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_Phamacovigilance
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.
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.
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

- Tablets: 58%
- Liquids & Gels: 14%
- Capsules & Powders: 11%
- Semi-solids: 17%
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.
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.

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

Results
- Degradation profiles
- Effects of spacecraft environmental factors on the physical and chemical properties of pharmaceuticals

Ground Samples

Flight Samples

Stability Payload
Pharmaceutical – packs A, B, C, & D

Post-Flight Analyses

Simulator Samples (OES)

Irradiated Samples (NSRL)

Ground Controls
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)
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

Flight Kit Locker

Pharmaceutical Stability Kit

Medication Flight Containers

Stability Kit

Transport Container
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.
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.
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

- Superficial Damage
- Uniformity Variation
- Hardiness & Durability Failure
- Content Analysis Failure (<95%)

Assessment Parameter

Percentage Shown

- Flight Kit
- Ground Kit
- OES Kit
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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