Shipping Qualification

Challenges Faced by Manufacturers in the Cold Chain Transportation and Different Scientific Approaches adopted

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Outline

- Global Trends
- Brazilian Transport Qualification regulatory requirements
- Model Document
- Qualification Structure
- Allowed Excursions
- Industry Collaboration
Global Regulatory Trends

• Good Distribution Practices (GDP) - Overall requirements increasing over time
  – Many countries/groups have issued GDP guidance
  – Some authorities mandate use of temperature monitoring
  – Shipping process and qualification receiving more attention during inspections

• Despite increasing operational requirements, submission requirements have remained steady in major markets
  – In our experience, there has been no significant change in submission requirements for Canada, Japan, European Union, United States

• Overall, increasing safety and security of drug transport while keeping submissions simple is a benefit to industry
  – This supports manufacturer’s ability to adapt programs with greater efficiency
  – Detailed review of shipping qualification can take place during a visit to a manufacturer’s site
Brazilian Regulatory Changes

• ANVISA has required more detail in recent years
  – Very detailed questions about shipping qualification

• Internal Response
  – Create regulatory submission model document to meet all requirements (which is being piloted)
  – Create qualification document templates to ensure all required data is captured

• Detailed submissions make it easier to verify compliance prior to approval
  – Disadvantage
    • Raises barriers to innovation due to perception of risk making post-approval changes
    • Increases complexity and cost of change
    • We believe it is better to review some data during site inspection (e.g. raw temperature data)
Submission Model Document

• Overview of product supply chain from Drug Substance to Finished Drug Product
  – Include locations, shipping method used, required temperature, travel distance, shipping duration, state of manufacture (e.g. Drug Substance, Bulk Drug Product, Finished Drug Product)

• Description of shipping systems, name of system, refrigerant type

• List of all qualification documents

• For each Operational Qualification - OQ and Performance Qualification - PQ
  – Description of study, routes used, routes bracketed
  – Seasonal conditions (looking for worst-case anticipated extremes)
  – Acceptance criteria
  – Minimum / maximum load of qualification vs. normal shipments
  – Number and location of temperature monitors in qualification and normal shipments
  – Data summary: study duration, high/low temperatures, maximum time without temperature excursion, worst-case location, ambient temperatures
  – Justification for worst-case test factors, product bracketing and anticipated excursions
    • ANVISA expects shipping systems to support product label requirements with very low excursion rates. But if you perform concurrent PQ you may see an occasional excursion that may be permissible with stability data. Such excursions in practice must be uncommon.

• Include copies of all protocols and reports with submissions
Qualification Structure

• The simplest format would be to have 1 OQ and 1 PQ for each shipping system
  – OQ must support anticipated temp in Brazil
  – PQ should ideally capture shipments into Brazil

• Build templates to ensure all applicable submission requirements are in your documents
  – Include science based rationale to support worst-case test strategy; this is commonly included in submissions to Canada, United States, European Union, Japan

• Everything needed in the submission should be summarized in the report for ease of verification

• Some reviewers have voiced a preference for qualification w/o excursion
  – This is possible with “middle-of-the-road” qualification studies
  – This cannot always work with worst-case shipping studies (e.g. per PDA TR 64)
  – A worst-case PQ tests a system near the boundary of anticipated worst-case performance. In such a test, it is expected that some excursions may occur. With the right monitoring strategy, you will be able to evaluate the product quality of the load and avoid unnecessary losses.
  – Should this occur during a PQ, be transparent about the data, support it with stability data, and demonstrate that your monitoring strategy is adequately mitigates risk
Allowed Excursions

• In our experience, many regulators accept excursions during worst-case testing and operations
  – Must have supporting stability data (e.g. PDA TR 53, ICH guidelines)
  – System must be maintained in a state of control
  – Maintain inherently low excursion rate
  – Ensure ability to detect and resolve problems
• Challenges with shipping systems that allow excursions by design
  – One system was initially seen as not qualified (later given OK) due to excursions during worst-case PQ
  – Multiple request and response cycles were needed to fully understand what was needed
  – Current state of our understanding with ANVISA requirements
    • Describe process to control product quality (e.g. monitoring)
    • Provide stability data
    • Demonstrate that product in submission is stable enough to tolerate the allowed excursion
    • Process must routinely operate without excursions
    • Excursions can be allowed occasionally if stability testing and controls are in place
Industry Collaboration

• Parenteral Drug Association (PDA) & Food and Drug Administration
  – PDA Science Advisory Board “is composed of a diverse group of experts drawn from industry, regulatory agencies, and academia… The SAB guides and supports the development of Technical Reports” and other documents.*

• Here are a few guidelines have been published via industry/FDA collaboration

• We support industry collaboration through this type of consensus building process

Summary

• There is a clear trend towards greater control in the pharmaceutical supply chain
  – Manufacturers need flexibility to adapt to change and drive improvements
  – Focusing submissions on key information and leaving data review to inspections would create an ideal synergy

• Tips to succeed
  – Focus on building a system that uses science-based decisions for managing quality attributes including stability
  – Organize your qualification studies to collect and easily present all relevant information
  – Leverage existing guidance from PDA, ICH, or other organizations when needed
Special thanks to Chris Renz
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