independent methods to verify compliance with design space quality standards is discussed. The utility of mass spectrometry and nuclear magnetic resonance spectroscopy as viable tools to broadly ensure compliance is discussed. These sophisticated techniques compliment compendia methods such as residue on ignition, metals testing by ICP emission spectroscopy, and residual organics by gas chromatography.



Risk Management

Pharmaceutical Quality System Mechanism Based Control Strategies

- Ensure a state of control is maintained: provide assurance of the continued capability of process and controls to meet product quality.
- Identify areas for continual improvement to understand and reduce process variability.

Q8 Pharmaceutical Development

- Product Quality and performance achieved & assured by design of effective and efficient manufacturing processes.
- Product specifications based on mechanistic understanding of how formulation and process factors impact product performance.

Q9 Quality Risk Management

- PD is basis for risk management based on process and product understanding.
- Product specifications based on mechanistic understanding of formulation and process factors that impact product performance.
- Process Risk: Critical Quality and Process attributes identify the risk.
- Environmental Risk: Contractors & Supply Chain, materials, shipping, etc.

PQLI Control Strategy Model

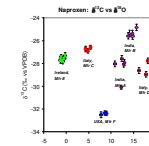
- 1: Identify Critical Quality Attributes:
- Implement control strategy based on Target Product Profile
- 2: Controls to Enable Product CQAs to be met include material attributes & components, raw materials, starting materials, excipients, & packaging materials.
- 3: Analytical Engineering & Other Control Methods. PAT (include process and control models), Analytics (off-line, at-line, in-line, on-line). Automated & manual controls

Process Independent Control Strategies

- Engineering a risk based analysis with decision based quality controls including chemometric analysis of process and production data.
- Includes establishing controls of external suppliers for incoming materials and other manufactured product.
- General controls based on material characterization: ICP-MS, GC-MS, ROI.
- Sophisticated controls based on molecular structure: 2D-NMR, MS, ICP, PXRD, NIR, IR.
- Isotopic Profiling: Techniques are well established to characterize the chemical history of a compound, the technique includes Isotopic ratio mass spectrometry (IRMS) and Isotopic Ratio NMR. Recent advances in include the use of ¹³C NMR to provide a quantitative assessment of batch history. Continued advances in data acquisition optimization and chemometrics may afford the proactive use of these sophisticated molecular fingerprinting tools to supply chain characterization.

References

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- 6.



IRMS bivariate isotope ratio graph illustrating manufacturer-specific isotopic composition