Design of Experiments to Establish Temperature and Humidity Limits for Temperature Excursions during Product Distribution

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Why is this an issue?

- Pharmaceutical manufacturers face increasing regulatory pressure to provide **data** to support claims that *product quality is unaffected* by transient temperature and humidity extremes encountered during storage, distribution and end use outside of storage conditions stated on the label.
  - Alternative is to use expensive packaging and stringent shipping control measures.

Example: European Medicines Agency

- Concept paper on Storage Conditions during Transport:
  - "The goal is to create new Good Distribution Practice (GDP) and GMP guidance and may lead to the need to revise the guideline on declaration of storage conditions (CPMP/QWP/609/96/Rev2). This current guidance was written in 1996 and revised in 2003, during this time significant changes continued to occur in the globalisation of manufacture with a consequent increase in the complexity and vulnerability in the supply chain, leading to a lack of clear guidance on the regulatory expectations for ensuring that medicinal products and APIs are ***not damaged*** during transportation." **[emphasis added]**

Example: Health Canada

- Health Products and Food Branch Inspectorate GUIDE-0069 Guidelines for Temperature Control of Drug Products during Storage and Transportation:
  - **"3.1.4** Written procedures should be available describing the actions to be taken in the event of temperature excursions outside the labelled storage conditions. All excursions outside the labelled storage conditions must be appropriately investigated and the disposition of the stock in question must be ***evidence-based*** (for example, stability data and technical justification)." **[emphasis added]**

Example: WHO

- QAS/04.068/REV.2: GOOD DISTRIBUTION PRACTICES (GDP) FOR PHARMACEUTICAL PRODUCTS:
  - "**8.11** Where special storage conditions (e.g. temperature and/or relative humidity), different from or limiting the expected environmental conditions, are required during transit these should be provided, checked, monitored and recorded. All monitoring records should be kept for a minimum of the shelf-life of the product distributed plus one year, or as required by national legislation. Recorded monitoring data should be reviewed on receipt of pharmaceutical products to ***assess whether required storage conditions have been met***." **[emphasis added]**

See also:

- United States Pharmacopeia (USP) Chapter <1079> *Good Storage and Shipping Practices*
- PDA Technical Report No. 39, *Guidance for Temperature-Controlled Medicinal Products: Maintaining the Quality of Temperature-Sensitive Medicinal Products through the Transportation Environment* (TR-39)

Some excursions can be, frankly, out of this world…

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Research Article

Evaluation of Physical and Chemical Changes in Pharmaceuticals Flown on Space Missions

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Abstract. Efficacy and safety of medications used for the treatment of astronauts in space may be compromised by altered stability in space. We compared physical and chemical changes with time in 35 formulations contained in identical pharmaceutical kits stowed on the International Space Station (ISS) and on Earth. Active pharmaceutical content (API) was determined by ultra- and high-performance liquid chromatography after returning to Earth. After stowage for 28 months in space, six medications aboard the ISS and two of matching ground controls exhibited changes in physical variables; nine medications from the ISS and 17 from the ground met the United States Pharmacopeia (USP) acceptance criteria for API content after 28 months of storage. A higher percentage of medications from each flight kit had lower API content than the respective ground controls. The number of medications failing API requirement increased as a function of time in space, independent of expiration date. The rate of degradation was faster in space than on the ground for many of the medications, and most solid dosage forms met USP standard for dissolution after storage in space. Cumulative radiation dose was higher and increased with time in space, whereas temperature and humidity remained similar to those on the ground. Exposure to the chronic low dose of ionizing radiation aboard the spacecraft as well as repackaging of solid dosage forms in flight-specific dispensers may adversely affect stability of pharmaceuticals. Characterization of degradation profiles of unstable formulations and identification of chemical attributes of stability in space analog environments on Earth will facilitate development of space-hardy medications.

KEY WORDS: chromatography; dissolution; pharmaceutical stability; potency; space radiation.

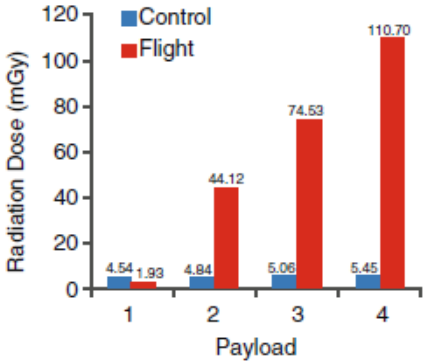


Fig. 7. Comparison of cumulative radiation dose between ground and spaceflight

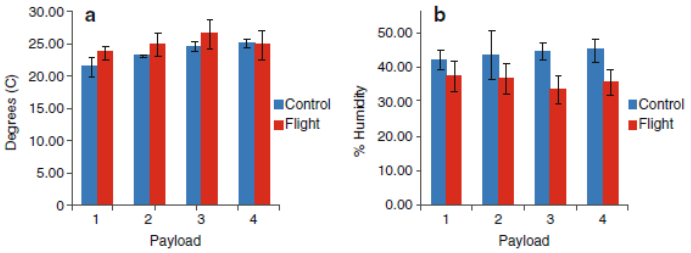


Fig. 6. Comparison of mean temperature (**a**) and relative humidity (**b**) conditions between ground and spaceflight

So, what is the problem?

- Stakeholders typically want manufacturers to prove a NEGATIVE—*no change* has occurred in product quality.
  - This, of course, is practically impossible, as the change may simply not be large enough to be detectable.
    - "The absence of evidence is not evidence of absence"—astrophysicist Martin Rees, as quoted by Carl Sagan
  - Goal needs to be reformulated: Acceptable changes in product quality are not exceeded.
    - Requires definition of an acceptable change, then showing that such a change has not been exceeded (specifications are met).
    - Analogous to problem of defining bioequivalence.
    - Measurement system must be capable.
    - WHO formulation of the problem *is* achievable.

Defining acceptable changes in critical-to-quality parameters

- In the case of critical-to-quality (CtQ) data, we set specifications with respect to CtQ parameters that the product is expected to meet throughout its shelf life.
  - Product quality is monitored by tracking critical-to-stability (CtS) parameters over time.
    - A change within specifications is acceptable.
    - Typical specifications are suggested in ICH guidelines.

Uncertainty: a sermon

- Every measurement is uncertain; there is none which is not uncertain. The right level of uncertainty distinguishes erratic noise from quantifiable signal.
  - [With apologies to Philippus Aureolus Theophrastus Bombastus von Hohenheim-Paracelsus (1493–1541), the father of toxicology, who said "Every substance is a poison; there is none which is not a poison. The right dose differentiates a poison from a remedy."].
  - How much measurement uncertainty is tolerable?
  - How does the *certainty* of measurement uncertainty impact experimental design?

Unknown unknowns, known unknowns and known knowns

- At the outset of any stability experiment, CtS parameters are at some initial value.
- With time, CtS parameters change for the worse.
  - At early times, the changes in CtS parameters are **too small to detect**.
    - These changes are *unknown unknowns*.
  - At slightly later times, the changes in CtS parameters, while detectable, are **too small to quantify** with acceptable uncertainty.
    - These changes are *known unknowns*.
  - Eventually changes in CtS parameters become large enough to quantify with acceptable uncertainty.
    - Only then do these changes become *known knowns*.

Current practice

- Specific protocols have been proposed to study temperature and humidity excursions.
- Two types of studies are in vogue:
  - Single excursion studies.
  - Repetitive cycling studies between two conditions.
    - In either case, one leg may be a control condition, or both legs may be extremes.

Example: Excursion study

Storage condition	Testing condition
Controlled room temperature 20-25°C	1) –20°C for 2 days 2) 60°C/75% RH for 2 days
Refridgerated condition 2-8°C	1) -20°C for 2 days 2) 40°C/75% RH for 2 days
Freezer condition -20 to –10°C	1) 25°C/60% RH for 2 days

Krause HJ. "GMP aspects of cold chain management for pharmaceutical products", 1st International Workshop Cold Chain Management, December 8-9, 2003, Bonn, Germany.

Example: Thermal cycling study

Storage condition	Testing condition
Controlled room temperature 20-25°C	–20°C for 2 days followed by 40°C/75% RH for 2 days Repeat for a total of 3 cycles
Refridgerated condition 2-8°C	-20°C for 2 days followed by 25°C/60% RH for 2 days Repeat for a total of 3 cycles
Freezer condition -20 to –10°C	-20°C for 2 days followed by 5°C for 2 days Repeat for a total of 3 cycles

Krause HJ. "GMP aspects of cold chain management for pharmaceutical products", 1st International Workshop Cold Chain Management, December 8-9, 2003, Bonn, Germany.

Current recommended "textbook" practice

- Three cycles with 4 days at extreme condition and 3 days at normal condition.
  - Testing done after completion of all cycles.
  - ***If drug product is sensitive, put on long-term stability for expiration period***…
    - Huynh-Ba K, Zahn M. Understanding ICH Guidelines Applicable to Stability Testing. In: Huynh-Ba K, Ed. *Handbook of Stability Testing in Pharmaceutical Development: Regulations, Methodologies, and Best Practices.* New York: Springer (2009).

Problems with current practice

- Changes that occur during single exposure or cycling experiments may be too small to detect (**unknown unknowns**)…
- …yet may still reduce shelf life (**known known**, but tedious to evaluate using conventional real time stability trials).

Is there a better way?

- Limited efforts have been made to model the effects of temperature excursions on shelf life.
  - Example: **Socarras S, Magari RT.** Modeling the effects of storage temperature excursions on shelf life. *J Pharm Biomed Anal* 49: 221–226 (2009).
    - Uses Arrhenius activation energy.
    - Assumes pseudo first-order degradation.
- This is a start in the right direction, but not necessarily the best approach.

Points to consider in designing excursion experiments (1)

- Should both low and high temperature/humidity conditions be evaluated in the same experiment?
  - Can we kill two birds with one stone?
- How long should excursion last?
  - Step changes in conditions are not instantaneous; some time is needed for equilibration.
    - Physical changes (e.g., freezing) take time to complete.
    - Moisture takes time to diffuse through packaging.
- Can we evaluate effect on shelf-life without doing real-time experiments?

Points to consider in designing excursion experiments (2)

- If no physical changes in dosage form occur (freeze/thaw, change in hydration state or polymorphic form of API or excipients), then the *Arrhenius model* for chemical reaction rates should apply.
  - If physical changes occur, even if they are reversible, reaction rates will not follow Arrhenius model.

Points to consider in designing excursion experiments (3)

- Chemistry: Reaction rate follows Arrhenius model:

$$\pm\frac{d\mathrm{CtQ}}{dt}=k_{T,g}=A_g e^{-E_a/RT}$$

  - Rate *k* depends on assumed mechanism *g* and temperature *T.*
  - Rate is positive (+) if you measure degradation products, negative (–) if you measure API potency.
- For solids, rate also depends on humidity *h*:

$$\pm\frac{d\mathrm{CtQ}}{dt}=k_{T,h,g}=A_g e^{Bh-E_a/RT}$$

- You can trade time for temperature!
  - But, you need to know E_a (and *B* for solids)

Points to consider in designing excursion experiments (4)

- Complex chemical mechanistic models can be approximated by simple empirical polynomial models in time *t* if extent of degradation is small.
  - For solutions, we can use a pseudo zero order model:

$$\mathrm{CtQ} = \mathrm{CtQ}_{t=0} \pm k_{T,g} t$$

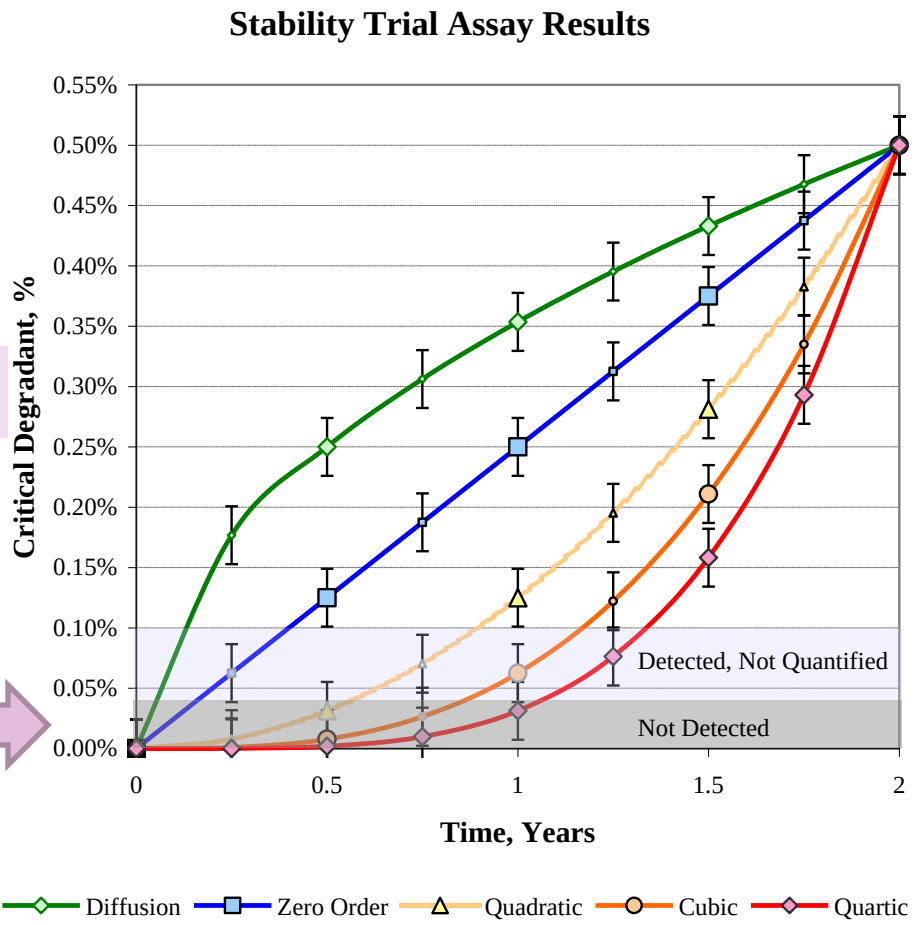
  - For solids, we can use a simple power law model, where r = ½, 1, 2, 3, 4:

$$\mathrm{CtQ} = \mathrm{CtQ}_{t=0} \pm k_{T,h,g} t^{r}$$

    - Again, (+) for degradation products, (–) for API potency.

Mechanistic model approximation

- All solid state degradation reaction mechanisms can be approximated by simple empirical models $\mathrm{CtQ} = \mathrm{CtQ}_{t=0} \pm k_{T,h,g} t^{r}$ if degradation is limited to very low levels per ICH guideline.
- Note that low degradant levels may not be *detectable* or *quantifiable*.



Points to consider in designing excursion experiments (5)

- If Arrhenius model is valid, you can balance high *T* with low *T* to keep mean kinetic temperature (*MKT) constant*.

ICH Q1A(R2), USP

$$\hat{T}_K = MKT = \frac{E_a/R}{-\ln\left(\frac{e^{-E_a/RT_1} + e^{-E_a/RT_2} + e^{-E_a/RT_3} + \cdots}{n}\right)} = \frac{E_a/R}{-\ln\left(\frac{\sum_i m_i e^{-E_a/RT_i}}{\sum_i m_i}\right)}$$

Assumes *equal time periods* at all temperatures, conventional model dependent on t^r, **r = 1**.

(m_i = # periods at T_i).

$$\hat{T}_K = MKT = \frac{E_a/R}{-\ln\left(\frac{t_1 e^{-E_a/RT_1} + (t_2 - t_1)e^{-E_a/RT_2} + \cdots + (t_n - t_{n-1})e^{-E_a/RT_3}}{t_n}\right)} = \frac{E_a/R}{-\ln\left(\frac{\sum_i (t_i - t_{i-1})e^{-E_a/RT_i}}{t_n}\right)}$$

Assumes *unequal time periods* at all temperatures, conventional model dependent on t^r, **r = 1**.

Points to consider in designing excursion experiments (6)

- If degradation follows an empirical power law model (fraction degraded proportional to t^r), then *MKT* depends on power law:

$$\hat{T}_K = MKT = \frac{E_a/R}{-\ln\left(\frac{t_1^r e^{-E_a/RT_1} + (t_2 - t_1)^r e^{-E_a/RT_2} + \cdots + (t_n - t_{n-1})^r e^{-E_a/RT_3}}{t_n^r}\right)}$$

Assumes *unequal time periods* at all temperatures.

NOTE : The definition of *MKT* recommended by USP, FDA, ICH *assumes* zero or first-order kinetic model, e.g., $r = 1$! Only in that case do the time terms factor out.

Points to consider in designing excursion experiments (7)

- If extended Arrhenius model is valid for solids, you can balance high *h* with low *h* to keep mean kinetic humidity (*MKh) constant* if *T* is kept constant.

$$\hat{h}_K = MKh = \frac{\ln\left(\frac{t_1^r e^{Bh_1} + (t_2 - t_1)^r e^{Bh_2} + \cdots + (t_n - t_{n-1})^r e^{Bh_n}}{t_n^r}\right)}{B}$$

- Assumes:
  - *unequal time periods* at all humidity levels,
  - constant temperature *T* and
  - empirical degradation rate model with degradation proportional to t^r. Again, if $r = 1$ then the time terms factor out.

Points to consider in designing excursion experiments (8)

- If extended Arrhenius model is valid for solids, you can balance high *h* with low *h* as well as high *T* and low *T* to control **both** mean kinetic humidity (*MKh*) and mean kinetic temperature (*MKT*):

$$B\hat{h}_K - \frac{E_a}{R\hat{T}_K} = \ln\left(\frac{t_1^r e^{Bh_1 - E_a/RT_1} + (t_2 - t_1)^r e^{Bh_2 - E_a/RT_2} + \cdots + (t_n - t_{n-1})^r e^{Bh_n - E_a/RT_n}}{t_n^r}\right)$$

  - Assumes un*equal time periods* at all humidity levels and temperatures. If $r = 1$, then the power terms in time can be factored out.
  - If both mean kinetic humidity and mean kinetic temperature are controlled, then the shelf life will remain unchanged. There are multiple pairs of *MKh* and *MKT* values that will keep shelf life unchanged.

Achieving *MKT* and *MKh*

- Q1: If a drug product is stored at 50 °C and 75% RH for 3 days, how many days must it be stored at 5 °C (and at what humidity *h*) so that *MKT* = 25 °C @ 60% RH assuming $r = 1$, $E_a = 83.1432$ kJ/mol* and $B = 0.05$ and the Arrhenius model is valid between 5 °C and 50 °C?

- Q2: To how many days at 25 °C and 60% RH is the combined storage conditions equivalent?

- A: By storing the product for 87 days at 5 °C and 50% RH, you nullify the effect of the temperature and humidity excursion to 50 °C at 75% RH for 3 days, and the shelf life at 25 °C at 60 %RH must be reduced by 90 days to compensate for the combined effects of high and low temperature/humidity storage.
  - HINT: You need to simultaneously vary the humidity and the storage time. There is more than one possible answer. The answer can be any point on the curve in *T*×*h* plane that satisfy conditions stated, so you can arbitrarily fix either *T* or *h*.

What if the product must be kept cold?

- This usually is important for liquid products containing biologics.
- You can use the *MKT* equation to calculate by how many days the shelf life at 5 °C must be reduced if the product is stored at higher *T.*
  - Using the previous value for E_a and r = 1, 3 days at 25 °C = 32 days at 5 °C, assuming no physical change occurs when a liquid product is heated to 25 °C, so the shelf life must be reduced by 32 days.

Challenge: Define the *T*×*h* design space!

- Find temperature and humidity range over which the extended Arrhenius model is valid.
  - Need to know E_a (and *B* and *r* for solids) for drug product for each CtS parameter.
    - These should be the same for all CtS parameters, but you need to verify this!
    - Get this information early in development—the sooner, the better.

Model-free methods

- So far, we have focused on rates and mechanisms, and used empirical models.
  - The Arrhenius rate $k_{T,g}$ is model-dependent.
  - But, time-to-failure $t_{f(T)}$ depends only on the empirical power law exponent r.
- A two-stage data evaluation technique, in which $t_{f(T)}$ is first estimated at a particular temperature T (and humidity h for solids), followed by an Arrhenius projection of shelf life, makes fewer assumptions.

Time-to-failure as a function of temperature for predicting shelf life

- The concept of using time-to-failure to predict behavior at “normal” temperatures PREDATES the use of kinetic models!
  - **Higuchi T, Havinga A, Busse LW.** The kinetics of hydrolysis of procaine. *J Amer Pharm Assoc Sci Ed* 39:405-410 (**1950**).

- Model-dependent methods were introduced later…
  - **McBride WR, Villars DS.** An application of statistics to reaction kinetics. *Anal Chem* 26:901–904 (1954).
  - **Garrett ER.** Studies on the stability of fumagillin. III. Thermal degradation in the presence and absence of air. *J Amer Pharm Assoc Sci Ed* 43:539–543 (1954).

Time-to-failure as a function of temperature for predicting shelf life

- It does not depend on conventional kinetic models.
  - Amirjahed AK. Simplified method to study stability of pharmaceutical preparations. *J Pharm Sci* 66(6):785-789 (1977).
- The FDA actually included it as a recommended method in an early guidance document!
  - —. Stability and expiration dating of drugs. FDA 72-3025, Division of Industry Liaison (BD-340), FDA, Bethesda MD (1971).
- Recently, this approach has been making a comeback…

Waterman's ASAP designs

- Ken Waterman at Pfizer has pioneered the use of time-to-failure designs in what he calls an "**A**ccelerated **S**tability **A**ssessment **P**rogram"
  - Explore temperature-humidity design space.
  - Waterman approach assumes $r = 1$.

- ASAP can be adapted to any CtS problem, not just initial screening!

ASAP: Simulating shelf life

- Using the extended Arrhenius model, you can use thermal and humidity (for solids) stress conditions to simulate longer term storage at a lower temperature (or humidity, for solids) by subjecting product to shorter term storage at a higher temperature (and humidity, for solids).
  - See, e.g., the cold chain example, where 3 days @ 25 °C = 32 days @ 5 °C for a product with E_a = 83.1432 kJ/mol, r = 1.
  - Add this stress condition as a finish to cyclic freeze-thaw studies, for example, instead of doing real time stability trials.

What about physical changes?

- Freeze/thaw studies
  - Are changes reversible? Or irreversible?
- Thermal denaturation studies for biologics
  - Gelatin cross-linking for capsule products
- Are changes in CtS parameters large enough to quantify?
  - Consider using ASAP design as finish.

Further thoughts…

- Design of temperature and humidity excursion experiments is likely to be product-specific due to differences in E_a (and B and r for solids) for each product.
  - No simple generic protocol.
- Physical changes (non-Arrhenius behavior) further complicates design.
  - Defining the temperature and humidity ranges over which the extended Arrhenius model is valid is essential to successful experimental design.

Experimental design solution: Establish the *T*×*h* design space

- If we can establish a range of temperature (*T*) and humidity (*h*) values within which the extended Arrhenius model correctly predicts shelf-life, then so long as a deviation from labeled storage conditions occurs during storage or distribution, we can *derate* the shelf life appropriately, by knowing the extent of the deviation and its duration.

Plan for excursions

- Stuff happens. Temperature and humidity excursions are *probable*.
  - Use historical distribution records to determine how probable.
    - Determine upper limit for probable increase in *MKT*.
  - Option 1: Design formal stability trials at label claim *MKT* to include added segment at higher *T*×*h* (within design space) to allow for excursions; include this extension in shelf life.
    - See, e.g., Friedman EM, Shum SC. Stability Models for Sequential Storage. *AAPS PharmSciTech*, 12(1):96-103 (2011).
  - Option 2: Conduct formal stability trials at higher *MKT* than needed to meet label claim.
    - May require change in stability chamber settings.

Take home message: Shrink time!

- By validating conditions under which the extended Arrhenius model is operable for your product, you can evaluate impact of process changes (new formulations, new manufacturing operations, changes in distribution supply chain storage & handling – any change that impacts CtS parameters) by using appropriate stress conditions at high $T \times h$ edge of design space.

Ask the RIGHT question! Do it ASAP!!

- Instead of attempting to measure impact of temperature excursions *directly*, consider instead to treat the temperature excursion experiment like any other process change, and measure impact on shelf life using a single ASAP *T*×*h* design space experimental design.
  - A single ASAP protocol can be designed for each drug product to evaluate all possible formulation, manufacturing and distribution process changes.
  - This one testing protocol answers the questions: Does this process change impact QtS parameters? In what way? By how much?
  - The ASAP protocol measures ONLY ***known knowns***.

References

- **World Health Organization (WHO)** Good Distribution Practices (GDP) for Pharmaceutical Products, Technical Report Series, No. 937, 2006
- **US Pharmacopeia** <1079> "Good Storage and Shipping Practices"
- **Health Products and Food Branch Inspectorate** GUIDE-0069 Guidelines for Temperature Control of Drug Products during Storage and Transportation [http://hc-sc.gc.ca/dhp-mps/compli-conform/gmp-bpf/docs/gui-0069-eng.php]
- **Lucas TI, Bishara RH, Seevers RH.** A Stability Program for the Distribution of Drug Products. *Pharm Tech* 86:68-73 (2004)
- **Socarras S Magari RT.** Modeling the effects of storage temperature excursions on shelf life. *J Pharm Biomed Anal* 49:221-226 (2009)
- **Krause H-J.** GMP aspects of cold chain management for pharmaceutical products [http://ccm.ytally.com/fileadmin/user_upload/downloads/Krause.pdf]
- **Haynes JD** Worldwide virtual temperature for product stability testing. *J Pharm Sci* 60:927-929 (1971)
- **Waterman KC, Carella AJ, Gumkowski MJ, Lukulay P, MacDonald BC, Roy MC, Shamblin SL.** Improved protocol and data analysis for accelerated shelf-life estimation. Pharm Res 24(4):780–790 (2007)

Questions?

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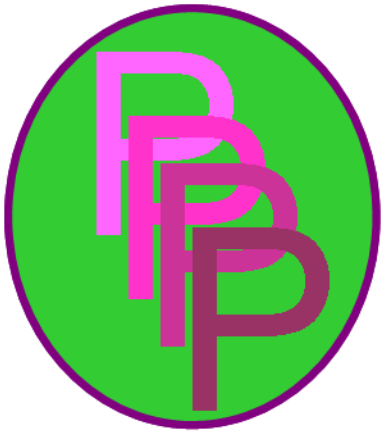

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