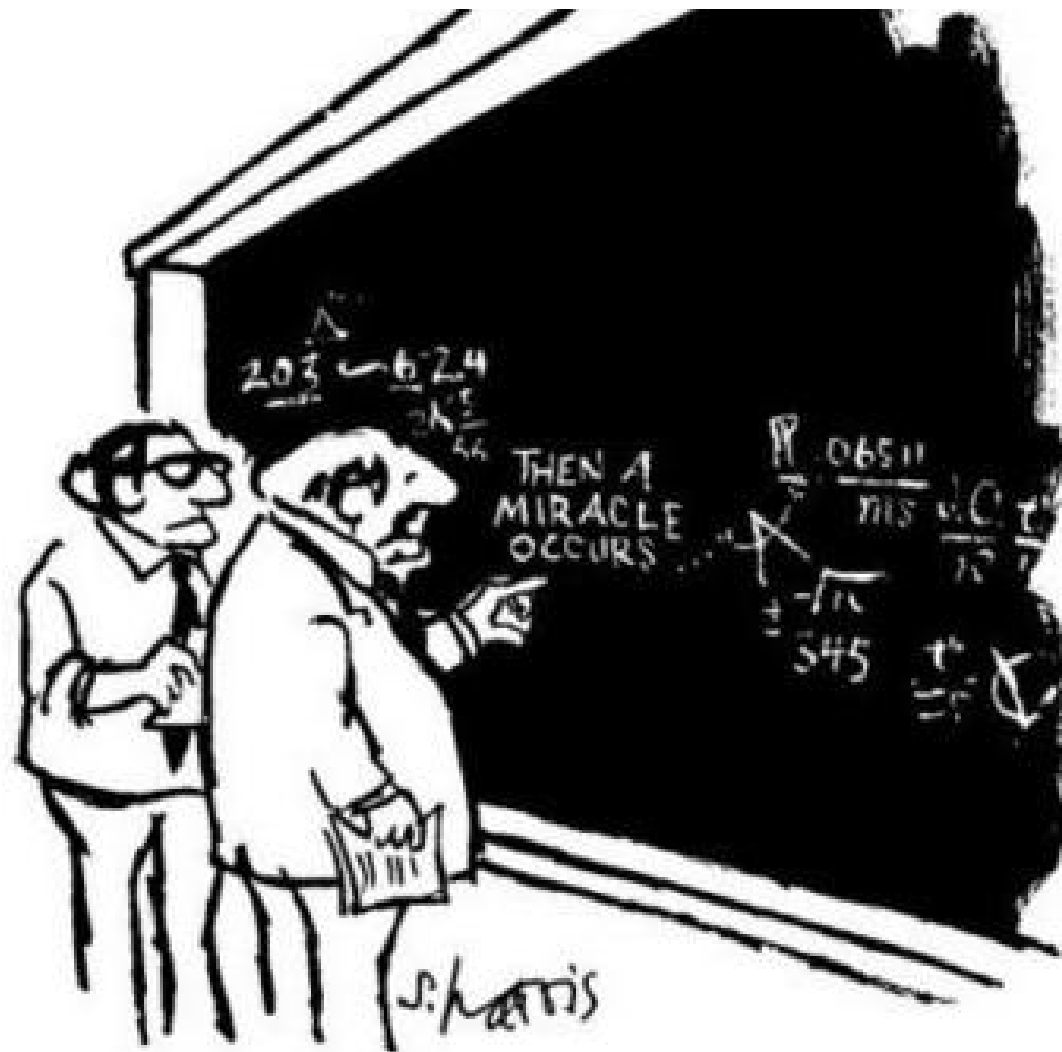


# **Cold Chain and Risk Mitigation of Humidity**

Bob Seevers

# The Old View of Cold Chain Distribution

- A Manufacturer's responsibility ended at its loading dock...



"I THINK YOU SHOULD BE MORE EXPLICIT HERE IN STEP TWO."

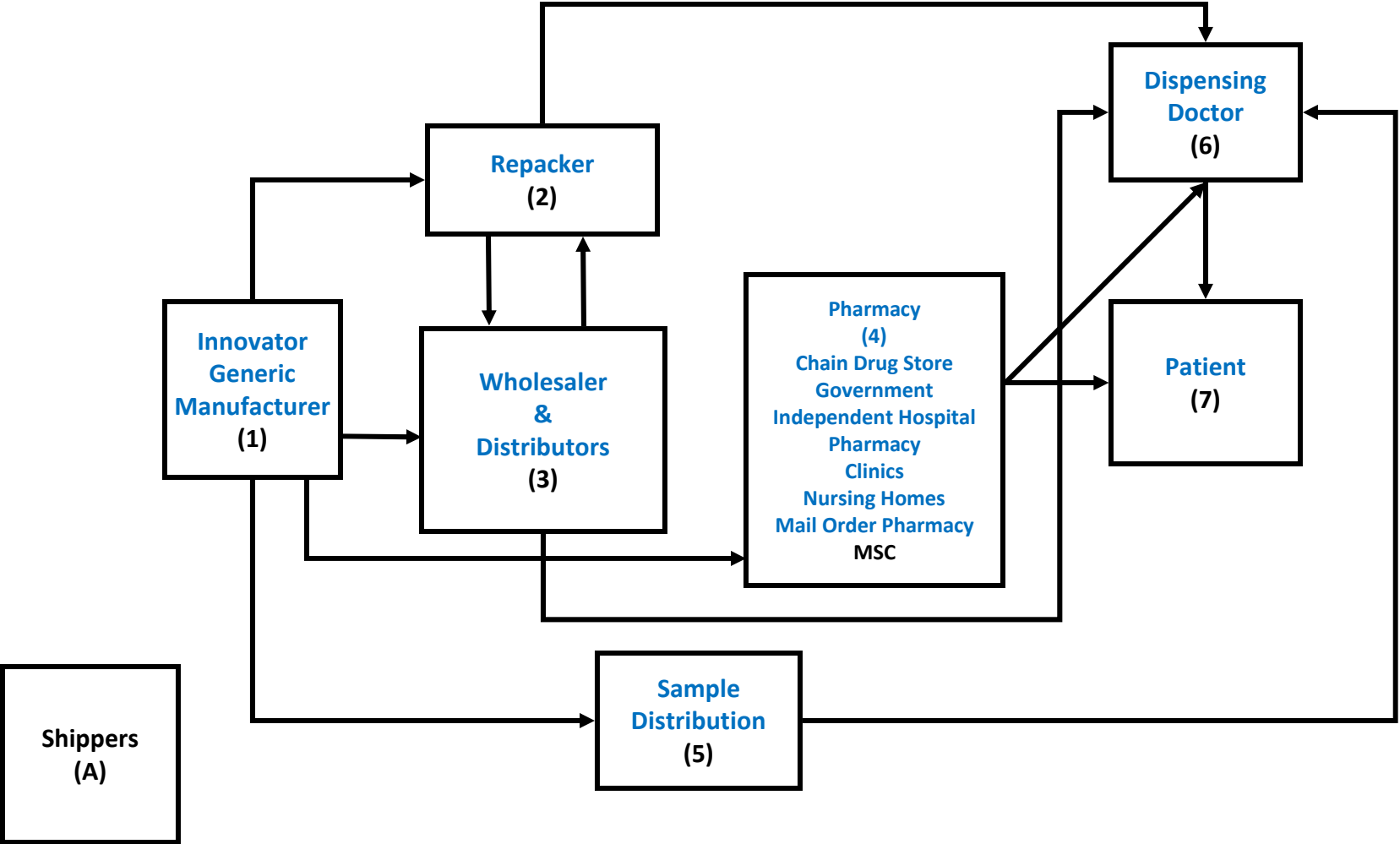
# Current View

- The **holding** of a drug includes distribution and is seen as a cGMP regulated process
  - WHO
  - EU
  - Canada
  - PDA Technical Report 39
  - FDA (from the podium, repeatedly)

# Scope

- What moves through the distribution channels?
  - Temperature sensitive raw materials
  - Intermediates
  - APIs
  - Bulk Drug Products
  - Finished Drug Products
  - Physician Samples

# USP <1079> Illustrates Complexity



# WHO

- Applicable to all persons and companies involved in the distribution of pharmaceutical products
- “Where special storage conditions (e.g.: temperature and relative humidity) are required during transit, these should be provided , checked and recorded.”
- “Temperature mapping of vehicles (where applicable) should support uniformity of the temperature across the vehicle.”
- “Recorded temperature monitoring data should be available for review.”
- Good Distribution Practices (GDP):Working Document QAS/04.68 (RESTRICTED), 2004

# European View

- 2001 Guidance on Good Distribution Practice
- “storage conditions are observed at all times, including during transportation”
- “products requiring controlled temperature storage should also be transported by appropriately specialised means.”
- So...how should excursions be addressed?
- Humidity monitoring has been raised from the podium by EU regulators

# Canadian Guidance (2009)

- Manufacturer, Distributer, & Wholesaler are responsible for ensuring that appropriate conditions are maintained from the point of manufacturing to up to the delivery of drugs at the final distribution site.
- Temperature is one of the most important parameters to control.
- The maintenance of proper conditions should be supported by written contracts between components of the distribution chain.
- Canadian regulators have also raised the humidity question

# An FD&C Act Requirement

- **FDA is authorized**
- **It is a prohibited act to:**
  - introduce into or deliver for introduction into interstate commerce an adulterated drug (301(a))
  - adulterate a drug in interstate commerce (301(b))
  - receive in interstate commerce a drug that is adulterated (301(c))

# Adulteration under CGMP requirement

## **FFD & C Act [501(a)(2)(B)]**

- A drug is adulterated if the facilities or controls used for its manufacture, processing, packing or holding do not conform to/are not operated or administered in conformity with current good manufacturing practice (CGMP)

# A CGMP Regulated Operation

- “Holding” of a drug occurs when the drug is
  - Being distributed
  - Being transported
  - Warehoused for distribution/transport
- “Holding” is storage

# An element of CGMP

- Storage of drug products under appropriate conditions is a requirement within current good manufacturing practice (CGMP) regulations for finished drugs and is a requirement for licensing biologics.

# Information from Manufacturer

- Storage statement
  - Immediate container
  - Secondary packaging
  - Package insert
- Stability
  - ICH long term and accelerated
  - Stress/excursion testing
  - Freeze/Thaw
  - Stability at Room temp in the hands of the end user

# The Humidity Issue

- Many drugs are adversely affected by moisture.
  - Degradation
  - Impurities
- Humidity monitoring is common during storage of controlled room temperature products
- Refrigerated & freezer materials are not subject to humidity monitoring due to low RHs
- Humidity monitoring is rarely done during transportation of drugs

# Regulatory Attention to Humidity

- FDA speakers have taken the approach: Justify why humidity monitoring is not needed, when the question has been raised at cold chain meetings
- Romanian regulators issued rules that stated humidity must be monitored during transportation in 2009. This was later withdrawn.

# So, What Do You Need to Do and How Do You Justify It?

- The limited time that drugs spend in transport may be used to justify lack of humidity monitoring
- Temperature excursions affect drugs in minutes to hours, but packaging protects from humidity through shelf life
- A transport segment typically lasts from a few hours to a few weeks
- A drug product's lifetime is typically 2-3 years
- This lifetime is achieved, in part, by using a container/closure system whose protective properties matches the moisture sensitivity of the drug

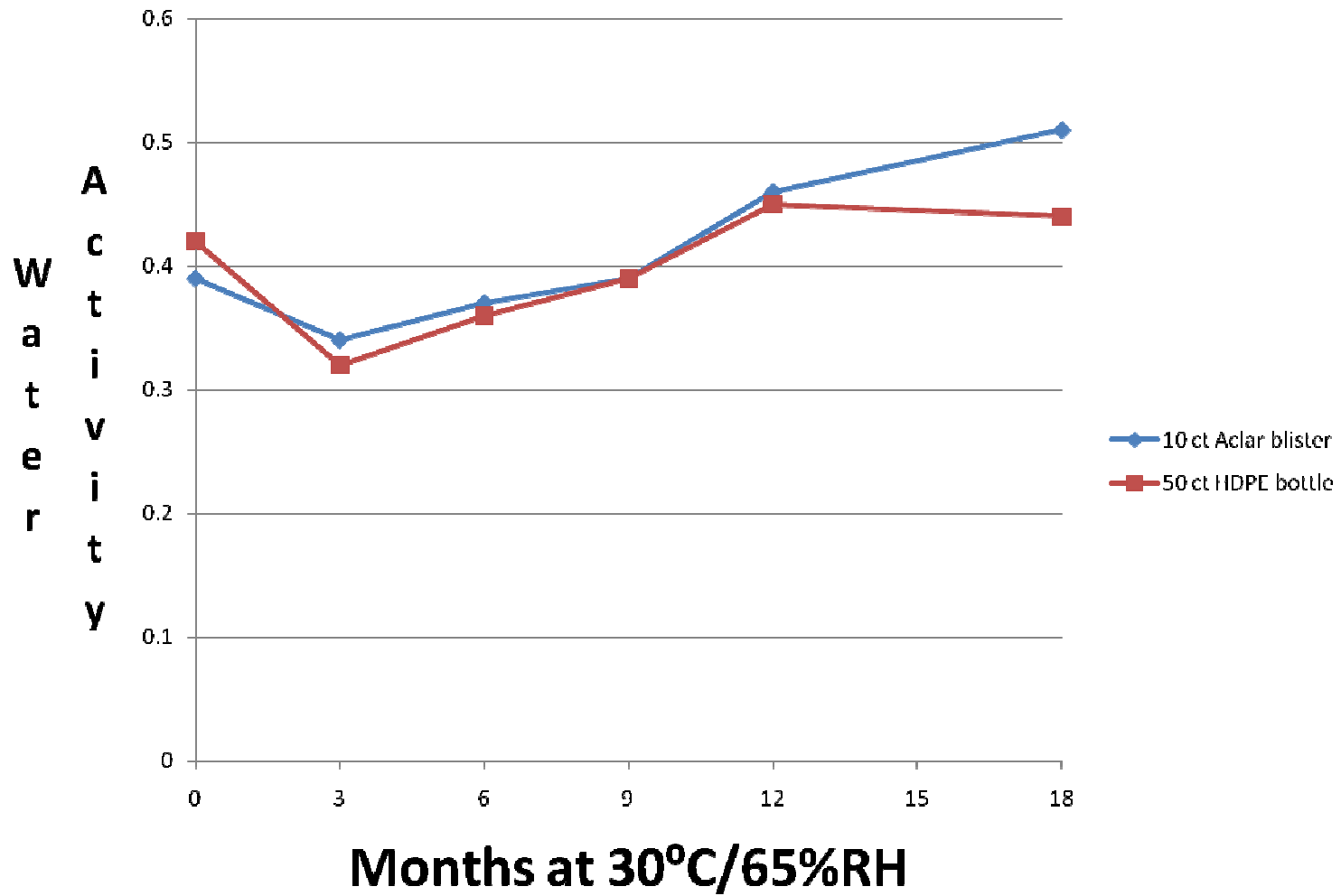
# Humidity vs. Relative Humidity

- It is important to understand the difference between these terms
- **Humidity** refers to the amount of moisture in the air
- **Relative Humidity** refers to the amount of moisture in the air compared to the maximum amount that the air could hold *at that temperature*
- Stability testing is done at fixed *Relative Humidity* for controlled room temperature products and ambient humidity for refrigerated and freezer materials.

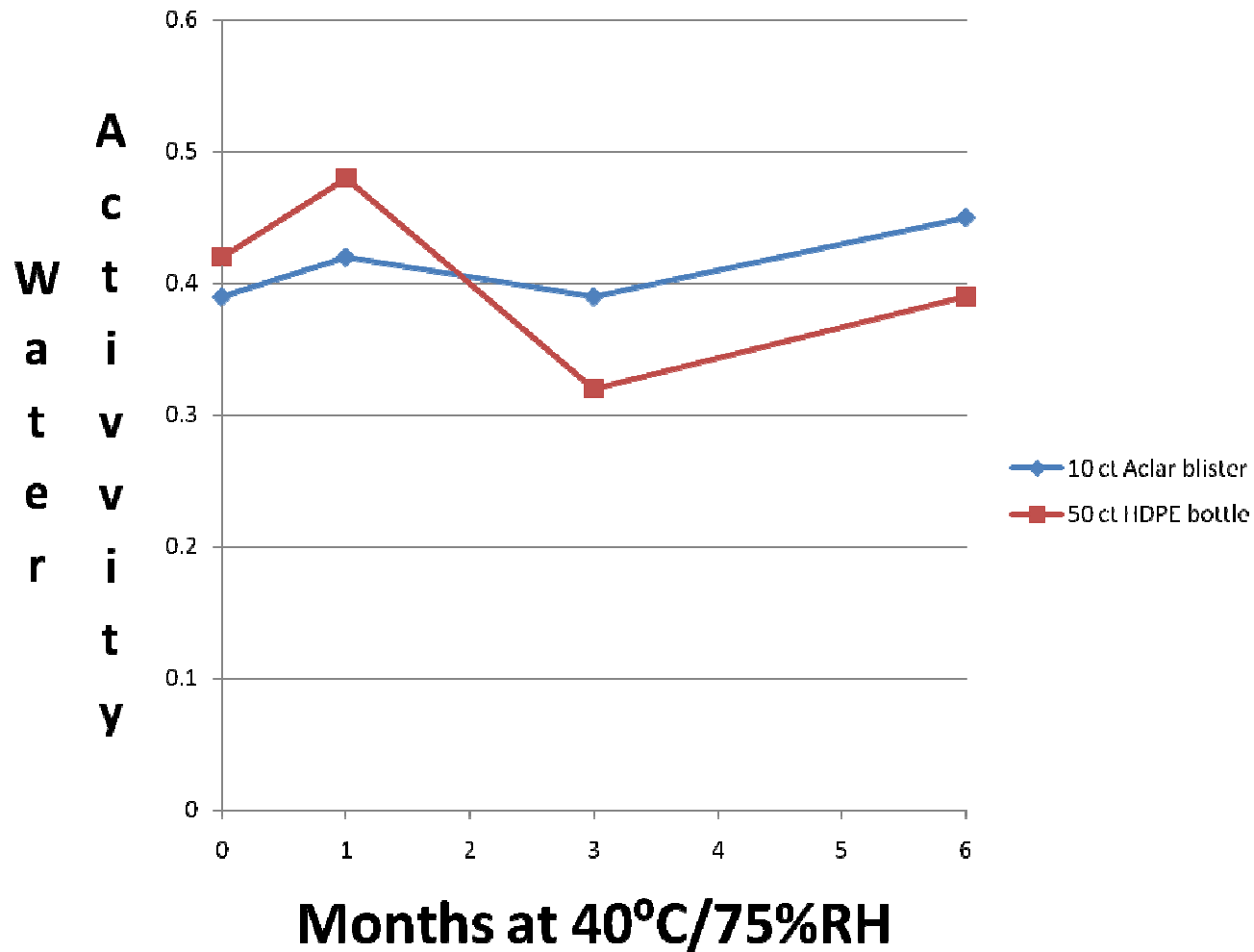
# So, why is it OK to not monitor humidity during transportation?

- We have a container/closure system documented by stability studies to protect the product
  - against 60% RH at 25°C for full shelf life
  - against 75% RH at 40°C for up to 6 months
- For refrigerated and freezer products, the relative humidity is so low, it is not an issue.

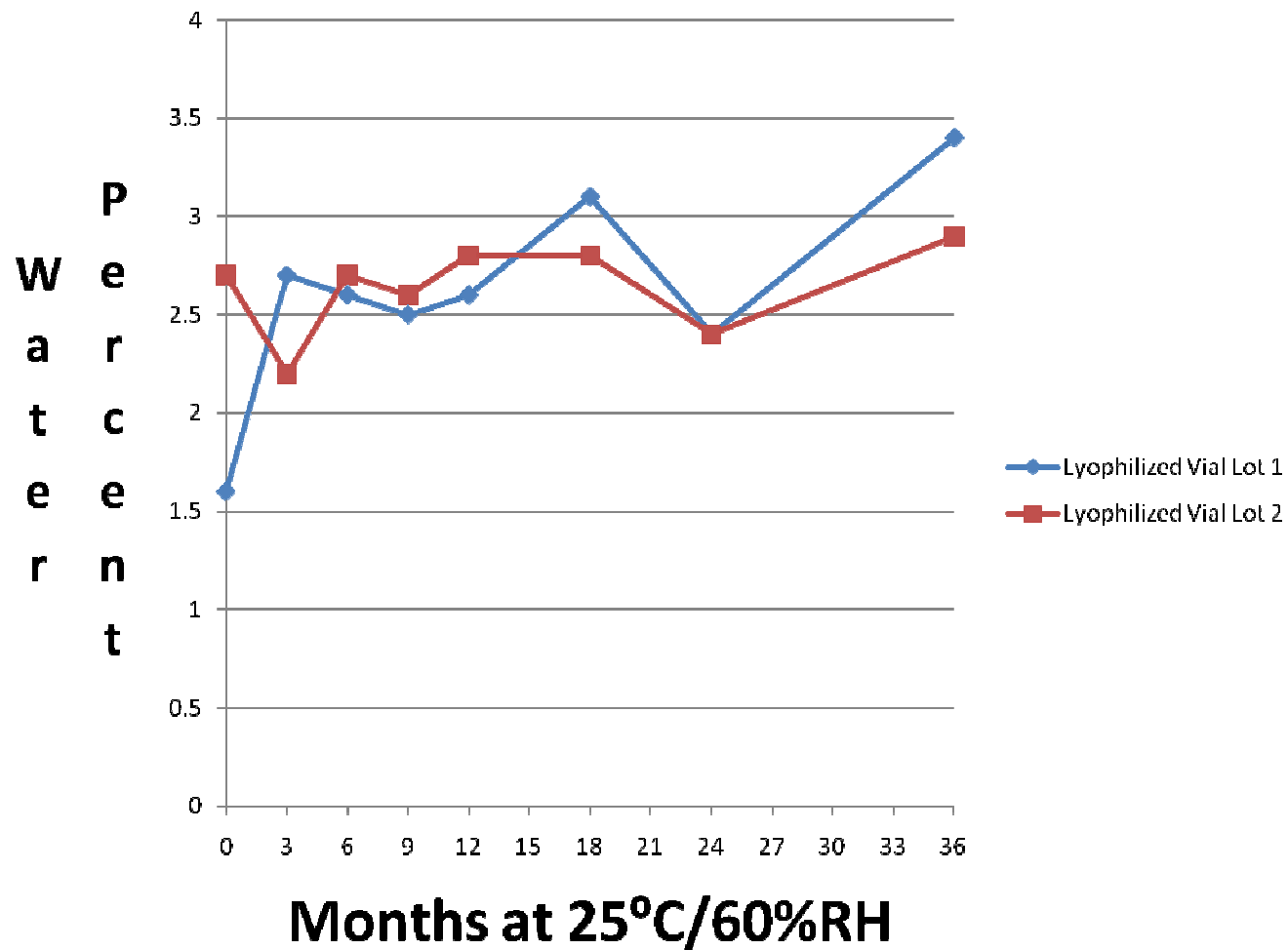
# Illustration: Solid Oral



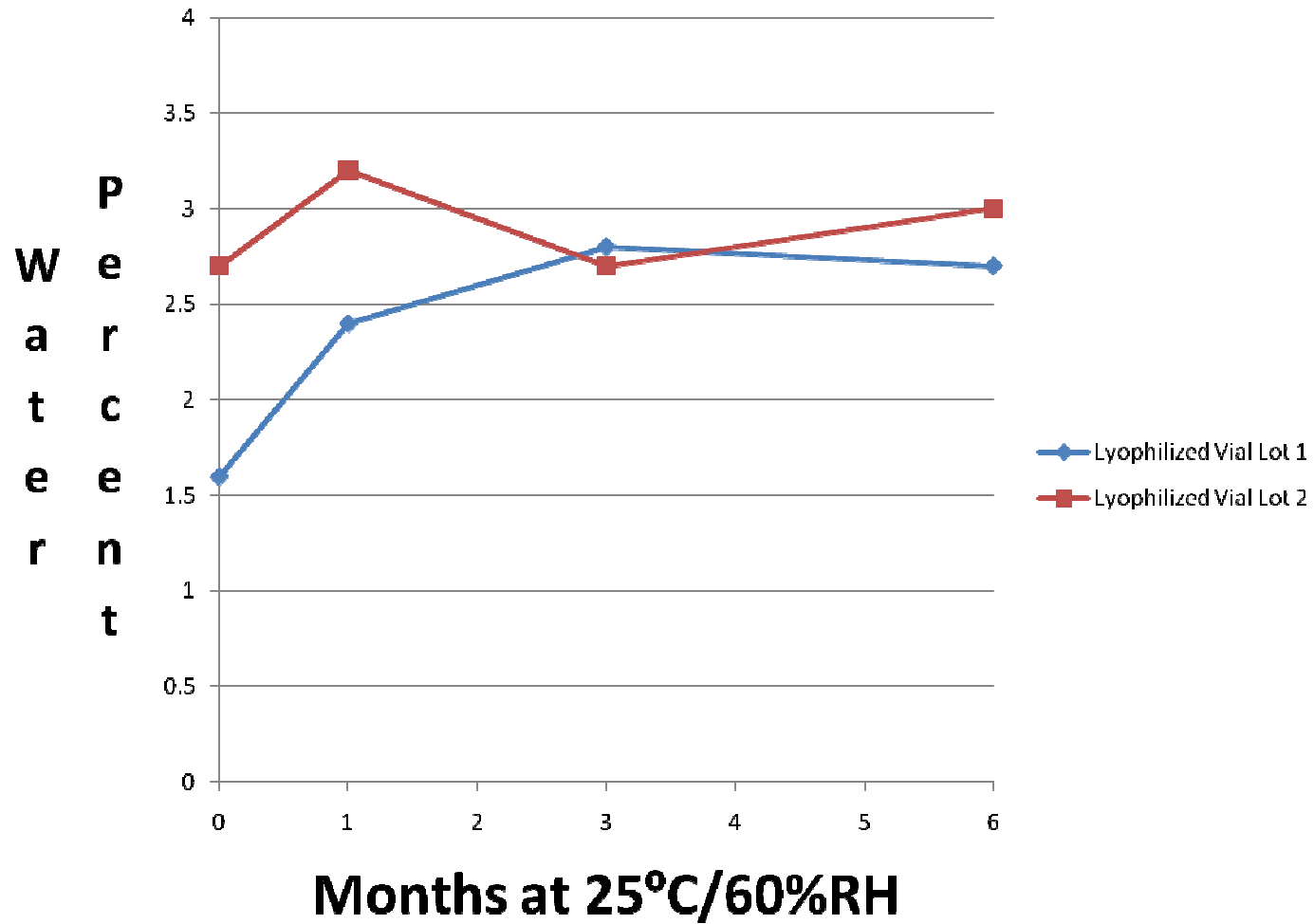
# Solid Oral Accelerated



# Illustration: Lyophilized Vial



# Lyophilized Vial Accelerated



# Conclusions

- The limited time that drugs spend in transport may be used to justify lack of humidity monitoring
- Temperature excursions affect drugs in minutes to hours, but packaging protects from humidity through shelf life
- Container/closure systems are chosen with protective properties that match a product's sensitivity to water. This is documented through stability studies.
- Humidity monitoring during transport is not necessary because the container/closure system limits moisture vapor transmission to such slow rates.
- Transportation is limited in time to hours-weeks.
- Humidity monitoring is required during storage due to the longer time frame.