INTRODUCTION OF GDP SYSTEM DEVELOPMENT

FROM THE PACKAGING ENGINEER POINTS OF VIEW

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INTRODUCTION

"The One the Patient Takes is Never Tested"

Source: The American Druggest, 1977 Eli Lilly & Co advertisement.

- Think SISPQ (Safety, Identity, Strength, Purity, Quality) first!
- Stability including sterility is the #1 priority.
- GMP or GDP are a requirement to demonstrate SISPQ.

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INTRODUCTION (CONTINUED)

- Distribution chain from the manufacturer to the patient
- Time required to establish the process
- Number of parties involved
  - Internal cross-functional groups: quality, regulatory, product development, distribution, etc.
  - External parties: distributor, wholesaler, pharmacy, hospital, government, etc.
- Regulated system – any error can delay or recall the products.

How packaging engineers in development can enhance the GDP system?

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REFERENCES

- 21 CFR 211 CURRENT GOOD MANUFACTURING PRACTICE FOR FINISHED PHARMACEUTICALS
- WHO Annex 5, good distribution practices for pharmaceutical products, 2010
- WHO Annex 9, Good Storage Practices, 2011
- European Commission guidelines on good distribution practice of medicinal products for human use, November 2013
- USP <1083> Good Distribution Practices
- ICH Q9 Quality Risk Management

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REGULATORY EXPECTATIONS

- Patient Safety and Product Quality!!
- Scientific knowledge of the product at the distribution environment from manufacturing to end users.

FDA observation:

"Your firm did not establish scientifically sound and appropriate specifications, standards, sampling plans, and test procedures designed to assure that components, product containers, in-process materials, and transport methods conform to appropriate standards of identity, strength, quality and purity."

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GDP REQUIREMENTS

Note: see the references for detailed requirements

- Quality System – management/organization, policy, SOP, CAPA, risk management
- Documentation – prevent error, retain at least 5 yrs (e.g., temperature profiles)
- Personnel – responsible person, continuous training
- Storage – security, sufficient space, temperature and environment control
- Equipment – calibration, validation
- Operation – qualification of suppliers
- Recalls – immediate action, written procedure and system

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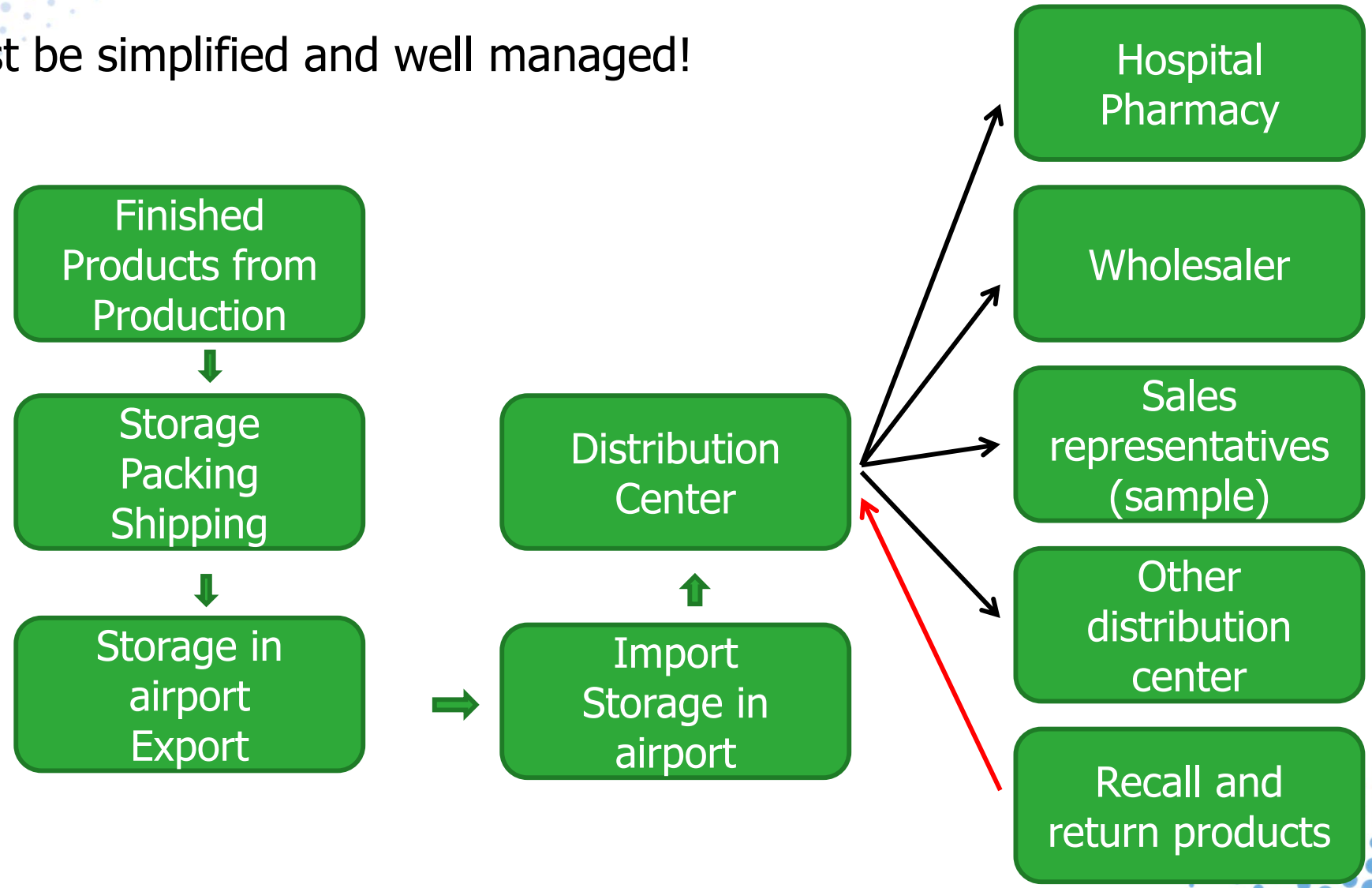
DISTRIBUTION CHAIN (EXAMPLE FOR EXPORT PRODUCT)

Must be simplified and well managed!



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SHIPPING VALIDATION
EXAMPLES FROM REFRIGERATED & FROZEN PRODUCTS

- Shipping from manufacturer to the end user
- Shipping condition should be maintained at desired conditions (e.g., 2-8°C, <-20°C) – insulated shipper or temperature controlled container?
- Insulated shipper: insulating material (e.g., EPS, PUR, etc.) + refrigerant (e.g., gel pack, dry ice, etc.)
  - Thermal conductivity: EPS (~0.03-0.06 W/m·K) > Polyurethane foam (~0.025 W/m·K)
  - Design the insulated shipper using heat transfer 1st principle and confirm experimentally
- Temperature controlled container: Electric heating and compressor cooling (e.g., Envirotainer)

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SHIPPING VALIDATION (CONTINUED)

- One time event but the entire shipping process from the manufacturer to the end user should be well understood.
  - Perform chemical stability and functional performance testing before and after shipping
  - Container closure integrity, glide force for syringes, etc.
- Apply quality risk management
  - Perform FMEA (Failure Modes Effect Analysis)

FAILURE MODE – TEMPERATURE EXCURSION

Situation: refrigerated product was stored in 2-8°C storage room and it was moved to a temperature controlled container. Figures 1-2 show the recorded temperatures.

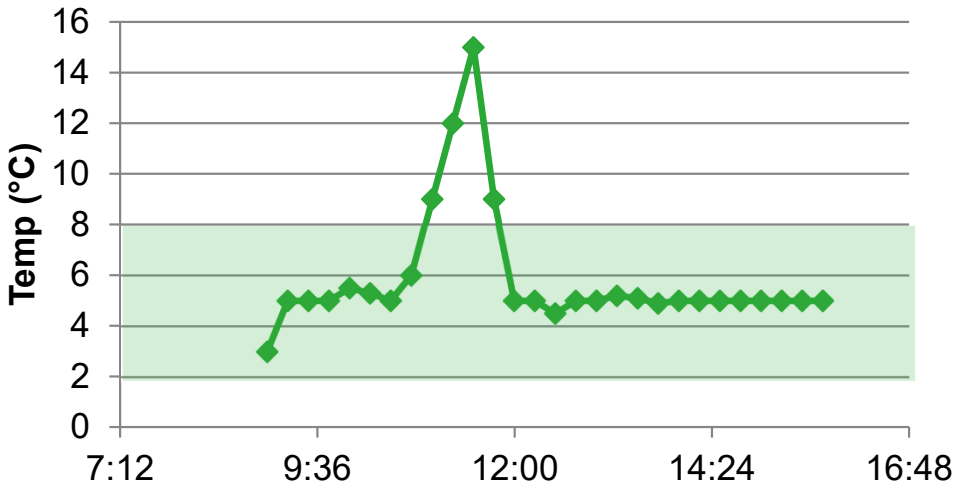

Figure 1

1 hour excursion MKT = 6.33°C

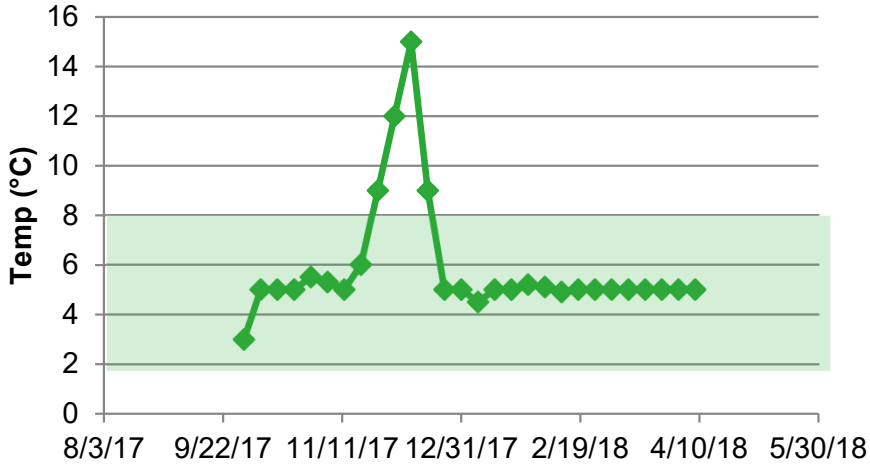

Figure 2

4 days excursion MKT = 6.33°C

MKT (mean kinetic temperature) – a way of expressing the overall effect of temperature fluctuations during storage or transit of pharmaceutical products

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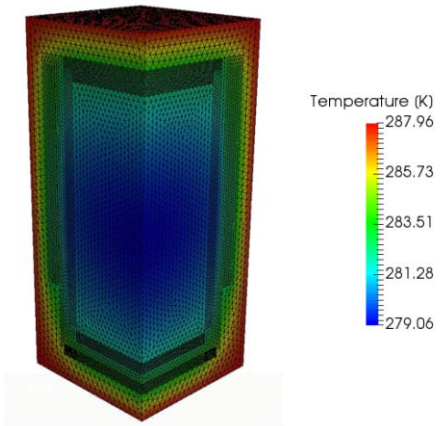
FAILURE MODE – TEMPERATURE EXCURSION (CONTINUED)

Prepare inputs to perform the analysis for a variety of unexpected situations

- Product kinetic study – the relationship between product stability and temperature.
- Thermal analysis (e.g., heat transfer modeling)



e.g., Quarter symmetric heat transfer FEA analysis

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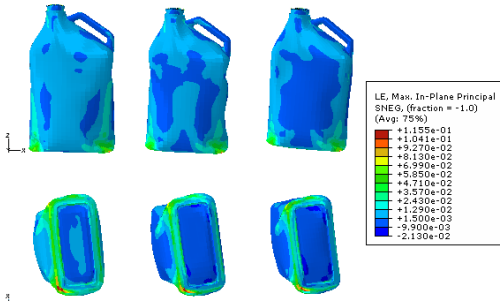
FAILURE MODE – CRACKED CONTAINER AT <-20°C

Situation: API solution was packaged in 5L HDPE jar and stored at -80°C. After several months storage, several leaking bottles were found during thawing.

Root causes analysis

- Material characterization: Tg, thermal expansion, stress-strain tensile
- Environmental stress crack test (ASTM D1693)
- Design analysis using FEA (finite element analysis)



Results

- Defect from the finishing process but potentially it can be caused from molding and handling.
- Stress in the defect area was concentrated, the defect could be propagated over time, and the container was eventually cracked.

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CONCLUSIONS
FROM THE PACKAGING ENGINEER POINTS OF VIEW

- GDP system must be developed and it will prevent errors.
- Time required to establish the system. Continuous training is important.
- Utilize the contractors as insourcing
- Risk based quality system can enhance the GDP system.
- Product kinetic, MKT and thermal analysis 1st principles are necessary to develop the system.

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