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Gaining Agreement With FDA On A Simplified, Rational Package And Shipping Qualification Program

Mid-West Regional Conference 23Oct2018
Clear Work Plans
Stable Job Environment
Work-Family balance
Where else can we make as big a difference?
Step back to 1994

- The Sony PlayStation changed video games forever
- The world's first smartphone, the IBM Simon, goes on sale. We have to wait another 13 years for the Apple IPhone
- QR code invented by Japanese company Denso
- Jerry Yang and David Filo create "Jerry's Guide to the World Wide Web", a hierarchically organized website. We know it as Yahoo
- FDA approves “ReoPro” (second approved mAB)
In 1994

- mAbs had promise but no commercial results
- Regulatory agencies shocked by Centoxin
- mAb filings lacked a pathway for approval
- Limited stability data outside of 2-8 °C
In 2018

- Regulatory Agencies have over 80 approved mAbs
- mAbs are the fastest growing segment
- Some companies have found a pathway
- But others...
Why are there...

- Submission Issues
- Information Requests
- Audit Findings
Keys for Success

- Create a story
- Start with the BLA section(s)
- Break your processes into work streams to form a coherent program
- Think of a spear!
This Spear Is A Tool, But It Is Meant To Inform

- How many times have you copied from previous filings?
- How many times is the BLA section THE LAST thing that’s drafted often under a deadline?
Control the things you can control; Demonstrate that the product can withstand the rest.

Credit to: Anthony Mire-Sluis CASSS CMC Forum 2015
Discussion

- Is The Process Defined?
- Consider This The Start Of A Distribution Validation Master Plan
- Do All Internal Stake Holders Understand & Buy-in?
Shipping everything everywhere is not a scalable solution

Begin simulated shipping prior to Phase 3 Clinicals
Control the things you can control; Show that the product can withstand the rest.

- Secondary/Tertiary Packaging and Handling procedures must:
  - Protect the product from temperature, humidity and light

- Product as formulated and filled must:
  - Resist degradation from shock, vibration, pressure
PDA & Guidance Documents

- PDA TR 53, Stability Testing to Support Distribution of New Drug Products
- ICH Q9, Quality Risk Management
- ANVISA Guide No. 02/2017, Guide for Biological Products Transport Qualification

Not Much Guidance…
It is unclear how the conditions used in the simulated transportation study as listed in Table “X” (Section 3.2.P.3.5 – Shipping Validation), relate to real-time shipping conditions and whether the simulated studies would be appropriate to support your DP shipping validation.

Simulation testing using a sequence (e.g., vibration followed by low pressure) would not generally be appropriate to represent the real-time shipping conditions, because the contributing factors that could potentially impact product quality during shipping may occur concurrently, (e.g., vibration and low pressure during air transport).

To support DP shipping validation, provide detailed information (e.g., vibration, atmospheric temperature and pressure) on the transport testing profile used in the simulation studies for bulk and assembled PFS, and provide a justification for the simulation conditions tested.
What is the FDA Saying About Product Transport Qualification?

- The “standard” ASTM-4169 testing may be suitable for some package testing, but when trying to replicate real world shipments of drug product:
  - The exposure times to vibration are too short and not representative
  - Shock exposures are not representative
  - Low pressure exposures are not representative

- The sequential application of the hazards are not representative

Testing must demonstrate that the product can withstand real world shipments

The proof must show that the post shipped product retains and is the same as unshipped product

Leading companies have recognized this and have adjusted their testing protocols
Discussion…

- Has this type of IR been shared within your company!

- If so, how has it changed your process?
Area of focus

- **Non- Product Specific**
- **12 Step Process**
- **Documents Process Capability**
## Key documents have been authored since PDA TR 39 was published in 2007

<table>
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<tr>
<th>Date</th>
<th>Document</th>
<th>URS</th>
<th>Identify Supply Lane(s)</th>
<th>Identify Shipping Solutions</th>
<th>Risk Assessment</th>
<th>Qualification Plan</th>
<th>Control Strategy</th>
<th>Design Qualification</th>
<th>Operational Qualification</th>
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Notes:
- 1- implicit reference
- 2- optional
- 3- URS - product/market centric

*General note: functional specifications should refer to shipping solutions*
Shipping Qualification Process

Proposed Practice

Current PDA TR 39

Verification to URS

- URS
- Identify Supply Lane(s)
- Identify Shipping Solution(s)
- Draft Control Strategy
- Qualification Plan

Product Knowledge

Risk Assessment

- Design Qualification
- Operational Qualification
- Performance Qualification

Process Design

Process Qualification

- Qualification Plan Complete
- Final Control Strategy

Ongoing Process Monitoring

Continued Process Verification

Verification to URS

Product Knowledge

Risk Assessment

- Identify Product, Stability Data, Mode of Distribution, and Temperature Sensitivity
- Identify Primary Package
- Consider Product Stability Profile
- Consider Transportation Process Flow
- Consider Secondary Package, Tertiary Package, Ancillary Components & Systems
- Develop Requirements, Document Component Specification Based on a Standard (e.g., ISTA)
- Perform Design Qualification(s), 1, 2 (vs. a Temperature Profile)
- Develop OQ and PQ Protocols
- Perform OQ Testing
- Perform PQ Testing
- Develop and Implement Training for Participants and Stakeholders
- Develop & Implement Quality Systems
- Audit the Distribution Chain
- Implement the Distribution Process
- Regulatory Perspective
- Monitor Performance (3)
Twelve Steps

1. Process Map/Value Map
2. URS
3. Candidate Container Cost Review (total delivered cost)
4. Risk Assessment
5. Container Selection
6. Lane Profile Analysis – use ISTA
7. OQ protocol & report or Assessment
8. Site readiness, facility, personnel, procedures <change control starts here>
9. Procedures in place (drafts are acceptable)
10. PQ protocol & report
11. Finalize Procedures
12. Periodic Monitoring
Process Map/Value Map

- Quantities Of Product
- Total Delivered VALUE
- Total Delivered COST
- Origin, Inter Node Points, Destination Defined
- Durations And Operations Defined
- Communication Tool Within Company
PQ protocol & report

Purpose: Ensure successful Tech transfer to site(s)

Performed by:

Reviewed by:

PQ Protocol confirms:
- OQ Report Available
- Procedures conforming to OQ report
- Facilities
- Specifications
- Ship Preparation
- Trained Operators
- Overall Performance in terms of time and temperature

PQ different in structure than an OQ!

Sometimes executed with placebo- but a caution with Customs!
Periodic Monitoring

- Common expectation- But this data goldmine is frequently ignored
- Defines Process Capability
- Use as an input to the simulated product exposures.
Completed

Now the task is to share your “state of control” with regulatory agencies.
The opening of section 3.2.P.3.5.3 Shipping Validation should contain an overview of your work streams.

Of primary interest is how well you understand the product and how the transport processes might affect the CQAs.

A mention of how the studies relate to your risk assessments and how it translated into your dVMP is helpful.
VMP

- The dVMP should be a smooth transition from the PV section of the BLA.
- The work stream visual helps in the transition
- A good rationale as to why there is a difference between product specific studies and process specific studies needs to be in place
- Some companies choose to use a structure of “Main Body” for process specific and “Addendum” for product specific work streams
The Most Important Slide!

- Now that you have a plan, you have a chance!
- The regulators have accepted properly executed transport simulation studies to compliment (not fully replace) real world shipments!
- Negotiate your approach with enough time built in so as to execute any requested studies without affecting the timeline!
Define the Plan
Gain Buy-in From Regulators
Execute
Be Happy!
Thank You

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