Temperature Risk Management for the Pharma Supply Chain

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IGZ – De Nieuwe GDP Guideline
Nieuwegein, 02-Sep-2013
Supply Chain

**Flow of Goods, Services, Cash and Information**

**Goal:** Maintain product quality, safety and efficacy by preventing product adulteration, counterfeiting, theft, and diversion.
Agenda

- Parenteral Drug Association (PDA)
- Critical stages in Temperature Controlled Distribution Management
- Risk Sources in the Supply Chain
- Case studies
- Summary
Parenteral Drug Association (PDA)

• Not for profit organization founded 1946
• International membership of 9500:
  • 1000 are active in task forces, chapters, interest groups and committees
• PDA is an influential voice and leading technical organization in the field of parenteral science and technology:
  • Applied Sciences: manufacturing, aseptic processing, process engineering/validation, biotechnology, microbiology
  • Quality & Regulatory: regulatory compliance (GMP), quality systems, supply chain, cold chain (GDP)
• Conferences / Workshops / Training
  • Pharmaceutical Cold Chain Integrity: 8-11 October 2013, Berlin
• Monitor Global Regulatory Activities:
  • Focus on Regulatory Agencies in EU, USA, Japan
  • ICH, PIC/S, EP, USP, WHO
  • Influence Global Regulatory Policies
• Meetings with EMA, FDA, PIC/S
  • Promote science – based regulations
  • Comments on draft guidelines
• Websites
  • PDA: http://www.pda.org/
  • PCCIG-EU: https://europe.pda.org/index.php?n1=&n2=702&n3=703


Problem:
- High complexity in the distribution network.
- No standard approach to execute a risk assessment for temperature controlled distribution.
- No guideline for either the shipper, logistic service provider (LSP), carrier and customer.

Objective:
- To develop FMEA examples.
- To develop a guideline that sets out the methodology to execute a risk assessment and to control risks in temperature controlled distribution for shipper, LSP, carrier and customer.
- To develop training material.
Risk Management for TC distribution

December 2009
- FMEA Temperature Controlled Truck
- FMEA Ocean Reefer Container
- FMEA Active ULD
- FMEA Thermal Packout by Courier
- FMEA Thermal Packout by Air

June 2010
- FINALIZED FMEA’S

January 2011
- Draft Risk Guideline
- Draft Exception Management Guideline

April 2011
- Risk Guideline for PDA PCCIG review

June 2011
- Risk Guideline for PDA Advisory Board review

September 2012
- Publication Technical Report 58
1. Introduction
2. Glossary of Terms
3. Temperature Controlled Distribution Management
4. Risk Assessment
5. Risk Control
6. Risk Review
7. Appendices
   - Five FMEA examples with key scenario information, process flow map (swimming lanes), FMEA rating table, FMEA results and recommended actions.
   - Incotermes
8. Additional Reading
9. References

PDA website: https://store.pda.org/ProductCatalog/Product.aspx?ID=1772
The ultimate goal of managing the risk in temperature controlled distribution is to make risk-based decisions to:

- preserve the quality, safety and efficacy of the product
- understand the distribution process
- reduce risk
- understand residual risk
- improve the effectiveness of the process

ICH Q9: The protection of the patient by managing the risk to quality should be considered of prime importance.
Temperature-Controlled Distribution Management

1. Requirements
   - Regulation
   - Product stability
   - Transport

2. Design & Qualification
   - Store
   - Container
   - Monitor
   - Database
   - Lane

3. Quality Management System
   - SOP
   - Training
   - Maintenance
   - KPI

4. CAPA Management
   - Deviations
   - Complaints
   - Audit
   - Trend

5. Change Control
   - Supplier
   - Shipper
   - LSP / Carrier
   - Customer
ICH Q9 - Quality Risk Management

- Quality risk management is a systematic process for the assessment, control, communication and review of risks to the quality of the drug (medical) product across the product lifecycle.

- **Risk**: Combination of the probability of occurrence of harm and the severity of that harm.

- The protection of the patient by managing the risk to quality should be considered of prime importance.

- Product quality should be maintained throughout the product lifecycle such that the attributes that are important to the quality of the drug (medicinal) product remain consistent with those used in the clinical studies.
Temperature Risk Management

Temperature Controlled Distribution Management

1. Requirements

2. Design & Qualification

3. Quality Management System

4. CAPA Management

5. Change Control

Quality Risk Management

Risk Assessment

Risk Control

Risk Review

Risk Assessment
Let’s define the Risk Sources!
Equipment and its components must be qualified/validated to eliminate and to reduce the risk of failures.
1. Pre-shipment
   - Planning
   - Procedures / SOPs / Process flows
   - Risk assessments
   - Contingency plans
   - Equipment qualification/validation
   - Packout assembly
   - Export documentation

2. In-transit
   - Loading/unloading transport vehicle
   - Transit nodes
   - Cargo handling processes
   - Communication processes
   - Custom inspection/clearance

3. Post-shipment
   - Roles and responsibilities towards temperature excursions
   - Storage of the goods
   - Inventory management

Application of Lean Six Sigma drives continuous improvement of processes and reduces failures.
Risk Sources – People

1. Skilled people
   – Knowledge, experience and understanding of equipment, processes and external factors.

2. Unskilled people
   – No or limited knowledge, experience and/or understanding of equipment, processes and/or external factors.

3. Bad actors
   – Skilled or unskilled people who on purpose mislead others and/or mistreat products including theft, counterfeiting and exposure to extreme temperatures.
Types of Human Error

1. Misunderstanding – Teach your written policies and procedures repetitively
2. Forgetfulness – Create a checklist or a Poka Yoke
3. Wrong identification – Mark, label, color, etc., for easy recognition
4. Lack of experience/skill – Improve your hiring or training systems
5. Willful ignoring of rules or procedures – Hold people accountable
6. Slowness – Remove bottlenecks; create standards of performance; measure results
7. Inadvertent or sloppiness – Apply an improvement methodology
8. Lack of standardization – Reduce and simplify; create procedures, templates, etc.
9. Intentional/sabotage/not caring – Warn or terminate the person immediately
10. Surprise – Unexpected, infrequent and random causes are more difficult to eliminate

Source: http://www.boxtheorygold.com/blog/bid/21820/Business-Systems-Dramtically-Reduce-Human-Error
Risk Sources – External factors

1. Environmental factors
   - Natural disasters
     • Storms
     • Flooding
     • Bush fire
     • Earthquake
     • Volcanic eruption
   - Extreme cold / hot weather
   - Diseases / pandemic

2. Geopolitical factors

3. Economic factors

4. Technological factors
   - Power supply
     • Power failure
     • Power surges (temporary increase in voltage in power lines)
     • Brownouts (power falls below the given amount from the utility)
     • Load shedding (rotating the availability of electricity between all customers)

Contingency plans are critical to handle external risk factors.
Risk Sources – External factors

Seasonal variation

Daily temperature variation

Altitude (-6.5 °C per 1000 m)

Sun insolation versus latitude
### Risk Sources – External factors

Disruptions most likely to provoke significant and systemic effects on supply chain or transport networks.

<table>
<thead>
<tr>
<th>Category</th>
<th>Risk Factor</th>
<th>Probability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Environmental</td>
<td>Natural disasters</td>
<td>59%</td>
</tr>
<tr>
<td></td>
<td>Extreme weather</td>
<td>30%</td>
</tr>
<tr>
<td></td>
<td>Pandemic</td>
<td>11%</td>
</tr>
<tr>
<td>Geopolitical</td>
<td>Conflict and political unrest</td>
<td>46%</td>
</tr>
<tr>
<td></td>
<td>Export/import restrictions</td>
<td>33%</td>
</tr>
<tr>
<td></td>
<td>Terrorism</td>
<td>32%</td>
</tr>
<tr>
<td></td>
<td>Corruption</td>
<td>17%</td>
</tr>
<tr>
<td></td>
<td>Illicit trade and organized crime</td>
<td>15%</td>
</tr>
<tr>
<td></td>
<td>Maritimo piracy</td>
<td>9%</td>
</tr>
<tr>
<td></td>
<td>Nuclear/biological/chemical weapons</td>
<td>6%</td>
</tr>
<tr>
<td>Economic</td>
<td>Sudden demand shocks</td>
<td>44%</td>
</tr>
<tr>
<td></td>
<td>Extreme volatility in commodity prices</td>
<td>30%</td>
</tr>
<tr>
<td></td>
<td>Border delays</td>
<td>26%</td>
</tr>
<tr>
<td></td>
<td>Currency fluctuations</td>
<td>26%</td>
</tr>
<tr>
<td></td>
<td>Global energy shortages</td>
<td>19%</td>
</tr>
<tr>
<td></td>
<td>Ownership/Investment restrictions</td>
<td>17%</td>
</tr>
<tr>
<td></td>
<td>Shortage of labour</td>
<td>17%</td>
</tr>
<tr>
<td>Technological</td>
<td>Information and communications disruptions</td>
<td>30%</td>
</tr>
<tr>
<td></td>
<td>Transport infrastructure failures</td>
<td>6%</td>
</tr>
</tbody>
</table>

*Source: World Economic Forum Supply Chain and Transport Risk Survey 2011*
Temperature Risk Management

- Temperature Controlled Distribution Management
- Quality Risk Management
- Risk Sources

1. Requirements
2. Design & Qualification
3. Quality Management System
4. CAPA Management
5. Change Control

Risk Assessment
Risk Control
Risk Review

Equipment
Processes
People
External factors

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Risk-based approach: FMEA

1. Assign team and lead for workgroup
2. Map the process
3. Assign ratings for
   - Severity
   - Probability of occurrence
   - Probability of detection
4. Describe (worst-case) shipping lane for FMEA
5. Execute FMEA
6. Calculate risk priority number (scale of 1 to 1000):
   - RPN = Severity x Prob. occurrence x Prob. Detection
7. Propose corrective and preventive actions
8. Re-calculate RPN
### Active and passive containers

<table>
<thead>
<tr>
<th>Description</th>
<th>Temperature controlled truck</th>
<th>Temperature controlled ocean container</th>
<th>Active ULD (RKN)</th>
<th>Thermal packout by courier</th>
<th>Thermal packout by air</th>
</tr>
</thead>
<tbody>
<tr>
<td>System</td>
<td>Active</td>
<td>Active</td>
<td>Active</td>
<td>Passive</td>
<td>Passive</td>
</tr>
<tr>
<td>Cooling by</td>
<td>Compressor</td>
<td>Compressor</td>
<td>Compressor</td>
<td>Gel packs</td>
<td>Gel packs</td>
</tr>
<tr>
<td>Volume</td>
<td>1-33 pallets</td>
<td>1-40 pallets</td>
<td>1 pallet</td>
<td>1-100 packs</td>
<td>Up to ~ 4000 packs</td>
</tr>
<tr>
<td>Shipment duration</td>
<td>1-5 days</td>
<td>10-30 days</td>
<td>2-5 days</td>
<td>24-48 hours</td>
<td>2-5 days</td>
</tr>
<tr>
<td>Temperature monitoring</td>
<td>GPS/GPRS, recorder, temperature monitor(s)</td>
<td>Recorder, temperature monitor(s)</td>
<td>Recorder, temperature monitor(s)</td>
<td>No</td>
<td>Temperature monitors</td>
</tr>
<tr>
<td>People</td>
<td>12</td>
<td>26</td>
<td>41</td>
<td>22</td>
<td>25</td>
</tr>
<tr>
<td>Sorting hub</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Customs</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Mode of transport</td>
<td>BiTemp Truck</td>
<td>Truck, ship, truck</td>
<td>Truck, air-plane, truck</td>
<td>Truck / Van</td>
<td>Truck, airplane, air-plane, truck</td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th>FMEA workgroup</th>
<th>Top risk</th>
<th>Recommended actions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Temperature controlled truck</td>
<td>Undetected temperature excursion of attached monitor by customer.</td>
<td>Limit use of monitors by trained operators; sign off of monitor handling cross check with training matrix.</td>
</tr>
<tr>
<td>Temperature controlled ocean container</td>
<td>Container not wired and alarmed during loading ship due to communication failures.</td>
<td>Carrier SOP for operations, monitoring and responses to failures or issues.</td>
</tr>
<tr>
<td>Active ULD (RKN)</td>
<td>Battery life impacted as container can not fly due to overcapacity or flight delay or custom delay due to incomplete documentation.</td>
<td>More stringent SOP coordinated with airlines, alternative contingency planning in place, better battery monitor status.</td>
</tr>
<tr>
<td>Thermal packout by courier</td>
<td>Storage conditions not the same as qualified during unload and wait at the hub.</td>
<td>Requalification of thermal packout, monitor hub, audit hub, use RFID or other monitoring system that alarms the correct people of issues.</td>
</tr>
<tr>
<td>Thermal packout by air</td>
<td>Flight delay at stop-over in Middle East.</td>
<td>Alert program and pro-active monitoring of shipment.</td>
</tr>
</tbody>
</table>
1. Driver turned cooling unit off forced by parking security.
2. Temperature < 2 °C due to cold outside (low alarm). Truck temperature monitoring system did not inform carrier headquarters as alarm settings were incorrect.
3. Cooling unit turned on and driver observed a flat tire at the border. Driver notified customs and contacted service station. Customs informed customer about the delay.
4. Customer sent a refrigerated van to take over the goods from the refrigerated trailer. Driver informed this transfer to carrier headquarters after the event.
5. Customer forgot to stop temperature monitors (high false alarm) upon storage.
Case study 2: Packout shipment

- Inside monitors
- Outside monitor
- Truck monitors
- Temperature controlled unit
Case study 2: Packout shipment

- Requested – Transport packout at 8-25 °C with set point at 15 °C to prevent impact of the cold weather
- Investigation revealed:
  - Temperature of outside packout monitor is different than the truck temperature data supplied by the carrier
  - No FRC certified van
  - No temperature control unit in the back of the van
  - Memory with temperature data erased just prior inspection of the van.
  - Temperature regulated with uncontrolled thermo stat located below floor.
  - Hot air inlet is about 100°C and it is not circulated and uncontrolled.
  - Temperature sensor attached to roof above air inlet.

- Draw your conclusion .....
• To maintain product quality, safety and efficacy, the risk towards product adulteration, counterfeiting, theft, and diversion must be mitigated by risk-based decisions using knowledge, experience and understanding of the risk sources in the supply chain:
  – Equipment
  – Processes
  – People
  – External factors
• Execution of a FMEA gives insights and understanding into the distribution processes, especially when suppliers and logistic service providers are part of the team.
• A potential hazard (risk source) may not have an impact on its own, but in combination with other hazards a failure (e.g., temperature excursion) may happen with a large impact towards the product quality, safety and efficacy.
• Contracts, SOP’s and training are measures to reduce human errors, however they will not eliminate them!
• Detection and communication of events are critical and they can fail too!
"Our greatest glory is not in never falling, but in rising every time we fall."

Confucius (551 — 479 B.C.)

A Chinese thinker and social philosopher
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