PHARMACOVIGILANCE IN SPACE

STABILITY PAYLOAD COMPLIANCE PROCEDURES

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Pharmacovigilance

- Pharmacovigilance is the science of, and activities relating to the detection, assessment, understanding, and prevention of drug-related problems.
- Over the last decade, pharmacovigilance activities have contributed to the development of numerous technological and conventional advances focused on medication safety and regulatory intervention.

Proactive Pharmacovigilance

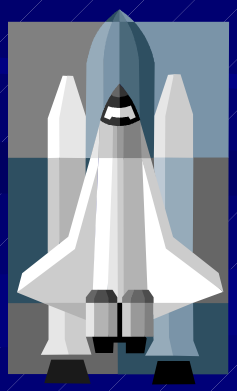
- The challenge today is to move pharmacovigilance activities from detection to prediction, or from a reactive to a proactive operation.

- Proactive pharmacovigilance identifies important areas of uncertainty and puts in place the studies which reduce those uncertainties.

*heads.medagencies.org/heads/docs/Section_6_**Pharmacovigilance***

A New Frontier

- As our civilization continues to expand its frontiers of exploration, there is a need to develop proactive countermeasures that reach beyond the scope of standard pharmacovigilance practice.
  - Therapeutic efficacy and safety of pharmaceuticals flown on the Space Transportation System (STS) and International Space Station (ISS) remain a critical issue for successful NASA medical operations.



Research Activities

The Pharmacotherapeutics Team at NASA – Johnson Space Center (JSC) developed a research project, (*Assessment of Pharmaceutical Stability in Analog Environments and in Space Missions: Ground and Flight Experiments – L. Putcha, P.I.*), designed to examine medication stability (shelf-life) after exposure to the conditions of Space (ISS and STS flights) utilizing a select group of medications from different:

- therapeutic indications
- dosage forms
- delivery systems

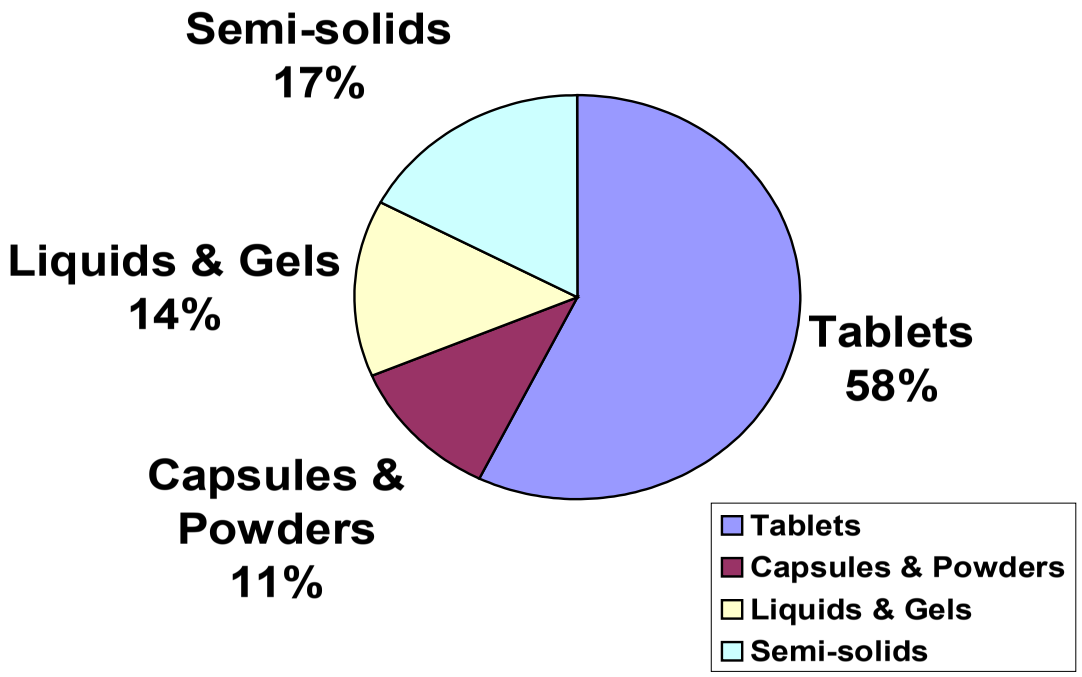
PROJECT PURPOSE

- Provide valuable data regarding the degradation of key pharmaceutical compounds under the conditions of spaceflight.
- Define requirements and deliver recommendations for formulation, packaging, shielding and shelf life of drugs for exploration class missions.

METHODS

- Sixteen pharmaceutical kits consisting of 35 different medication formulations were packed at JSC and transported to Kennedy Space Center (KSC) under identical conditions to support three experimental conditions:
  - Spaceflight
  - Ground – Simulation
  - Ground Control
- Fourteen similar pharmaceutical kits consisting of 19 different medication formulations were customized and packed at JSC and transported to NASA Space Radiation Laboratory (NSRL), to support the ground – simulation experimental condition.
- All pharmaceutical kits will include a Temperature Data Logger and Passive Dosimeter recorder to record temperature, humidity, and radiation levels, respectively.

Flight Stability Kit Components



Experimental Conditions

- Spaceflight (STS, ISS)
  - A payload containing 4 kits of medication will be flown on board the STS-121 for stowage on the ISS, and brought back after predetermined increments of space exposure for analysis on the ground.
- Ground – Simulation
  - 4 kits identical to the 4 kits designed for flight will be placed into a Orbiter Environment Simulator (OES) chamber in the Space Life Sciences (SLS) facility at NASA – KSC, simulating environmental conditions of the flight kits while on the STS and ISS.
  - 14 additional medication kits were assembled with medication formulations found in the flight kits; as well as additional medications of interest, and sent to NSRL for testing with a combination of radiation energies and heavy ion energies similar to those frequently encountered in space.
- Ground Control
  - The remaining 8 Identically packaged stability kits of medications will be stored in secured facilities at KSC on the ground, until returned to JSC with the flight and OES kits.

Research Project Logistics

I-13 | I-14 | I-15 | I-16

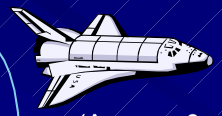
Sep 2006 | Mar 2007 | Sep 2007

ULF1.1
STS-121
July 2006

A
B
C
D

A

ULF1.1
STS-121
July 2006



B

(Approx. 6 months)
13A
STS-117
Mar 2007

C

Approx. 12 months)
10A
STS-120
Aug 2007

D

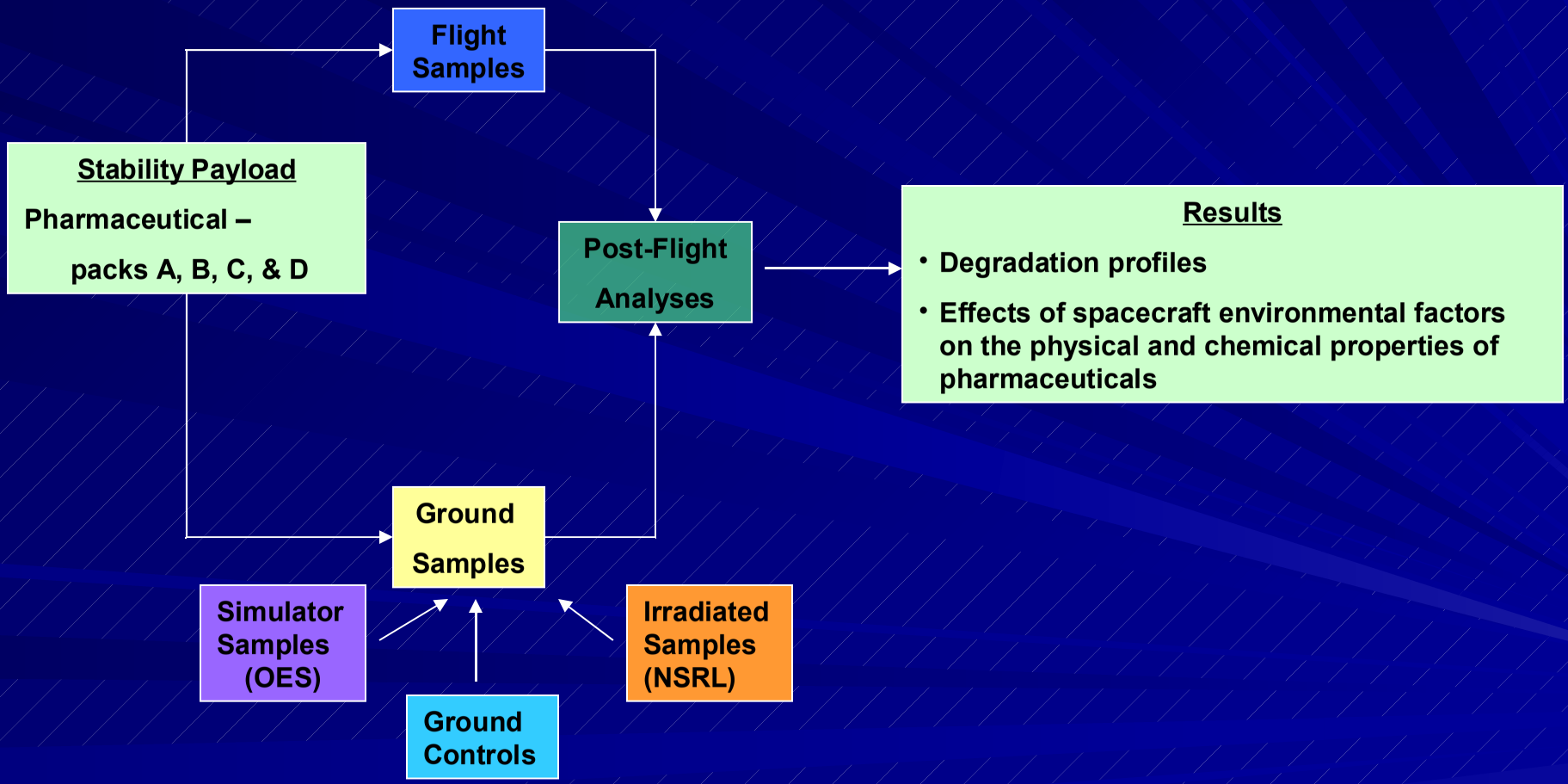
Approx. 18 months)
1J
STS-TBD
Feb. 2008

Flight Samples – transported to ISS and stored for various time durations prior to return for analysis
A,B,C, and D kits are identical and will contain pharmaceuticals, food, a dosimeter and temp. sensor.
NOTE: *All flight information is from the SPP Launch CR currently in review – not approved by program*

A → A
B → B
C → C
D → D

Ground Controls – identical packets stored for durations equivalent to flight samples prior to analysis

Research Plan



Pharmaceutical Stability Research Project

Pharmacovigilance Aspects

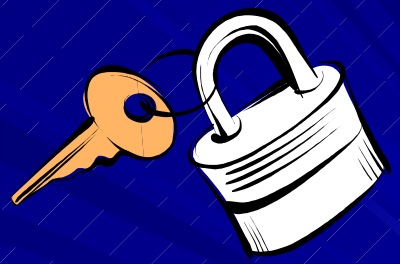
A. **Security / Control**
   1. Regulatory Compliance
   2. Storage
   3. Medication Accountability

- **Packaging / Containment**
   1. Flight Crew Safety
   2. Environmental Barriers

C. **Shelf-life Assessment**
   1. Physical Characterization
   2. Chemical Analysis (HPLC / UPLC)

Security / Control

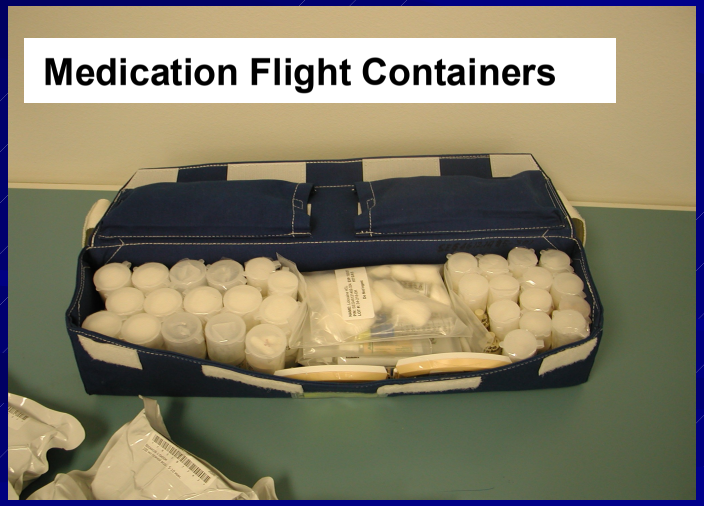
- The first pharmacovigilance action was to identify regulatory concerns with medication:
  - Transport and storage
  - Acquisition
    - Pharmacy state and federal regulations
    - Custody and control
    - Access
  - Accountability
    - Maintenance of required logs and files



Packaging / Containment Actions

- Customized Flight Hardware was designed and developed to:
  - Package the medication
    - Plastic pharmaceutical vials with attached snap lid
    - Zip-locked baggies
  - Contain the medication packages
    - Fabric medication kits with secured Velcro straps
  - Secure the stored medications during flight, and while being stored as Control group components on the ground
    - Locked and integrity sealed transport containers
- Materials were selected to:
  - Contain the medications sufficiently to avoid Crew injury from loose debris
  - Comply with weight and space limitations

Packaging / Containment Actions



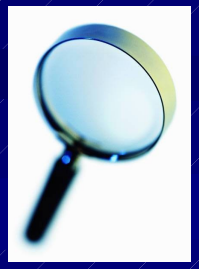
Shelf-Life Assessment

Adverse effects on pharmaceutical stability compromise medication safety and efficacy, by increasing risk of :

- treatment failure
- development of toxic degradation products

Stability Assessment Parameters

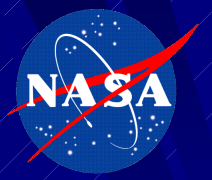
- Physical Parameters
  - Medication samples will be visually inspected, measured, and photographed to document their physical characteristics:
    - Weight Variation
    - Size / dimensions
    - Description (appearance)
    - Clarity, texture



Stability Assessment Parameters

- Physical parameters for Solid dosages
  - Tablets will be subjected to two quality control test used to evaluate the effects on dosage uniformity potentially resulting from the rigors of transport, storage, and flight.
    - Tablet hardness test
    - Tablet Friability test
  - Solid-filled capsules and dry powders will be microscopically examined to acquire particle size measurements.
  - Aqueous formulations will be examined for changes in pH.
  - Sterile formulations will be tested for microbiological contamination.

Stability Assessment Parameters



- Chemical Content
  - The medication samples will be analyzed for Drug Content Uniformity to assure the uniformity of the active ingredient using validated stability-indicating assays.
    - High Performance or Ultra Performance Liquid Chromatography (HPLC, UPLC)
    - Samples that show a significant loss (*10% or more)* of active ingredient compared to the labeled strength will be further analyzed using LC-MS to identify degradation products.
  - Solid and semisolid medication samples will be tested for rate at which the active ingredient is released from the dosage form using a standard dissolution or diffusion testing apparatus.

Chemical Content Analysis

UPLC for Content
Uniformity Assessment

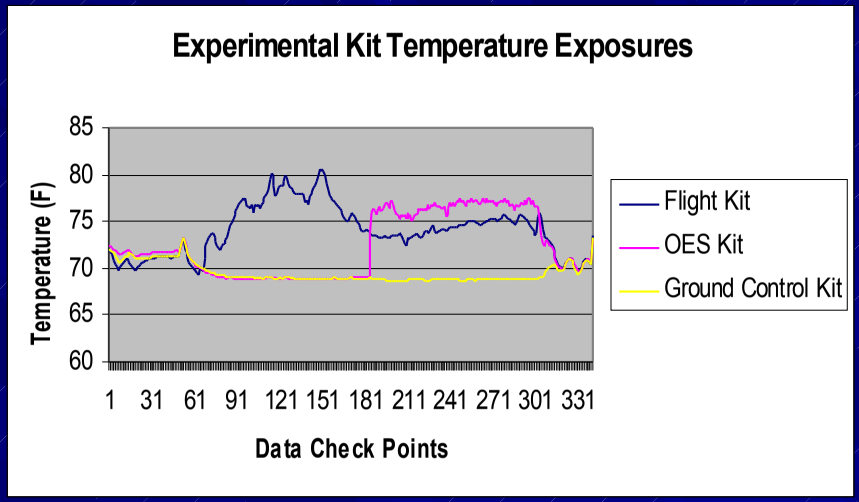
Dissolution Testing Apparatus

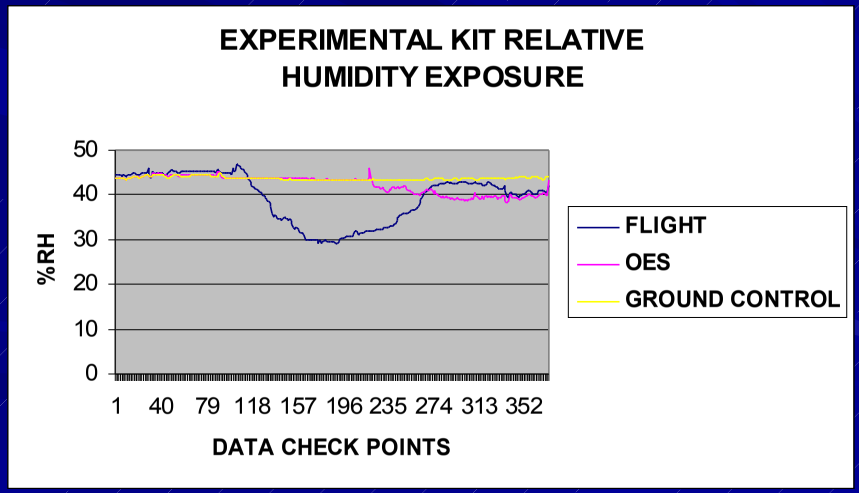
Preliminary Results

- The first kit flown on a shuttle flight was returned
- Ground control environmental conditions data, temperature and Relative Humidity have been compiled
- Physical assessment and chemical analyses have been completed for all flight and ground analogue samples.
- Dissolution and diffusion rate determinations of active compound for all dosage forms is currently in progress

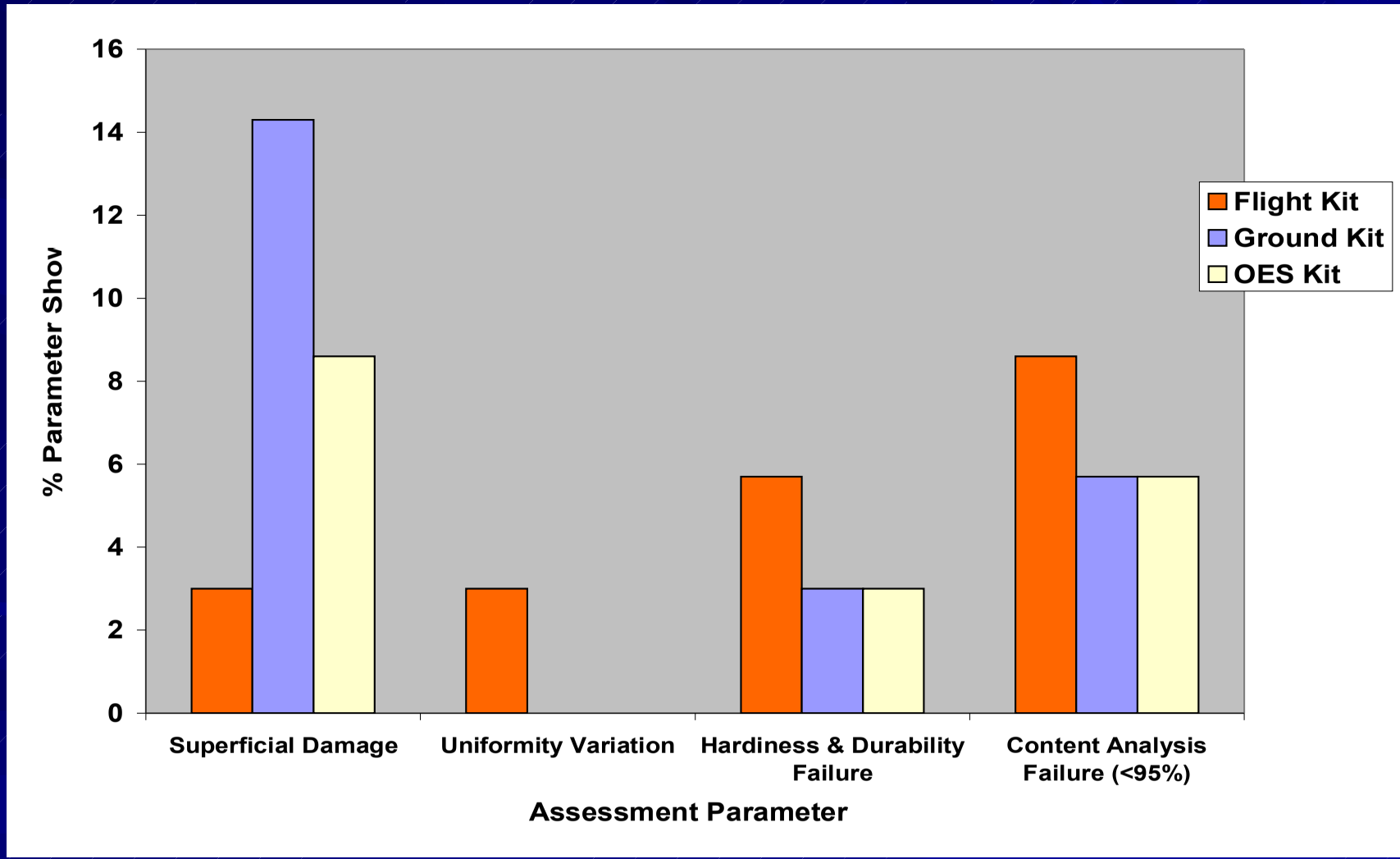
Temperature / Humidity

- The temperature and humidity data loggers recorded 12 data points/day (q2h).
- Data points obtained pre-flight from 6/22/06 @ 6:00AM (1 hour prior to kits removal from the storage lab locked cabinet for STS-121 Bench Review), until 7/20/06 @ 2:00PM post-flight (when the kits were placed back in their initial storage lab locked cabinet).





Changes in Physical and Chemical Assessment Parameters



Observations

- For this first flight increment, at least 80% of medications in the three flight experimental kits (flight, ground simulator (OES), ground controlled), performed well, as demonstrated by lack of physical or chemical assessment criteria failure.
- None of the medications in either of the three flight experimental kits were discolored.

Conclusions

- The science of pharmacovigilance should begin to explore customized regulatory and pharmacy practice interventions that address the unique concerns of space travel and exploration.
- These interventions will be crucial in the development of a blueprint for the next frontier of pharmaceutical research and clinical practice.

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