QUANTITATIVE ANALYSIS OF SPACEFLIGHT DRUG STABILITY DATA TO SUPPORT A STRATEGY FOR PREDICTIVE PHARMACEUTICAL TESTING

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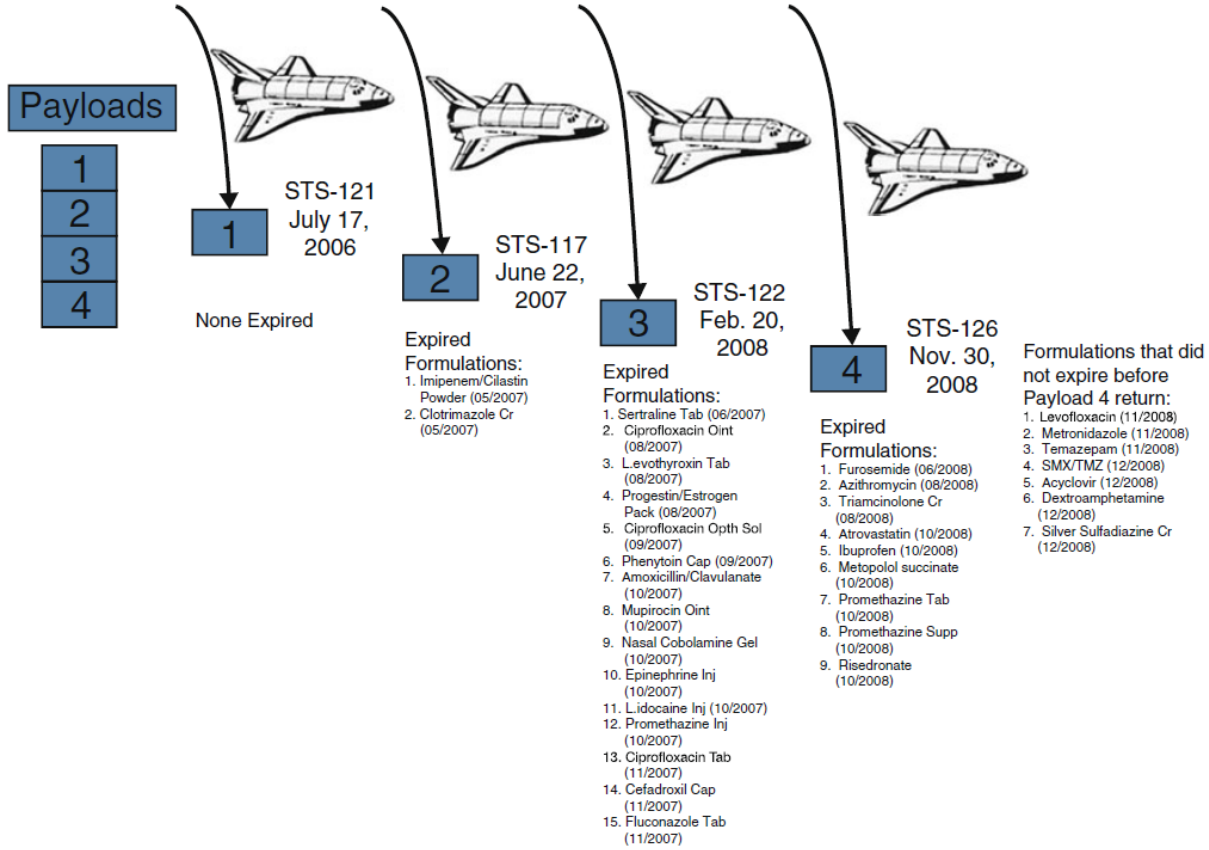
Expanding the Boundaries of Space Medicine and Technology

Background: Pharmaceutical Stability Studies

- Most comprehensive study to date: Du et al., 2011.
  - 36 Active pharmaceutical ingredients (APIs) (33 formulations)
  - Two conditions: Spaceflight and “analog” terrestrial chamber
  - Four timepoints: 13 days, 332 days, 596 days, 880 days
  - Terrestrial control and flight samples were from matched manufacturing lots
  - Summary data available from supplementary tables through publisher website!
  - **Solid oral formulations repackaged in plastic containers**



Du et al., The AAPS Journal, Vol. 13, No. 2, June 2011
DOI: 10.1208/s12248-011-9270-0

Background: Intersection Among NASA Drug Stability Studies

Opportunistic Spaceflight Medication Stability Studies.					
Study	Corey et al., 2017	Corey et al., 2016	Wotring, 2016	Wu and Chow, 2016	Wotring and Khan, 2014
Space Platform	ISS	ISS Medical kit	ISS Medical kit	ISS Medical kit	ISS (retest of Du samples)
Published or NASA report	NASA Report	NASA Report	Published	NASA Report	NASA Report
Terrestrial controls	No	Unmatched (controls are different lots)	No	Unmatched (controls are different lots)	Matched and unmatched present
Repackaged	All flight samples repackaged; controls packaging not described.	All flight samples repackaged; controls packaging not described.	All medications were repackaged.	All flight samples repackaged; Controls packaging not described.	All flight samples repackaged.
APIs Tested	Amoxicillin, Aspirin‡, Pseudoephedrine‡	Levofloxacin, Ibuprofen, Phenytoin, Valacyclovir, Sertraline	Aspirin‡, Acetaminophen, Ibuprofen, Loratadine, Loperamide, Melatonin, Modafinil, Pseudoephedrine‡, Zolpidem	Promethazine, Promethazine_Inj Azithromycin, Ibuprofen	Levothyroxin, Levofloxacin, Azithromycin

Drugs in red intersect with the list of 36 active ingredients tested by Du et al (2011)

Study Rationale and Hypothesis

Rationale: For exploration space missions, we need to understand how spaceflight affects drug stability.

Objective: To perform a statistically robust meta-analysis of all spaceflight studies performed to date to inform the design of future drug stability studies.

Hypothesis:

H_0: Drug samples exposed to controlled spacecraft environments undergo degradation that is no different than paired lot-matched terrestrial samples stored under similar (but not identical) conditions.

H_A: Spaceflight exposure accelerates drug degradation.

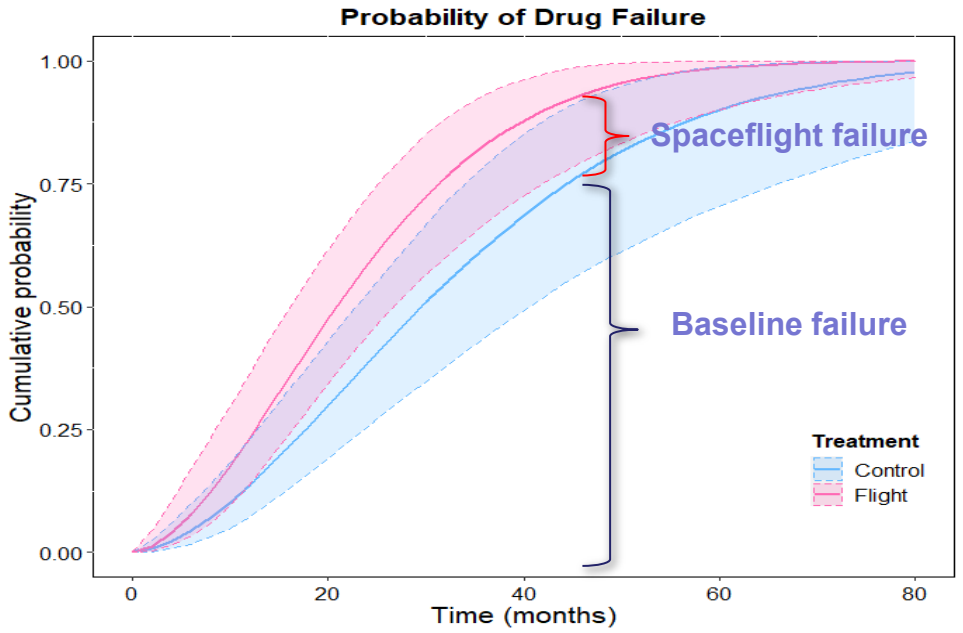
Results: First-order Degradation – Degradation Rates

Representative degradation rates and shelf-life predictions for expedition-duration missions

API Tested	Control Degradation Rate (%/day)	Spaceflight Degradation Rate (%/day)	Rate ratio (F/C)	Estimated Control Half-life (Years)	Estimated Spaceflight Half-life (Years)	Control, Percent remaining after 3 years	Spaceflight, Percent remaining after 3 years
ciprofloxacin	-1.60E-04	-2.03E-04	1.26	11.84	9.36	83.9	80.08
ciprofloxacin_(o)	-7.97E-05	-1.37E-04	1.72	23.82	13.86	91.64	86.07
ciprofloxacin_(s)	-2.65E-05	-5.90E-05	2.22	71.63	32.2	97.14	93.75
promethazine	-9.33E-05	-1.49E-04	1.59	20.36	12.77	90.29	84.97
promethazine_(pr)	-6.47E-05	-1.70E-04	2.63	29.35	11.18	93.16	83.03
promethazine_(i)	-1.40E-04	-1.64E-04	1.18	13.58	11.55	85.8	83.52
atorvastatin	-2.70E-05	-9.78E-05	3.62	70.33	19.41	97.09	89.84

Results: Probability of Drug Failure

- Accelerated Failure Time Model
  - Drug degradation is a continuous variable, so…
    - Lower bound of the confidence 95th percentile confidence interval
    - Failure defined as current USP specifications for API content.
  - Data are fully censored (statistically)
  - Bayesian parametric (Weibull distribution); does not assume proportional hazard
- Results
- Spaceflight increases the risk of drug failure, but only incrementally over the baseline risk.
- Conclusion
- The MAJOR risk of failure is associated with storage time observed in control samples.
- Why? Repackaging is the most likely explanation



Accelerated failure time model of drugs stored under terrestrial and spaceflight conditions

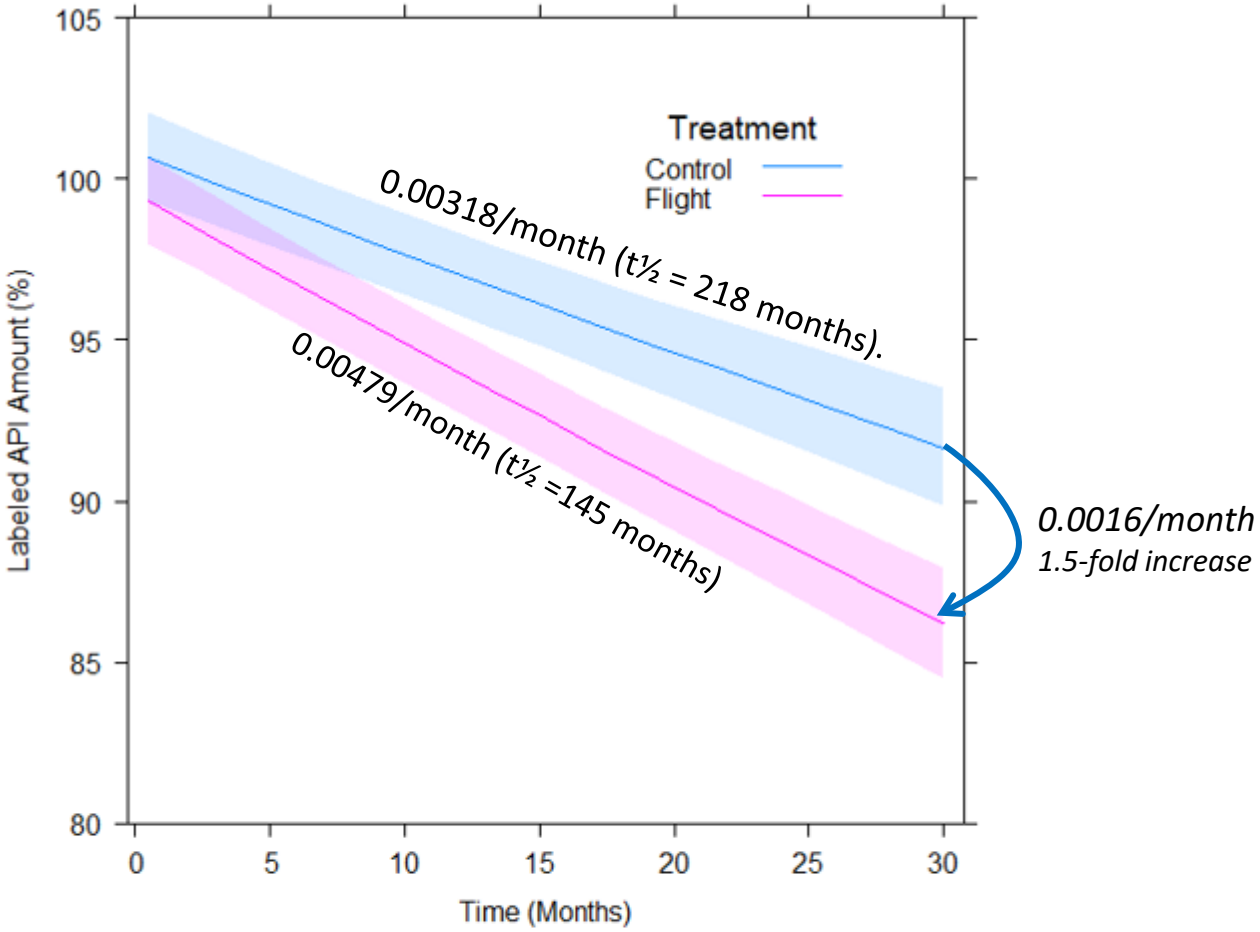
TABLE 5. Drug failure probabilities at specific time points

Median Probability ± std	Storage Duration (Months)			
	1	12	24	36
Terrestrial storage	0.003 ± 0.003	0.136 ± 0.039	0.382 ± 0.068	0.615 ± 0.090
Spaceflight storage	0.006 ± 0.005	0.241 ± 0.060	0.584 ± 0.073	0.821 ± 0.068

Results: Aggregate Analysis

- What is the aggregate effect of spaceflight across all drugs?
  - Method:
    - Mixed effect model
    - Generalized estimating equation (GEE) model
- Results
  - Spaceflight increases 1st order drug degradation rate 1.5-fold.
  - > 70% of unexplained model error is associated with random intercept – need that zero timepoint!
  - ≈ 20% of model error associated with API slope (degradation rate)
  - Mixed effect model and GEE give very similar results.
- Conclusion:
  - Spaceflight increases drug degradation rate generally, but not much – 1.5-fold
  - The majority of degradation is attributable to factors other than space flight (blue control).

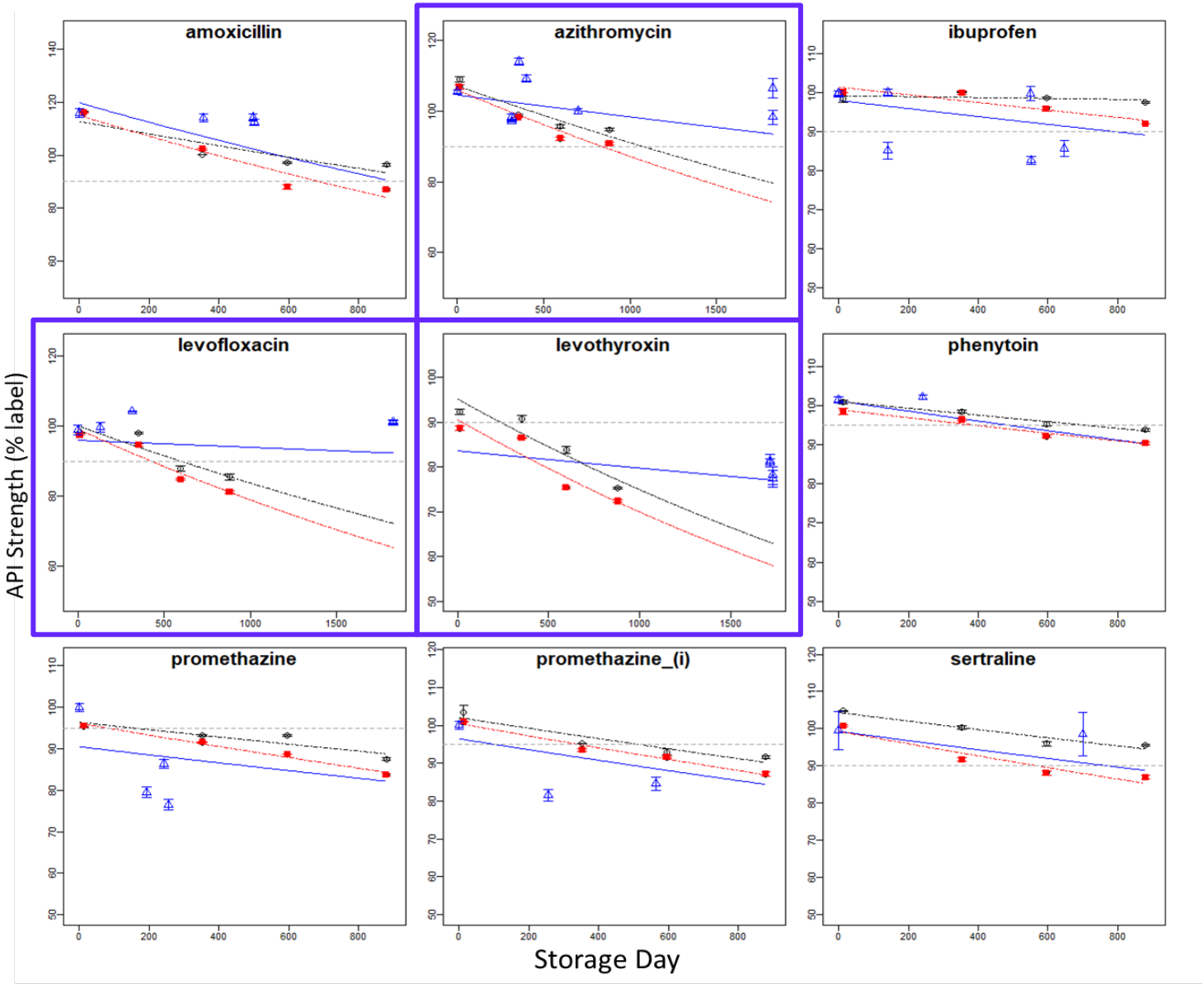
Generalized Estimating Equations model for API content



Figure·3.·Mixed-effect·model·with·API·degradation·rates·control·(blue)·and·flight·samples·(red)·for·all·APIs.·Shaded·area·is·95%·confidence·interval.·Note·the·narrow·range·on·the·y-axis·is·80·to·105%.··¶

Results: Analysis of Overlapping Studies

- How do the results of Du et al. compare to other studies where similar drugs were tested?
- Results
  - Azithromycin Levofloxacin and Levothyroxine (blue boxes) were retested at the FDA analytical lab >2 year later
    - EXACTLY the same samples tested by Du et al (2011); analyzed at FDA
    - Results showed minimal degradation over time
  - Other anecdotal studies show similar degradation trends for different drugs.
- Conclusion
  - FDA results suggests the possibility of inefficient extraction of API from some drugs and an under estimate of drug content.



Conclusions

- Null hypothesis is rejected for spaceflight samples studies by Du et al. (2011)
  - Spaceflight accelerated overall degradation by 0.5-fold, with a ~2-fold increase in the time-dependent failure probability
  - However, *both* control and flight samples exhibit significant degradation.
- Preliminary NSRL studies with ionizing radiation have not shown a consistent effect of ionizing radiation on drugs
- It is hypothesize that the packaging of solid oral medications is a major factor contributing to facilitated degradation observed in BOTH control and flight samples
  - If true, then it is critical to develop and validate ***protective*** packaging methods
  - If true, then it is critical to identify the key environmental factors and/or medication attributes that contributing to accelerated drug failure
- Most medications (clavulanate excluded) appear to show slow first-order degradation rates, that can predict expected drug degradation and failure for long-duration missions

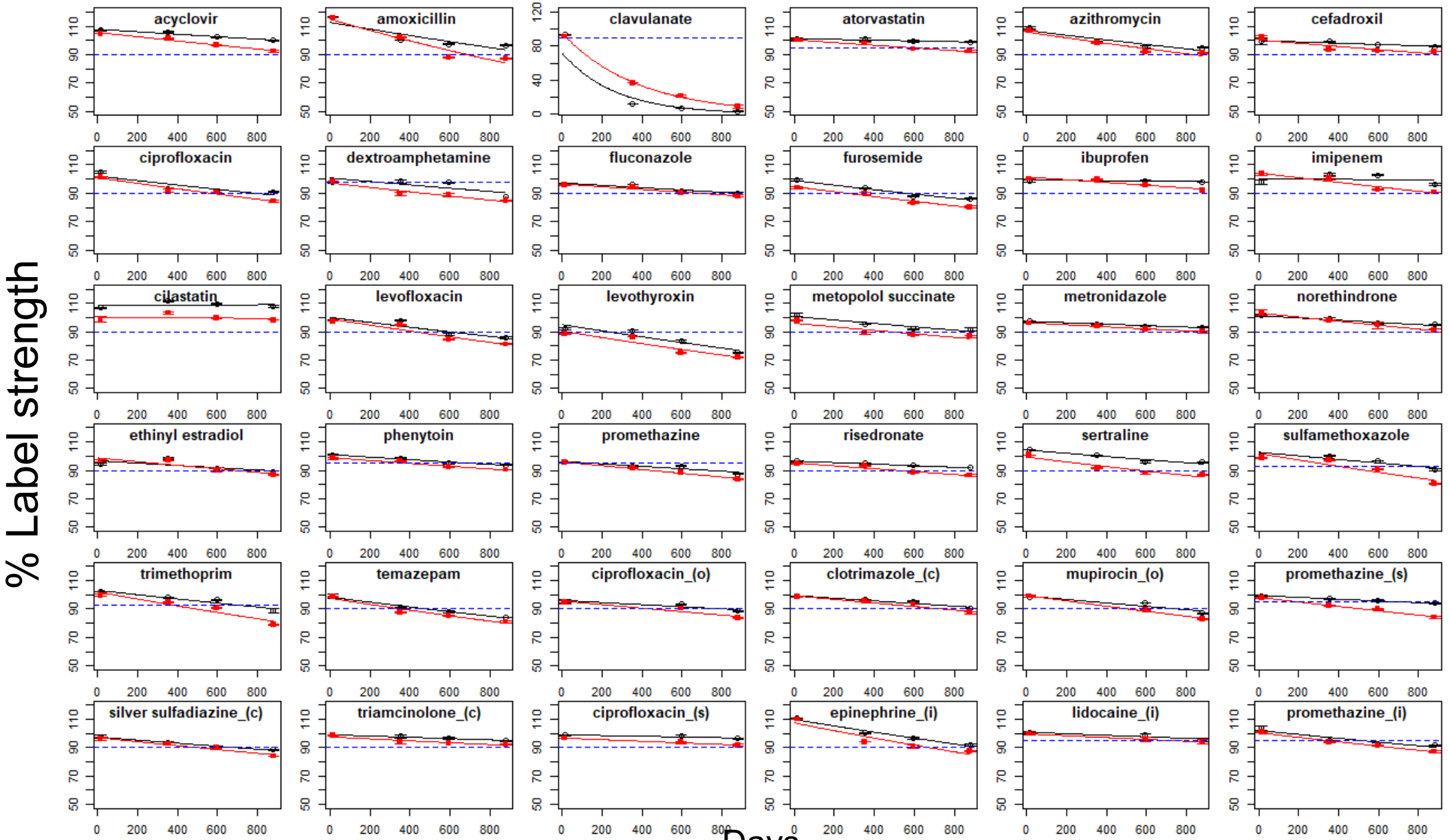
Limitations

1. All previous studies have been observational studies that can only show associative relationships, not causation
2. All previous studies have used very different methodologies that make it difficult to compare results across studies
   - Most studies are not controlled studies
3. All studies have focused on solid oral medications that were repackaged
   - Atmospheric permeation is a likely confounder for evaluated studies
   - Aqueous drug formulations need to be tested

Questions/Comments?

Supporting Slides

Results: First-order Degradation – Trend Analysis



Results: Delta analysis

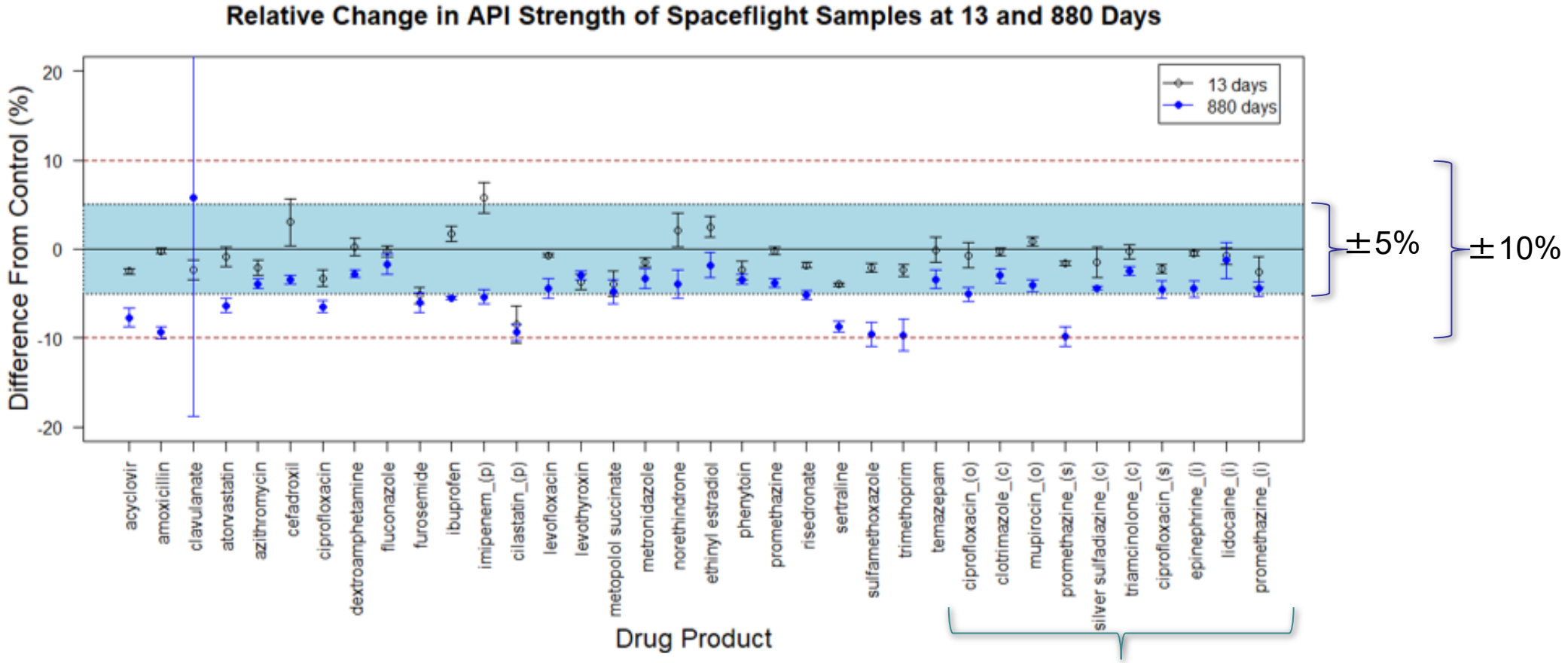


Figure 1. Plot of the **difference** between pair-matched control and spaceflight drugs stored for either 13-days (o) or 880-days (●) samples. Values are calculated as API strength (%) in control – API strength (%) in matching spaceflight samples. *Values are calculated as API strength (%) in control – API strength (%) in matching spaceflight samples. Standard deviations consist of propagated error for control and spaceflight samples. The blue shaded area represents a 5% difference in API strength; the red dashed line represents a 10% difference. A value of zero indicates no difference between control and spaceflight samples. Over the course of the entire 880-day storage experiment, no flight-based drug exhibited more than a 10% change from control API levels.*

Drug Stability - Overview

Dosage Form

Drug substance

Active pharmaceutical Ingredient (API)

Excipients

Inactive Ingredient

Chemical Degradation

- Oxidation
- Hydrolysis
- Photolysis (UV)
- Racemization

Reactive Impurities

- Aldehydes
- Peroxides
- Metals
- Alcohols

Physical degradation

- Appearance (size/shape/color)
- Content Uniformity
  - Separation
  - Sedimentation
  - Crystal growth
- Dissolution
- Sublimation

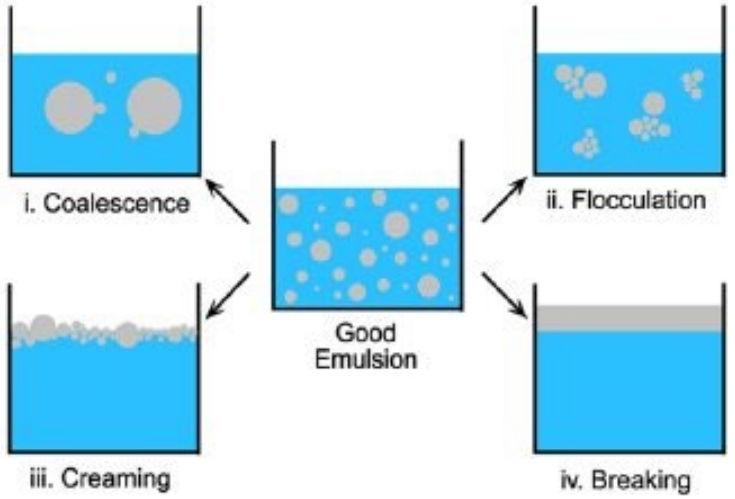


Figure: Pavle Mijovic et al. 2017
https://www.researchgate.net/publication/290430041_Influence_of_processing_on_cosmetic_pharmaceutical_and_food_emulsions_quality_stability_and_rheology/figures?lo=1

Supplemental results: NSRL Study

- What about the effect of ionizing radiation?
  - Four solid oral drug exposed to ionizing radiation to a doses of 0.5 or 1 Gy (Day = 0).
  - Samples stored under controlled conditions for ~1, 2 or 3.5 years (covid delayed final timepoint)
  - Drugs at the GLP UMB Applied Pharmaceutics Lab
- Preliminary results
  - Irradiated samples do not appear to undergo greater degradation compared to matched controls
  - All samples undergo degradation regardless of treatment
  - All medications were repackaged prior to irradiation.
  - Promethazine degraded much more rapidly than expected in both control and irradiated samples.
- Conclusion
  - With flight studies, data support a conclusion that packaging is a greater concern for solid drugs than ionizing radiation at doses ≤ 1 Gy