Evidence Report:

Risk of Ineffective or Toxic Medication During Long-Duration Exploration Spaceflight

Human Research Program

Exploration Medical Capability (ExMC) Element

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Risk of Ineffective or Toxic Medication During Long-Duration Exploration Spaceflight

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I. LIST OF ACRONYMS

Acronym/Abbreviation	Definition
API	active pharmaceutical ingredient
BUD	beyond use date
DAG	directed acyclic graph
DoD	Department of Defense
DRM	design reference mission
EMA	European Medicines Agency
EMC	European Medications Compendium
EU	European Union
eV	electron volt
ExMC	Exploration Medical Capabilities (Element)
GCR	galactic cosmic radiation
GCRsim	simulated galactic cosmic radiation
GeV	giga-electron volt
Gy	Gray
HBEL	health-based exposure limits
HRP	Human Research Program
HZE	high atomic number (Z) and energy
ICH	International Council for Harmonisation
ISS	International Space Station
JSC	[Lyndon B.] Johnson Space Center
KeV	kiloelectron volt
kg	kilogram
kGy	kilogray
LC-MS	liquid chromatography-mass spectroscopy
LEO	low Earth orbit
LET	linear energy transfer
LLOD	lower limit of detection
LLOQ	lower limit of quantitation
LTH	long-term health
lux	unit of illuminance, equal to one lumen per square meter
MeV	megaelectron volt
Mfr.	manufacturer

Acronym/Abbreviation	Definition
MoA	mode of action
MS/MS	tandem mass spectroscopy
NAS	National Academy of Sciences
NASA	National Aeronautics and Space Administration
NDC	national drug code
NOAEL	no observed adverse effect level
NSRL	NASA Space Radiation Laboratory
PEG	polyethylene glycol
PD	pharmacodynamics
PK	pharmacokinetics
POD	point of departure
RH	relative humidity
SAS	space adaptation syndrome
SLEP	Shelf Life Extension Program
SODF	solid oral dosage formulations
SPC	summary of product characteristics
SPE	solar particle event
STS	Space Transportation System
U.S. FDA	United States Food and Drug Administration
USP	United States Pharmacopeia
UV	ultraviolet
WHO	World Health Organization

II. RISK TITLE: RISK OF INEFFECTIVE OR TOXIC MEDICATION DURING LONG-DURATION EXPLORATION SPACEFLIGHT

Risk Statement: Given that no method currently exists to sufficiently characterize how the quality and performance of medications that are exposed to the crewed environment during long-duration exploration missions relate to their stability and potency, provisioning of a safe and effective drug treatment may be significantly limited, which could impact the health and performance of crewmembers.

III. STATUS

- *Active*: Work and research are ongoing to address this risk.

IV. EXECUTIVE SUMMARY

The scope of this report is limited to evaluating drug stability with respect to spaceflight. The effects of spaceflight on drug pharmacokinetics (PK) or drug pharmacodynamics (PD) are not addressed in this report: these topics will be reviewed in future reports. This is the first report of the available evidence pertaining to the chemical and physical stability of drugs in the context of drug impurity, drug repackaging, and exposure to ionizing space radiation. Previous studies are discussed within this report and, where possible, the data are interpreted and contextualized with regards to drug stability.

Pharmaceuticals are used during space missions to treat a range of medical conditions, and to prevent or mitigate health-related concerns known to occur during spaceflight. The pharmaceuticals that will be selected for future human exploration space missions must remain adequately safe and effective throughout the duration of the mission. Evidence that medications degrade during spaceflight comes primarily from one controlled drug stability study that reported a loss of potency and physical changes for some drugs after approximately 2.5 years of spaceflight exposure (Du, et al., 2011). Several other opportunistic studies have provided mixed anecdotal evidence that some medications degrade during spaceflight; however, the design of these studies precludes comparison of spaceflight aging and normal aging in a terrestrial environment. Overall, the risk that drug degradation imposes for exploration human space missions is unclear because only a fraction of National Aeronautics and Space Administration (NASA)-supported studies have been published, and most do not include matched terrestrial controls or a series of timepoints that enable degradation rates to be compared between these environments.

Many studies have assessed the stability of pharmaceuticals, and the literature associated with these studies is abundant. In part, this is because the stability of drugs reflects the aggregate effect of factors that include product formulation, manufacturing process, storage condition, and environmental exposure on

the chemical and physical properties of each drug product. It is very well established that environmental factors, particularly humidity, can facilitate physical and chemical degradation of drugs. Consequently, the pharmaceutical containers in which drugs are marketed are considered an integral part of the drug product itself, and critical for ensuring stability of the product over its expected shelf life. To minimize mass and volume for space missions, NASA's current practice is to remove solid oral dosage formulations (SODFs) from their sealed, manufacturers' packaging and repackage them in plastic zip-lock baggies. Although appropriate for current mission scenarios, this process jeopardizes the expected shelf life of many oral medications and could be a concern for long-duration exploration missions. This is particularly problematic because many of the drug products currently being considered for exploration space missions have shelf lives that are inadequate for the duration of these missions and non-protective repackaging heightens this concern. Whereas the risk of therapeutic failure related to the loss of a drug's active pharmaceutical ingredient (API) can be straightforward to assess, health risks imposed by degradation impurities must be assessed by addressing fundamental elements of hazard analysis, dose-response, exposure, and risk characterization (National Research Council, 1983).

Despite the evidence currently available, it remains unclear whether spaceflight has any measurable effect on pharmaceutical stability. All currently available spaceflight studies have substantive method and design limitations, including inadequate experimental transparency and the absence of matched terrestrial controls. Furthermore, ionizing radiation in the range of acceptable human exposures appears to have little to no dose-related effect on pharmaceuticals. Available evidence strongly supports the conclusion that vapor- and gas-permeable packaging is likely detrimental to the long-term stability of some SODF (tablets and capsules). Compounding this problem is that the shelf life for many spaceflight formulary medications, even under labeled terrestrial storage conditions, is inadequate for long-duration exploration missions. Repackaging medication exacerbates the shelf-life problem and may potentiate the comparatively minor effect of ionizing radiation.

V. INTRODUCTION

NASA and its international partners are developing capabilities to conduct human exploratory space missions beyond low Earth orbit (LEO). A roundtrip mission to Mars is expected to last 2–3 years (Drake and Watts, 2014; Smith, 2020). Unlike the International Space Station (ISS), which can be regularly resupplied, planetary missions will be too distant for resupply. For this reason, future exploration-class spaceflight missions will need to be increasingly Earth-independent. Long-duration space missions will expose crews to new and increased hazards, leading to increased potential for adverse health effects. Pharmaceuticals are a critical resource for maintaining crewmembers' health and performance and for managing highly probable and potentially severe medical conditions that may arise during deep-space missions. Concurrent with the increased risks of adverse health effects, the limitations of mass, volume, and power for these missions will result in constrained pharmaceutical resources (Patel, et al., 2020). Therefore, pharmaceuticals must be carefully selected and packaged to ensure stability and therapeutic efficacy throughout the entire duration of an exploration mission (Hanson, et al., 2019).

All the NASA-supported studies of drug stability conducted so far have provided an inconsistent and incomplete picture of drug stability during spaceflight. Results from the only controlled study of drug stability during spaceflight indicate that the majority of both terrestrial and spaceflight medication (61.5 ± 9.0% and 82.1 ± 6.8%, respectively) failed to meet U.S. Pharmacopeia (USP) standards for drug potency after 880 days of storage (Reichard, et al., 2023). Five additional NASA-supported opportunistic spaceflight studies have produced inconsistent results (Table 1). All 6 flight-based investigations have limitations in design that make quantitative comparisons across studies difficult, and result in large qualitative uncertainties. One characteristic common to all these spaceflight drug stability studies is that they have focused on repackaged solid oral drug forms (tablets or capsules). Only the study by Du et al. (2011) included a small subset of non-solid formulations that remained in the manufacturer's packaging. It is well established that, in the absence of protective packaging, environmental exposure facilitates the chemical reactions responsible for degrading most pharmaceuticals [e.g., (Asafu-Adjaye, et al., 2011; Berendt, et al., 2012; Yang, et al., 2010)]. This fact is the basis for the U.S. Food and Drug Administration's (FDA) guidance on packaging (U.S. Food and Drug Administration (FDA), 2017; U.S. Food and Drug Administration (FDA), 2020a) and on shelf life testing (U.S. Food and Drug Administration (FDA), 1999; U.S. Food and Drug Administration (FDA), 2003), and for USP specifications on packaging (United States Pharmacopeia, 2020a; United States Pharmacopeia, 2020b).

Drug stability contributes directly to the risk of ineffective or toxic medications and is applicable to the knowledge gaps for PK and PD. Chemical reactions degrade drug products (Appendix 1), leading to a loss

of the API, which reduces therapeutic efficacy. Changes in inactive ingredients (excipients) can alter dissolution rate of oral drugs. Chemical reactions mediating the loss of API concurrently produce degradation impurities that can have adverse toxicological outcomes and may further influence API stability. These effects, API loss, impurities, and altered excipients are interrelated. Chemically degraded drugs do not deliver the dose of API required to attain blood and tissue concentrations (PK) needed to achieve the desired PD effects. Physical degradation can impact factors such as dissolution rate, which in turn affects absorption and bioavailability (PK), and consequently PD. Increases in dissolution can increase API, which increases the rate of absorption of API and results in elevated blood concentrations and an increased risk of side effects. If dissolution rate slows, absorption and bioavailability of API may be reduced, resulting in lower concentrations of API in the blood and, potentially, an increased risk of therapeutic failure. Both chemical and physical properties of pharmaceuticals deteriorate due to interaction of drug ingredients and environmental factors. Thus, the strategy of NASA's Human Research Program's (HRP) Exploration Medical Capability (ExMC) Element is to evaluate both the chemical and the physical characteristics of drug stability.

VI. EVIDENCE

A. PRINCIPLES OF DRUG DEGRADATION

1. PHYSICAL AND CHEMICAL DEGRADATION OF DRUGS

Pharmaceuticals contain one (or more) API, which is the active drug substance, in combination with other active or inactive ingredients, known as excipients. For example, an aspirin tablet contains the drug substance acetylsalicylic acid, which is the API, as well as several therapeutically inactive excipients. The API gives the medication its pharmacological activity, whereas excipients are important for the manufacturing process and give the medication all its physical characteristics. The term *drug* is an ambiguous term but is used here as shorthand for *pharmaceutical, medication, or drug product*.

a. *Brief Overview of Drug Degradation*

Drugs degrade in 2 principal ways: physical degradation and chemical degradation. Physical degradation affects the drug's physical characteristics, such as its appearance, hardness, or dissolution rate, which can impact the drug's behavior. Dissolution rate, as noted above, is important because it regulates the release of API from solid medications and influences concentrations in the blood. Many other forms of physical change affect the physical integrity of drugs, which often depend on the dosage form. One example is *phase separation,* which can occur with topical emulsion (e.g., creams, ointments) if the homogeneous dispersion of the ingredients breaks down into its constituent parts. Another example of a physical change is

moisture adsorption by a hygroscopic excipient in a tablet formulation that causes the tablet to become soft and crumbly.

Chemical degradation changes the molecular content of a drug by reducing API content and producing impurities. Although these chemical reactions can mediate the breakdown of either the API or the inactive excipients, the loss of API is usually of greater concern because this can reduce therapeutic efficacy. Excipients, which are pharmacologically inactive but *not* chemically inert, can also undergo degradation reactions and in some cases they contribute to API loss (Challenger, 2019; Narang, Desai and Badawy, 2012; Wu, Y., et al., 2015).

The chemical and the physical properties of a drug can degrade from interactions with the environment or from interactions between the ingredients (or impurities) in the drug formulation itself (e.g., incompatibilities). In many instances physical and chemical stability are interrelated; for example, adsorption of water by hygroscopic excipients in compressed tablets can promote hydrolysis of active ingredients and can also impact tablet hardness and dissolution rate (Carstensen, 1988; Waterman, et al., 2002).

2. KINETICS OF DRUG DEGRADATION REACTIONS

The chemistry of drug degradation is the chemistry of functional groups (a.k.a., moieties)—groups of atoms in a molecule that contribute to a chemical's characteristic reactivity. A particular functional group (i.e., amide, carbonyl, alcohol) will undergo the same or similar chemical reactions regardless of the rest of the molecule's composition (Bokser and O'Donnell, 2013; Guillory and Poust, 2002; Wigent, 2013). Therefore, knowledge of a molecule's functional groups can be used to predict pathways of degradation. The most common pathways mediating chemical degradation are hydrolysis, oxidation, and photolysis (Baker, 2019). For example, drugs containing amides, lactams, esters, imides, or acetal moieties are susceptible to hydrolysis, in order from most to least, respectively (Roy, et al., 2018; Waterman, et al., 2002). Although susceptible to hydrolysis, the rate of reaction for any of these groups can vary widely and is often modified by factors including neighboring structures in the molecule, other ingredients in the medication, and environmental conditions. Hence, although ester hydrolysis is among the most common reactions contributing to drug instability, esters, depending on the drug formulation, can be stable for years, if protected from humidity and stored at cool temperatures (Guillory and Poust, 2002). With a knowledge of functional groups and environmental conditions, it is possible to anticipate environmental susceptibilities of a drug (Guillory and Poust, 2002).

The effect of environmental factors on APIs is well established. For example, Leeson and Mattocks (1958) showed a correlation between the rate at which solid aspirin (tablets) degrade and the atmospheric vapor pressure. It was later shown that moisture adsorbs onto the surface of the aspirin, which results in a film of water surrounding each aspirin particle (Carstensen, 1988; Nelson, Elwyn, Eppich and Carstensen, 1974). The water film is rapidly saturated in solid aspirin (i.e., an equilibrium is established), and as hydrolytic decomposition rapidly removes aspirin molecules, they are instantly replaced in solution by new aspirin molecules that form the particles' surface. When abundant moisture is present, the kinetic rate at which the aspirin degrades appears to increase linearly with the concentration of the aspirin (i.e., pseudo-first order), and at a rate related to moisture that is independent of concentration (i.e., pseudo zero-order) (Carstensen 1988). Similarly, furosemide, a potent diuretic, is very susceptible to moisture, and is also susceptible to pH and oxygen changes in aqueous solutions (Asafu-Adjaye et al. 2011).

The rate of a chemical reaction is governed by the laws of thermodynamics. A brief overview of the chemistry of drug degradation and rates of chemical reactions is presented in Appendix 1. Chemical reaction rates are critically important for the rationales regarding drug packaging, the shelf life of drug products, and the effect of temperature on chemical reaction rate. One practical implication of the dependence of reaction rate on temperature for exploration space missions is that low temperature storage slows the rate at which drugs degrade, which prolongs shelf life. The USP permits medications requiring controlled room temperature storage to be stored at cool or refrigerated temperatures (United States Pharmacopeia, 2021a), unless otherwise specified, which is in contrast to strict restrictions on the exposure of medications to temperatures above labeled storage conditions (United States Pharmacopeia, 2020c).

B. DRUG EFFICACY DURING SPACEFLIGHT

1. EVIDENCE

Three studies appear to have reviewed astronaut medical records to evaluate medication use and efficacy. Two of these studies have been published (Putcha, et al., 1999; Wotring, 2015), and a third unpublished report—*Data mining - Pharmacotherapeutics of Space Motion Sickness* by Putcha (2009)— was cited in (Wotring, 2011) but could not be located.

Putcha et al. (1999) evaluated medication effectiveness by reviewing astronaut medical debriefings collected after 79 Space Shuttle missions. A total of 94% of the 219 medical records (each representing one person-flight) recorded the use of medication. The reviewed medical records revealed that 47% of the medications were used to treat space motion sickness, and 45% were used to treat sleep disturbances.

Space motion sickness, now called space adaptation syndrome (SAS), often develops during the first 6 hours of spaceflight. Approximately 60–80% of astronauts experience SAS within 2–3 days after launch, with symptoms peaking about 24–48 hours after onset and resolving 72–96 hours after onset (Davis, Jennings and Beck, 1993; Heer and Paloski, 2006). About 84% of the crewmembers who took drugs to treat SAS perceived the drugs to be effective, and most reports of ineffective treatments occurred during the first mission day (Putcha, et al., 1999). It was concluded that medications for treating SAS, regardless of type, were nearly always reported to be effective: 54% of the medications were reported as very efficacious, 30% moderately efficacious, and 7% mildly efficacious. Only 8% of the drug treatments were reported as not efficacious. No analysis was conducted to assess if treatment failures were associated with concomitant with emesis, which can result in the purging of an orally administered medication before dissolution or is absorbed; however, intramuscular promethazine seemed to be more effective than oral or rectal promethazine. If this is correct, then the greater effectiveness of intramuscular injections, compared to the oral and rectal administered drugs, is likely because injection bypasses pre-systemic clearance by the liver, yielding greater bioavailability. It can be concluded that because space shuttle missions are short (< 18 days), the drugs observed to be ineffective would not have had time to degrade (see PRINCIPLES OF DRUG DEGRADATION). This is supported by the observation that most astronauts had good therapeutic response to administered drugs, indicating that drugs retained their potency. Drug failures are more likely to be related to other factors, such as symptom severity, drug selection, dose, and route of administration.

A second study assessed medication usage by 24 ISS crewmembers during long-duration missions (mean = 159 ± 36 days) from 2002 to 2012 (Wotring, 2015). The subject group consisted of 18 men and 6 women; of these, 2 men and one woman reported using no medication during their missions. Data sources consisted of anonymized mission medical records and physician's notes taken during the private medical conferences that were conducted weekly during each mission. The study found that the only medications reported to be ineffective were treatments for skin rash and SAS. Six crewmembers took drugs to treat skin rashes: a total of 46 treatments were reported. Two individuals indicated that treatment failure drove the use of repeat doses or a switch to a different pharmaceutical. Importantly, treatment failures for topical medications used for dermal disorders cannot be attributed to altered pharmacokinetics. Twelve instances of medication were used for the treatment of SAS symptoms, including 9 uses of promethazine, 2 uses of scopolamine, and one use of meclizine (Wotring, 2015). The medication was considered ineffective in 2 of the 5 cases where symptoms were the driving factor for medication use: promethazine was used in one case and scopolamine in the other. Because SAS and rash both affected crewmembers during the first days of the mission, drug stability cannot be the cause of drug failure because the kinetics of drug degradation preclude

such rapid loss of potency during this time frame (see PRINCIPLES OF DRUG DEGRADATION). Furthermore, other subjects were successfully treated with the same medications, indicating the drugs were active for most crewmembers, and Du et al. (2011) showed promethazine maintains stability for almost a year during spaceflight (Du, et al., 2011; Reichard, 2023).

The NASA evidence report titled *Therapeutic Failure Due to Ineffectiveness of Medication* discusses the results of an unpublished data mining study that retrospectively reviewed portions of anonymized medical debriefs from 511 crewmembers who flew on 88 Shuttle missions (Putcha 2009 as cited in (Wotring, 2011). The study appears to be an update to the original Putcha et al. (1999) study. The cited study could not be located for review, so we rely on secondary sources including Wotring (2011) and 2 separate but nearly identical reviews (Putcha, et al., 2013; Putcha, et al., 2016). Investigators retrospectively reviewed postflight medical debriefings collected from astronauts who flew on Space Shuttle missions 1 through 94 (STS-1 – STS-94). During these debriefs, 132 crewmembers reported taking medications to treat SAS: 387 total doses. Because this investigation appears to be an extension of a previous study, it likely includes many of the same study subjects as the earlier study but is updated with more recent records; however, without access to the original report this cannot be verified.

The review of medical debriefing records found that promethazine was the most commonly taken medication (201 total doses). Overall, 130 crewmembers (65%) reported that promethazine provided relief of SAS. Less often, promethazine was taken in combination with dextroamphetamine (45 instances), and slightly more than half of the crewmembers who took both medications reported symptomatic improvement. In contrast to the Putcha et al. (1999) report, a large percentage of some medications used to treat SMS were described as ineffective and a substantial number of treatment failures were reported. The combination of scopolamine and dextroamphetamine was effective only 37% of the time: 36 of 97 total doses resulted in symptom improvement (“much or somewhat better”), and 24% of doses were ineffective. Comparisons of the effectiveness of the different dosage forms of promethazine revealed that intramuscular injection was most effective for alleviating symptoms: after the injection 55% felt much better, 16% reported some improvement, and 7% reported no improvement or worsening symptoms, which is consistent with earlier reports (Davis, Jennings and Beck, 1993; Putcha and Cintrón, 1991). Symptom severity is not available for these data, so it is possible that crewmembers who experience severe symptoms took the combination of medications expecting this would provide greater relief. This is a good example of why it is important to collect information on symptom severity when assessing subjective efficacy of medication. Neither raw data

nor a complete report containing study methods and detailed results was available for review. Promethazine was the most common medication taken for SMS.

2. CONCLUSIONS

An important limitation of all the studies described above is that they rely on retrospective documentation of medication use. Since 1989, information on medication use has been collected during the private medical conferences between flight surgeons and crewmembers (Davis, Jennings and Beck, 1993; Wotring and Smith, 2020). These records suffer from recall bias and collection bias: recall bias because crewmembers are asked to recall the types and frequency of medications used over a period of time, often well after the medication(s) were used, and collection bias because the flight surgeon has the discretion to document in the record only what is deemed pertinent to the maintenance of crewmembers' health (Wotring and Smith, 2020). The level of confidence in these records is further reduced because only 62% of the crewmembers responded to their medical debrief questionnaires, of which 32% were incomplete—hence, an overall completion rate of 42% (Wotring, 2011). Furthermore, documentation of medication use by ISS crewmembers has been reported to be incomplete (Wotring, 2015; Wotring and Smith, 2020). The large amount of missing data raises a concern for reporting bias, which occurs when that missing information is not randomly distributed.

Overall, reports that drug efficacy is *reduced* during spaceflight are inconclusive. First, no comparable terrestrial controls exist to compare the changes in drug efficacy during spaceflight. It might be possible, for example, to compare drug efficacy rates for SAS to effectiveness rates of medications for similar symptoms under terrestrial conditions, such as drug efficacy for the treatment of motion sickness or nausea induced by certain types of chemotherapeutics. In the absence of comparisons to terrestrial drug failure rates, therapeutic failure of SAS treatments during space missions cannot be deemed better or worse than therapeutic failure of terrestrial treatment of motion sickness. Therefore, available evidence neither supports nor rules out the possibility that some medications are less (or more) effective during spaceflight than terrestrially. Second, the severity of the symptoms was not considered as a potential factor correlated with medication ineffectiveness—that is, the possibility exists that the severity of a symptom influences the degree to which a subject experiences acceptable symptomatic relief. It is likely that symptomatic severity could not be analyzed because these studies all involved retrospective review of medical conference records that probably did not consistently capture severity information, and are subject to recall, collection, and reporting biases.

When using Bradford Hill criteria (Fedak, et al., 2015) for evaluating evidence of causation, it can be concluded that decreased efficacy of medication during *short-term* space missions is not likely caused by a loss of drug potency (e.g., degradation). The following evidence supports this conclusion:

- Temporal association: Most of the medication efficacies were evaluated during short-duration missions (< 18 days), and most of the medical conditions associated with medication failure occurred within the first day of the mission. This time period is too short to allow clinically significant changes in drug potency (Reichard, 2023), as is discussed below (section PRINCIPLES OF DRUG DEGRADATION)
- Consistency of effect: The same medications appear to be effective for some individuals and ineffective for others, and for a single crewmember a medication may be therapeutically ineffective at one time and effective at another time.
- Strength of association: Generally, reports that medications are ineffective have been infrequent and not consistently associated with a single drug product, route of exposure, or medical condition. It appears more plausible that medication ineffectiveness during short-duration missions is attributable to drug selection, symptom severity, administered dose, and individual PK and PD variability; not drug stability.
- Dose-response relationship: Because drug degradation depends on the rate of chemical change over time, as a drug's duration of exposure to the spaceflight environment increases, the drug's potency, and hence its efficacy, will decrease. This time-dependent loss of efficacy has not been observed. Instead, most instances of ineffective medication occur early in a mission when drugs are most potent.

Unlike short-duration space missions that have been the focus of past medication use and efficacy studies, long-duration Mars missions will preclude resupply. It is plausible that time-dependent loss of potency for some drugs (Reichard, 2023) will result in a loss of efficacy and an accumulation of impurities during these missions. Hence, the risk that a drug will lose potency or accumulation degradation impurities is much more important for long-duration missions than for short-duration missions, which have traditionally lasted only a few weeks to months.

C. EFFECT OF SPACEFLIGHT ON DRUG CONTENT

1. CONTEXT: BASIS FOR DETERMINING DRUG STABILITY AND QUALITY

Classifying medication quality as "acceptable" is critical for determining drug stability. The scope of USP quality specifications and the FDA stability requirements must be understood before they can be

correctly applied to the use of medications beyond their labelled expiration date during exploration space missions. Key regulatory concepts for interpreting the stability and shelf life of drugs are presented and discussed in Appendix 2.

2. EVIDENCE: EFFECTS OF SPACEFLIGHT ON DRUG CONTENT

a. *Summary*

An *association* between spaceflight and degradation of pharmaceuticals has been reported in a single pilot study (Du, et al., 2011). In this study, repackaged solid drug products and non-solid drugs in their original manufacturer's packaging were exposed to spaceflight and compared to lot-match control samples stored in an environmentally controlled chamber at Johnson Space Center (JSC). The study suggests that nearly all spaceflight-exposed drugs either failed[1] before their specified expiration dates or exhibited a greater degree of degradation than the matched terrestrial controls (Blue, Rebecca S., et al., 2019; Du, et al., 2011; Wotring, 2016). Mechanisms that have been proposed to explain the difference in drug stability include microgravity, vibration, CO_2, ionizing radiation and humidity (Blue, R. S., et al., 2019; Du, et al., 2011; Mehta and Bhayani, 2017; Putcha, et al., 2016). However, a *causal* relationship between spaceflight environmental factors and accelerated drug degradation has not been demonstrated, and the mechanisms that have been purported to explain the observed differences in API content are untested supposition.

NASA has previously supported at least 6 investigations into the stability of drugs after prolonged storage on board the ISS (Cory, et al., 2016; Cory, James and Mangiaracina, 2017; Du, et al., 2011; Khan, M. A. and Wotring, 2014; Wotring, 2016; Wu, L. and Chow, 2016). Only 2 of these 6 studies have been published (Du, et al., 2011; Wotring, 2016), and the remaining 4 investigations are described in non-peer reviewed NASA reports, of which one reanalyzed 3 medications that were initially tested and reported by Du et al. (2011) 3 years earlier (Khan, M. A. and Wotring, 2014). All studies, except the study by Du et al. (2011), were opportunistic by design (Table 1). Each opportunistic study analyzed sui generis medications after various periods of spaceflight storage, but none of the studies included lot-matched controls to compare stability of drugs during spaceflight with stability in terrestrial conditions. In contrast, Du et al. (2011) conducted an 880-day longitudinal drug stability study consisting of 4 time points, and assessed spaceflight drugs and terrestrial controls from the same manufacturing lot. Despite the advantages of this longitudinal design with lot-matched controls, the Du et al. (2011) study was limited because the analysis provides a

[1] Based on the USP thresholds for API content or physical characteristics.

qualitative assessment of drug stability instead of an overall assessment of relative drug stability, and because it did not provide statistical significance of the changes reported.

Table 1. Opportunistic Studies of the Stability of Spaceflight Medications

Study	Cory et al., 2017	Cory 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)
Publication status	NASA Report	NASA Report	Published	NASA Report	NASA Report
No. of drug products/APIs	3/3	5/5	9/9	4/3	3/3
Spaceflight time points	3 time points; different timepoints for each medication	One time point; different duration for each medication	Single time point of 550 days	2 time points for promethazine inj; 3 for all others	2 time points but also includes prolonged period of terrestrial storage
Control time points	One per API; no storage time points	One per API; no storage timepoints	No controls	One per API; no storage timepoints	Mixed. Some Correspond to spaceflight time points, some do not
Matched or unmatched design	Unmatched	Unmatched	N/A	Unmatched	Each flight sample has lot-matched control
Independent replicates	Independent between-lot analyses for the same drug; unclear if within-lot replicates are independent (n=10 replicates)	Independent between-lot analyses for the same drugs; unclear if within-lot replicates are independent (n=9 or 10 replicates)	Independent replicates of a Single lots. (n = 4 or 5 replicates)	Independent replicates; likely tested a single lot for each drug and timepoint (n=3)	Independent replicates: Analytical analysis performed at FDA per USP monograph and repeated on separate days.
Spaceflight Storage time	51–501 days	132–700 days	550 days	140–699 days	316 or 880 days
No. of lots tested	3separate lots/flight medication + an unmatched control for each medication	One lot/flight medication + unmatched controls for each medication.	Not discussed; likely one lot per medication	Different lots for each time point/control; no indication samples were from the same mfr. at each time point	Different lots tested for each drug or time point (one control is pair-matched to one flight sample)
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.

Table 1. Opportunistic Studies of the Stability of Spaceflight Medications

Study	Cory et al., 2017	Cory et al., 2016	Wotring, 2016	Wu and Chow, 2016	Wotring and Khan, 2014
APIs Tested	**Amoxicillin**[2], Aspirin[1], Pseudoephedrine[1]	**Levofloxacin**, **Ibuprofen**, **Phenytoin,** Valacyclovir, **Sertraline**	Aspirin[1], Acetaminophen, **Ibuprofen**, Loratadine, Loperamide, Melatonin, Modafinil, Pseudoephedrine[1], Zolpidem	**Promethazine**[3], **Azithromycin**, **Ibuprofen**	**Levothyroxine**, **Levofloxacin**, **Azithromycin**
Analytical instrumentation	HPLC with electrospray LC-MS	HPLC with UV or electrospray LC-MS	HT HPLC with PAD detector or UV DAD detector	UPLC-MS/MS	HT HPLC with DAD
Analytical performance (API)	Not discussed	Not discussed	Not discussed	Accuracy, precision, LLOQ, LLOD	Accuracy, precision, specificity, LLOQ, LLOD

[1] APIs that were not among the drugs tested by Du et al. (2011).
[2] Du et al. (2011) tested amoxicillin in combination with clavulanate whereas Cory et al. (2017) tested amoxicillin as a single API drug product.
[3] Both tablet and injectable formulations.
Bolded APIs were among the drug substances tested by Du et al. (2011), although product manufacturers may be different between studies.
API, active pharmaceutical ingredient; ISS, international space station; HPLC, High-performance liquid chromatography, UPLC, Ultra-performance liquid chromatography; MS/MS, tandem mass-spectroscopy; DAD, Diode Array Detector; PAD, Pulsed Amperometric Detector, LLOQ, lower limit of quantitation; LLOD, Lower limit of detection; LC-MS, liquid chromatography-mass-spectroscopy; UV, ultraviolet; inj, injection

b. *Lot-Matched Controlled Study of Drug Content*

The USP defines potency[2] (i.e. content) as the amount of API in a drug product. The USP specifies the acceptable range of potency relative to the label claim (i.e. strength) of the dosage unit. Drug labelers guarantee that the potency of a drug will exceed the minimum USP acceptance criteria through the drug's expiration date. Du et al. assayed the API content of 33 medications at 4 different time points. The medications were store in 8 medical kits: 4 medication kits were stored on board ISS and 4 were stored terrestrially in an environmentally controlled chamber at JSC. Across all medical kits each drug product was

[2] The definition of potency used by USP is different from that is other biomedical sciences which consider potency to be the amount of drug required to produce an effect of a given intensity. In this evidence report, the USP definition of potency as content of API is used exclusively.

from a single manufacturing lot; hence, the analyses at each time point were conducted on samples (spaceflight and terrestrial) from the same manufacturing lot. Terrestrial samples were stored under comparable temperature and humidity conditions as the flight samples. Twenty-two of the 24 solid oral dosage forms (SODFs) were removed from the manufacturer's container and repackaged in rigid polypropylene containers. These medication containers are not assumed to be protective because they are not clearly described in the publication and there is no record that the packaging was sealed or tested for vapor transmission (United States Pharmacopeia, 2020d; United States Pharmacopeia, 2021b). Analytical testing included only the amount of API in each formulation at each time point; degradation products were not evaluated, and degradation mass balance was not determined. Because this study was intended as a pilot study, the study methods were not described in detail in the report and no analytical methods (i.e., API extraction procedure, chromatographic conditions, method suitability evaluation, number of independent replicates, batching of samples for processing and analysis) were provided. The absence of a detailed methods section reduces the level of confidence in the overall conclusions from this study. One critical limitation is that the authors appear to have tested only a single sample of each drug (Wotring, 2016), therefore, the standard deviation represents only analytical variability (which is usually very low) not experimental variability. Experimental variability is critical for hypothesis testing, and this variability could account for the reported differences between the 2 treatment groups. For this reason, the information presented in the paper by Du et al. (2011) *does not* test whether individual spaceflight drugs degrade differently than the same drugs under terrestrial conditions. However, because each drug is tested independently, all the tested drugs together can be statistically evaluated for a spaceflight effect (Reichard, 2023).

The study by Du et al. (2011) reported that after 880 days of storage the API content in 25 of 36 spaceflight medications (69.4%) and 17 of 36 terrestrial medications (47.2%) fell below USP standards for labeled API strength (i.e., “failed”). The number of formulations that failed to meet specifications for API content increased with the duration of spaceflight exposure. On the basis of these results, the authors concluded that “*…a number of formulations tested had a lower potency or percent content of API after storage in space with a consistently higher number of formulations failing USP potency requirement after each storage period interval in space than on Earth.*” This conclusion, based on dichotomized quantitative API content (i.e., pass/fail outcomes), has been repeatedly cited as evidence that latent factors associated with spaceflight increase the risk of drug failure. However, quantitative analysis of API content can provide

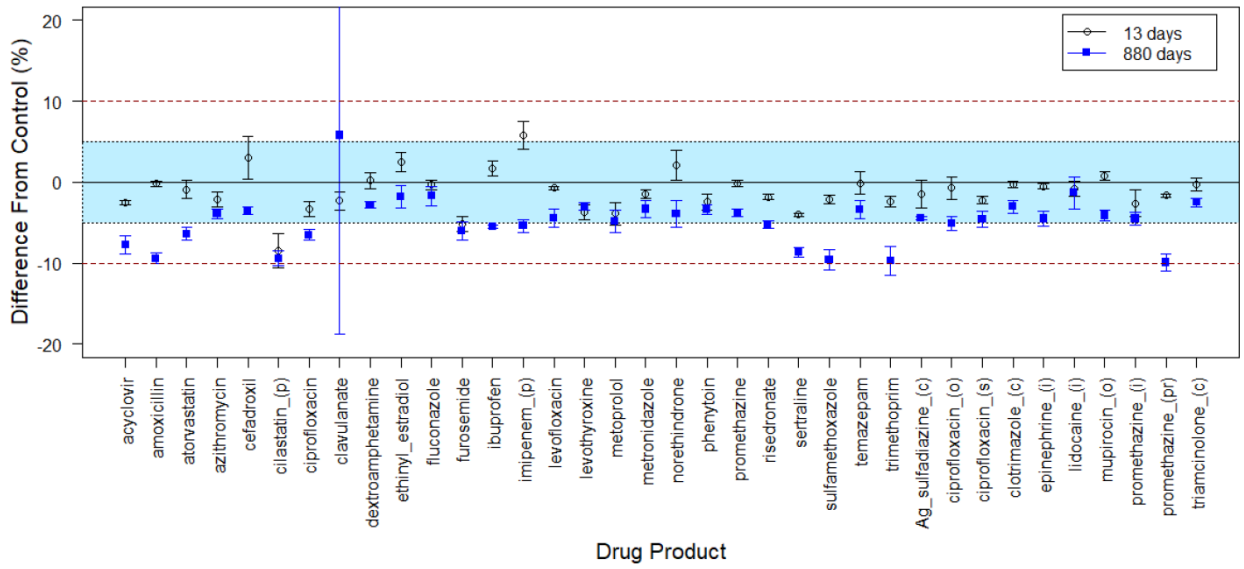

Figure 1. Relative change in the strength of active pharmaceutical ingredient (API) after 13 and 880 days of spaceflight. Values represent API potency (%) of terrestrial samples minus API potency (%) of matching spaceflight samples after either 13 days (○) or 880 days (■) of storage. Error bars reflect ± one standard deviation. The blue shaded area represents a difference of ± 5% in API potency; the dashed line represents a ±10% difference in potency. A value of zero indicates no difference between the API content of the matched control and spaceflight samples (Reichard, 2023).

more insight into how spaceflight affects drug stability. After 13 days of storage the API content of spaceflight samples and corresponding lot-matched controls varied by less than ±5% for most drugs (34 of 36) (Figure 1). After 880 days of storage, 39% of spaceflight drugs (14 of 36) remained within ±5% of control potency, and the API content of all spaceflight drugs and corresponding controls differed by no more than 10%. Taken together, this supports a conclusion that spaceflight exposure has little effect on drug stability (Appendix 3).

No investigations have determined individual factors unique to spaceflight that might contribute to increased rates of API degradation. It is pertinent, however, that other NASA-supported studies (see section Opportunistic Spaceflight Studies of Drug Content) have tested SODF that were repackaged into nonprotective packaging for spaceflight (See section PACKAGING AND DRUG STABILITY). Drugs are repackaged to minimize mass and volume. No study has evaluated the effect of the NASA repackaging process on long-term stability of SODF by directly comparing the stability of repackaged medications to the stability of the same medications in their sealed manufacturer's packaging or other protective packaging. The study by Du et al. (2011) is the only spaceflight investigation that has included multiple drugs that were not repackaged (14 of the 36 drugs tested). Of these drugs, 10 are an assortment of non-solid formulations, including solutions, ointments, creams, and a suppository. The remaining 4 APIs that were not repackaged

were combination products containing 2 APIs: imipenem with cilastatin (lyophilized powder for injection) and ethinyl estradiol with norethindrone (blister pack oral tablets).

After 880 days of spaceflight, the API content of only 2 of 14 spaceflight drugs (~14%) that were stored in the manufacturer's packaging deviated from their corresponding controls by more than 5%, whereas the API content of 9 of 22 (41%) repackaged spaceflight medications differed from the corresponding controls by more than 5%. Similarly, the mean failure time for drugs that failed during the 880-day storage period was 707 days (n = 8) for the repackaged drugs, most of which were non-solid formulations (the one exception is ethinyl estradiol), and 633 days for repackaged drugs (n = 12), all of which are either capsules or tablets. The more frequent and earlier failure of SODF is unexpected because solid formulations typically have longer shelf lives than non-solid formulations of the same API, which suggests that repackaging may have contributed to drug degradation. The effect of drug repackaging on drug stability has not been a concern for LEO missions because the ISS can be readily resupplied; however, resupply will be much more limited, if not impossible, for exploration space missions. Therefore, repackaging must provide more protection than repackaging used on the ISS to ensure drug stability throughout the full duration of an exploration mission

Reichard et al, 2023 showed that the potency of spaceflight and of terrestrial drugs (as assessed by API content) are highly correlated (r = 0.894), with a nearly 1:1 correspondence in drug content across all the drugs they tested (Figure 2). Linear regression of these paired terrestrial and spaceflight potencies yields a slope coefficient of 1.012, which is virtually equivalent to unity, indicating that, overall, drugs under both conditions degraded at nearly the same rates. The offset of the y-intercept (-4.64%) may reflect an inconsistency in the analytical method, the details of which were not discussed in the published paper or provided as supplementary information.

Du et al. (2011) determined that a few individual oral drugs appeared to degrade faster in spaceflight than in terrestrial conditions, and suggested this may be due to factors such as exposure to ionizing space radiation, the physical effects of vibration and microgravity, the effects of increased levels of

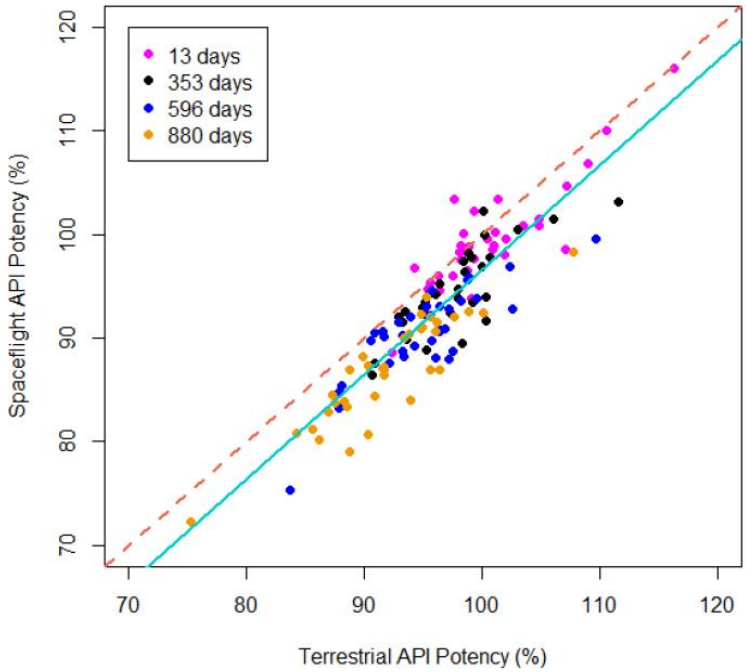

Figure 2. Potency relationship between spaceflight matched controls. Mean potency of spaceflight-exposed drugs are plotted versus matched controls and are highly correlated (Pearson, r = 0.894). The slope of the solid regression line (cyan, slope = 1.012) is close to unity, which is indicated by the hashed line (slope = 1 and intercept = 0).

atmospheric CO_2, or off-nominal environmental conditions (e.g., temperature) before, during or after flight. It is well established that many medications are susceptible to atmospheric factors, particularly water vapor and oxygen (Asafu-Adjaye, et al., 2011; Carstensen, 1988; Leeson and Mattocks, 1958). What is notable about all the tested medications, except for promethazine suppositories, is that only the SODF exhibited extensive degradation, and all these medications were removed from protective manufacturers' containers and repackaged into non-protective packaging (United States Pharmacopeia, 2020a; United States Pharmacopeia, 2021a). This is an unexpected observation given liquid formulations are typically less stable than solid formulations of the same IPA and are *much* more sensitive to ionizing radiation (Abramowicz, Zuccotti and Pflomm, 2016). As shown in Table 1, a common factor associated with all reports of spaceflight-induced degradation of SODF is non-protective packaging that permits ingress of atmospheric constituents, including O_2, CO_2, and vapor, which are known to mediate chemical and/or physical degradation of medications, and hence U.S. FDA and USP stability testing and packaging requirements.

Reichard et al. (2023) used the results of the longitudinal Du et al., (2011) to estimate the rates at which individual drugs lost potency during LEO spaceflight: results are provided in Appendix 4. Overall, the degradation rate of spaceflight drugs is approximately 1.5-fold greater than the degradation rate of drugs

stored in the terrestrial environment; that is, uncharacterized factors in the spaceflight exposure increase the basal degradation rate by ~50%. However, it is crucial to note that both the spaceflight samples *and* the matched terrestrial controls in this study exhibited a substantial time-dependent likelihood of failure (Reichard et al. 2023) that is greater than expected. Nine of 24 (38%) *terrestrial* (e.g., control) SODFs failed before their expiration date, as based on their API content. This number is surprising because manufacturers must demonstrate that their medications meet UPS requirements for potency through the labeled expiration date. Because these medications are terrestrial controls, spaceflight factors did not contribute to their failure, meaning repackaging is the most likely factor contributing to premature failure. Consequently, the drug repackaging process is the largest single contributor to drug failure, whereas other environmental factors associated with spaceflight appear to have a minor role in contributing to drug failure. Because no NASA-supported study has included drugs in sealed manufacturer's packaging as a control, the relative contribution of nonprotective drug repackaging on long-term stability has not been evaluated. Although manufacturer's packaging is not perfect (see PACKAGING AND DRUG STABILITY section of this report), it remains the bench mark for comparison with other packaging (U.S. Food and Drug Administration (FDA), 1985; United States Pharmacopeia, 2020e). Hence, a critical need exists to evaluate how NASA's current drug repackaging practices affect drug quality when compared to stability in the manufacturer's packaging.

In conclusion, quantitative reanalysis of spaceflight drug stability data suggests that baseline degradation (i.e., the deterioration of drugs under controlled terrestrial control) is the dominant factor contributing to shortened shelf life. Spaceflight contributes an additional time-varying effect on degradation (Reichard, 2023). For the few drugs with publicly available data on shelf life, both terrestrial and spaceflight shelf life determined in NASA studies was less than the labeled shelf life, and substantially less than the extended shelf life reported by the U.S. FDA for a some drugs (Lyon, et al., 2006). However, no NASA-sponsored study has attempted to elucidate which factor(s) are the most significant contributor(s) to the drug deterioration, or whether repackaging practices contribute to the increase probability of failure associated with spaceflight. These mechanisms of damage must be elucidated before countermeasures can be identified and evaluated for prolonging the shelf life of medication, ensure therapeutic efficacy, and minimize the risk of toxic degradation products.

c. *Opportunistic Spaceflight Studies of Drug Content.*

NASA has supported 5 opportunistic studies of drug stability during spaceflight (Table1) (Cory, et al., 2016; Cory, James and Mangiaracina, 2017; Khan, M. A. and Wotring, 2014; Wotring, 2016; Wu, L. and Chow, 2016). All these studies, apart from Khan and Wotring (2014), assessed medications flown on board

the ISS. A summary of all data manually extracted from individual reports is provided in Appendix 5. The design and the results of each study are briefly summarized below, and a summary of all the findings is provided at the end of this section.

Khan and Wotring, 2014: This study involved a comprehensive analysis of several aged medications in partnership with U.S. FDA (Khan, M. A. and Wotring, 2014). The study design is ad hoc because it used samples leftover from the Du et al. 2011 study that had been stored in an environmental chamber at JSC at controlled room temperature until analyzed by the U.S. FDA. Three medications were analyzed for API content: Azithromycin 250 mg tablets, levofloxacin 500 mg tablets, and levothyroxine 0.025 mg tablets. When possible, medications exposed to spaceflight were lot-matched with terrestrial controls, however different lots of the same drug were also tested. Only a few dose units were available for study at each timepoint and no more than 2 spaceflight time points were assessed for each medication. In one case, products from 2 different manufacturers were used for the 2 different time points (azithromycin: Sandoz and Greenstone). In all cases, different medication lots were tested at different time points. It should be noted that typical investigations of drug stability will use medications from a single manufacturer and lot and include at least 4 time points or more to enable linear modeling of degradation. Experimental details for each medication are provided in Appendix 10.

Overall, this study, along with the studies by Cory et al, 2017, provide the most comprehensive description of sample processing, analytical methods, and quality assurance. In addition, complete metadata are provided for each sample tested, including manufacturer, national drug code (NDC), lot number, expiration dates, launch and landing dates, and analysis dates. This data transparency provides a high level of confidence in the study results, enables independent evaluation of the data, and allows this study's methods and results to be compared with the results of other studies. The most important characteristic of this study is that it re-tested several of the same samples that were originally tested by Du et al. (2011), in addition to a few samples returned from other missions. However, unlike the Du and colleagues' study, Wotring and Khan demonstrated system suitability, including system calibration, response factor, precision, accuracy, sensitivity, quantitative range, and variability. These are fundamental criteria that should be provided to support all analytical studies.

Because this study re-tested the same medications that were originally tested by Du et al. (2011) a few years earlier, it was expected that their API content would be substantially less than reported by Du et al. (2011) due to ongoing degradation in the intervening years of storage. This is not the case, however. All medications, except for the levothyroxine samples that were stored for 13 days in space, had significantly

greater amounts of API than originally reported by Du et al. (2011), as shown in Table 2. The levothyroxine samples that had been stored in space for 13 days would have been well within their expiration date at the time they were first analyzed by Du and colleagues, and the sample medications were 1609 days past their expiration data when tested by the FDA. FDA testing showed that, in fact, all levothyroxine tablets contained very similar amounts of API, suggesting that the duration of spaceflight exposure did not appear to be associated with increased degradation because spaceflight samples seem to have higher potency than corresponding terrestrial samples.

Table 2. Comparison of Lot-matched Pharmaceuticals Tested by Du et al. and by the FDA.

Drug tested	Timepoint	Lot number	Treatment	Du et al. 2011 % Potency	FDA	
					Analysis date	Amount % Potency
Azithromycin 250mg tablet	880 days	5HP059A	Control	94.8 ± 0.39	5/2012	106 ± 2.8
		5HP059A	Flight	90.9 ± 0.37	5/2012	98.3 ± 2.0
Levofloxacin 500 mg tablet	880 days	6AG613	Control	85.6 ± 0.89	5/2012	101.2 ± 0.42
		6AG613	Flight	81.2 ±0.31	5/2012	101.1 ± 0.61
Levothyroxine 0.025 mg tablet	13 days	C05T0861A4	Control	92.3 ± 0.66	1/2012	77.38 ± 1.89
		C05T0861A4	Flight	88.6 ± 0.51	1/2012	78.12 ± 1.99
	880 days	C05T0861A5	Control	75.3 ± 0.14	1/2012	80.91 ± 0.91
		C05T0861A5	Flight	72.3 ± .03	1/2012	81.39 ± 1.47

The conclusions of the FDA analyses, which were based in part on API content as well as impurity content (see Appendix 2), were as follows:

- Azithromycin: Storage during spaceflight followed by prolonged terrestrial storage beyond the drug's expiration date did not impact the quality of the Greenstone Azithromycin product. This finding is consistent with the Du et al. (2011) results, which found Azithromycin potency was within USP specifications.
- Levofloxacin: The potency of the aged samples from the NASA flight kit were no different than the potency of an unexpired commercial drug product (i.e., a different, much more recent lot of levofloxacin) from the same manufacturer. These results seem to indicate that the stress of both the spaceflight and the space environment had no effect on the potency of this medication. However, this cannot be ascertained conclusively by this study because the flight and the control

samples had expired and had been stored for a considerable length of time in controlled environment after they were returned from space.

- Levothyroxine: No significant differences were detected in remaining levels of levothyroxine (content) in the flight and the control samples that were aged for 13 days or 880 days. This contrasts with results of the previous analysis (Du et al, 2011) where levothyroxine was shown to degrade faster when stored in space than in a terrestrial environment. However, no details about the sample preparation and extraction procedure were provided in the study by Du et al. (2011). It is very challenging to extract levothyroxine from a tablet matrix and a slight variation in extraction procedure could be detrimental to its recovery, which can falsely appear to indicate reduced potency (Shah, R. B., et al., 2010; Shah, R. B., et al., 2008).

Khan and Wotring, 2016: This opportunistic study tested the hypothesis "…that medication degradation on the ISS does not differ from what is typically seen on Earth" (Wotring, 2016). This cross-sectional study measured API content in 9 different drugs stored on the ISS for 550 days. Medications were analyzed 3–5 months after return to Earth. All medications tested in this study were oral solid formulations—either tables or capsules. Consistent with normal operational procedures, all the tested medications were repackaged into zip-lock bags for transfer to the ISS medical kit. The published description identifies the expiration date for each medication, as well as the general analytical approach (Appendix 2).

Of the 9 medications, 3 (ibuprofen, loperamide, and modafinil) were still within their expiration dates at the time of analysis, while the remaining 6 medications were expired, ranging from 151 (acetaminophen) to 334 days (pseudoephedrine) beyond their expiration dates at the time of analysis. Eight of 9 medications tested had an API content that was at least 96% of the label strength, all of which exceeded USP acceptance criteria for API content[3]. Melatonin, which was 11 months past expiration at the time of analysis, was the only drug that did not meet minimum USP acceptance criteria for potency with 89.2% of label strength, which is less than the required 90% of label strength. On the basis of qualitative judgment (i.e., not statistical testing), the authors concluded that their results were consistent with the hypothesis that the levels of chemical degradation are no different in LEO spaceflight than on Earth. Although no terrestrial

[3] The authors state that acetaminophen did not meet the USP acceptance criteria, which at the time may have been between 98–102% of label strength. Prior to this, the acceptance threshold was a minimum of 97.0% of the label strength, which the test article did meet. Currently (11/2023) the acceptance criteria for acetaminophen tablets is 90.0% to 110.0% of the labeled strength – which would allow this medication to pass USP protency specifications. .

controls were included in this study, the fact that no excessive degradation was observed does appear to support a conclusion that if spaceflight does affect drug stability, then the effect on these medications is quite small.

The hypothesis proposed for this study is based on a relative comparison,—i.e., the degradation of drugs on the ISS is different than degradation on Earth. This hypothesis requires a statistical comparison of spaceflight samples to a control group. Therefore, matched terrestrial control samples are required to test the null hypothesis that degradation of drugs during spaceflight is no different from terrestrial degradation. The study did not include a terrestrial control arm. Instead, the API content of each medication was compared to USP API acceptance criteria, which are quality-based threshold standards that do not give insight into "typical" terrestrial degradation. USP specifications do not account for the time-dependent change in API content that occurs with any drug. Using USP acceptance criteria as a surrogate for measured terrestrial stability has 2 problems: first, USP acceptance criteria are only applicable if medications are tested *before* their expiration date (here, 6 of the 9 medications were tested after expiration); second, USP monographs are not fixed; USP continuously reviews and revises drug monographs, meaning that USP specifications are subjective benchmarks. Although the study design does not test the proposed hypothesis, the results do provide "free floating" estimates of absolute API content and impurities for each tested medication and indicate that spaceflight does not have any substantive effect on SODF.

Cory et al., 2016: This study measured API content and impurities in 5 medications previously stored on the ISS at "conditions more extreme than those recommended by the manufacturers" (Cory, et al., 2016), however, the report does not discuss how extreme these conditions were or whether they include off-nominal temperature, humidity, or other factors (e.g., radiation). This cross-sectional study assayed API content at a single timepoint that was different for each drug tested. The study compared the API content of medications returned from ISS to the API content of terrestrial "controls" that were from the same manufacturer but not the same lot. In fact, the terrestrial controls ranged from 7 months older than the flight samples (valacyclovir) to more than 60 months newer than the flight samples (Sertraline) (Appendix 10). Although the different lots and ages of the corresponding flight and terrestrial samples made it difficult to interpret the results, the API content was only slightly different for the terrestrial and spaceflight treatment conditions, indicating that spaceflight had very little effect on drug stability.

Overall, no unusual loss of API occurred in the flight medications. The drug exhibiting the lowest potency after spaceflight, relative to its labeled strength, was sertraline 50 mg tablets that were stored on the ISS for 700 days. Sertraline retained 98.6% ± 5.8% of its label potency despite being more than 40

months past its expiration date and having spent 700 days in space. Whereas the terrestrial sertraline samples retained 99.5% ± 5.2% of their label potencies and where well within their shelf life (i.e., not expired at the time of testing). Although no statistical testing was performed, it is unlikely that these mean potencies differ based on the large standard deviations reported. None of the drug products exhibited a loss of potency relative to USP acceptance criteria, and the potency of all medications was similar to the potency of the terrestrial controls. In fact, the mean API content of the spaceflight samples of Levofloxacin (132 days on the ISS), ibuprofen (140 days on the ISS), phenytoin (241 days on the ISS), and valacyclovir (498 days on the ISS) were *higher* than the API content of the corresponding terrestrial samples, although these differences were not analyzed for statistical significance.

Because this is a cross-sectional study, results can be compared only to similar timepoints in the Du et al. (2011) study. Based on these comparisons, only the sertraline results are discordant: Du et al. (2011) reported that sertraline failed after 353–596 days of spaceflight, whereas Cory et al. (2016) determined sertraline was well within USP specification after 700 days of spaceflight. Possible explanations for the different findings include the likely possibility that Cory et al. (2016) tested different brands and formulations of the tablets than Du et al. (2011) did, or that packaging, storage location on the ISS, sample preparation, or analytical methods where different (which were not described in Du et al. 2011). Packaging and location could affect atmospheric exposures, whereas location could conceivably contribute to off-nominal temperatures and influence radiation exposure related to shielding. Radiation evidence is presented in THE EFFECT OF IONIZING RADIATION section below and in Appendices 8 and 9.

Wu and Chow report, 2016: The goal of the research project was "…to develop and validate *predictive degradation* models for select pharmaceutical preparations contained in the ISS medical kits". This was an opportunistic study that assessed medications that were stored on board the ISS and returned to Earth at various asynchronous periods of time. Because this was an opportunistic study, parallel lot-matched controls were not available and baseline potency assays were not measured at the start of the experiment, concurrent with repackaging for flight. Four drug products were analyzed: promethazine 25 mg tablets, promethazine 25 mg/mL injection solution, azithromycin 250 mg tablets, and ibuprofen 400 mg tablets (Appendix 10). The API content of each drug product was assessed at 2–3 timepoints. The report does not give manufacturer information for any of the samples, therefore it cannot be determined if the sets of drugs were from the same manufacturer or not. The report does provide a detailed description of the analytical methods and robust documentation of analytical quality metrics for each test, such as intra- and inter-day accuracy, quantitation and detection limits, and precision for the liquid chromatography with tandem mass

spectrometry (LC-MS/MS) assays. However, despite the careful analytical reporting, the report is missing critical information on each medication, particularly for azithromycin, that limit interpretation. Importantly, the report does not provide any type model (linear or otherwise) for *"predictive degradation" of* medications over time, which was the stated goal of the research.

The 4 pharmaceuticals returned from ISS contain less API content than the corresponding unmatched terrestrial "controls": Ibuprofen tablets, 14–17% less API; promethazine tablet, 14–23% less API; promethazine injection solution, 15–18% less API; and azithromycin tablet, 17–27% less API. However, these differences probably do not reflect changes due to spaceflight, for several reasons.

First, the spaceflight medications were well past their expiration when they were analyzed. The authors provided expiration dates for half (7 of 14) of the spaceflight medications tested, all of which expired between Oct. 2013 and Sept. 2015[4]. The report is dated 11/29/2016, so presumably the samples were analyzed in early 2016, meaning that the flight medications were about 1–3 years past expiration when they were analyzed. This is a serious problem because controls were *not* from the same manufacturing lot as the spaceflight samples. The authors did not give the expiration dates for any of the terrestrial controls; however, it appears medications were new because they were used as baseline controls and assumed to contain API at 100% potency. Therefore, this experiment only gives API content of expired medications relative to new, unexpired medications from the same manufacturer, and does not assess the effects of spaceflight.

Second, the duration of spaceflight exposure was much shorter than the duration these samples were stored terrestrially. The mean duration of terrestrial storage was 406.6 days, 420.5 days, 236.7 days, and 225.7 days longer than the mean spaceflight exposure for promethazine tablets, promethazine injection, azithromycin, and ibuprofen, respectively (Appendix 10). This postflight storage substantially contributes to the time available for the API to degrade. The authors did not report how the spaceflight medications were packaged, however, repackaging could increase the rate of degradation.

Third, the report is missing important information needed to evaluate time-related changes. Expiration dates for controls samples were not provided so it is not clear if the control and the spaceflight

[4] Mission landing dates are available for all spaceflight medications and range from October 2012 to May 2015.

drugs are comparable in age. Additionally, launch dates, landing dates, repackaging dates (if applicable), brand information, and lot information was not provided for the products tested. For these reasons, no meaningful post hoc analysis of these data is possible. which can provide important insights into spaceflight factors that contributed to the decreased potency

In summary, the Wu and Chow study provides limited description of drug content and does not provide *a predictive degradation model*. The results show no apparent association between API content and the number of days in space; however, no statistical testing was performed to rigorously test for a relationship. The report is missing important information on many of the medications that makes it impossible to determine whether changes in API content are attributable to spaceflight, time past expiration, or brand variability.

Cory et al., 2017: This is an opportunistic study that measured API content and impurities in 3 medications stored on board the ISS for different durations: amoxicillin, aspirin, and pseudoephedrine (Appendix 10). For each medication, all samples were from the same manufacturer, but were from different manufacturing lots with different expiration dates. Additionally, all treatments are compared to a single unmatched terrestrial reference sample. All the terrestrial controls were well within their shelf life (i.e., not expired), whereas all the spaceflight medications were 3–37 months past their expiration date. Consequently, the flight samples do not represent a clear continuum of change over time, and exposure-related changes in content are confounded by the different ages of each medication at the time of analysis. Analysis of the results is challenging because a scientific method normally holds all variables constant except for the dependent variable. Here, as with the other opportunistic studies, the experimental variables that affect potency include days in space (51–501 days), days past expiration (91–1185 days), and period of terrestrial storage after spaceflight (338–1231 days). It is strongly recommended that future studies avoid such complicated designs because changing multiple experimental variables obscures the relationship between spaceflight duration and potency.

No clear time-related difference in API content was detected for any of the spaceflight exposed aspirin or amoxicillin samples relative to corresponding terrestrial samples. For pseudoephedrine, however, an apparent difference was detected (no statistical comparison was performed). Interestingly, however, the spaceflight samples of pseudoephedrine retained substantially *greater* API levels (103.4–107.6%) than the corresponding terrestrial samples (91.0% ± 2.0). It is noteworthy, however, that although all formulations of pseudoephedrine 30 mg tablet were from Major Pharmaceuticals, the NDC number of the terrestrial pseudoephedrine sample (00904-*6338*-60) given in the report is different than the NDC of the spaceflight

samples (00904-*5053*-60), indicating that both the spaceflight and the terrestrial samples were produced by the same manufacturer (00904 = Major Pharmaceutical), but are different products of different ages (6338 ≠ 5053). The formulations of these products are very different[5]. Differences in formulation can significantly affect the efficiency of the extraction when processing the drugs for analysis. Because the spaceflight samples were all the same product but different from the terrestrial sample, it is possible that the extraction process optimized for the spaceflight samples yielded inefficient extraction of the terrestrial samples, and hence an apparent low potency estimate for this medication. Alternatively, it is possible that, for whatever reason, the repackaged terrestrial product experienced a significant degree of degradation despite being well within its expiration date.

Overall, this study provides no indication that prolonged spaceflight has any unusual effect on drug stability.

d. *Conclusion from all available opportunistic spaceflight studies*

Across all 5 opportunistic studies, the types of medications tested were much narrower than that of Du et al. (2011). The Du et al. (2011) study included several non-solid formulations and 23 SODF APIs. The opportunistic studies were more focused on analytical quality control and characterizing impurities. Three of the opportunistic studies included terrestrial controls for each spaceflight exposed medication; however, these controls were from different lots with different expiration dates (Cory, et al., 2016; Cory, James and Mangiaracina, 2017; Wu, L. and Chow, 2016), and one study includes both unmatched and *some* lot-matched controls (Khan, M. A. and Wotring, 2014).

Nine medications assessed in the 5 opportunistic studies (Table 1, bolded) were also tested by Du et al. (2011). Ibuprofen, the most commonly tested drug, was evaluated in 4 of 6 spaceflight studies. Two medications that were assessed in all 5 opportunistic studies were not included in the Du et al. (2011) study (‡ superscript in Table 1), and the remaining drugs were evaluated in only a single study. The study by Wotring and Khan (2014) is distinct from the other 4 opportunistic studies in that the 3 medications tested are *identical* to the medications originally tested by Du et al. (2011) a few years earlier. In this respect, these were independent assessments of the same Du et al. (2011) samples that were conducted after a considerable period of terrestrial storage after their spaceflight exposure. Figure 3 shows scatter plots of

[5] https://www.medschat.com/NDC/0904-6338?srcq=tcl016
https://www.medschat.com/NDC/0904-5053?srcq=tcl016

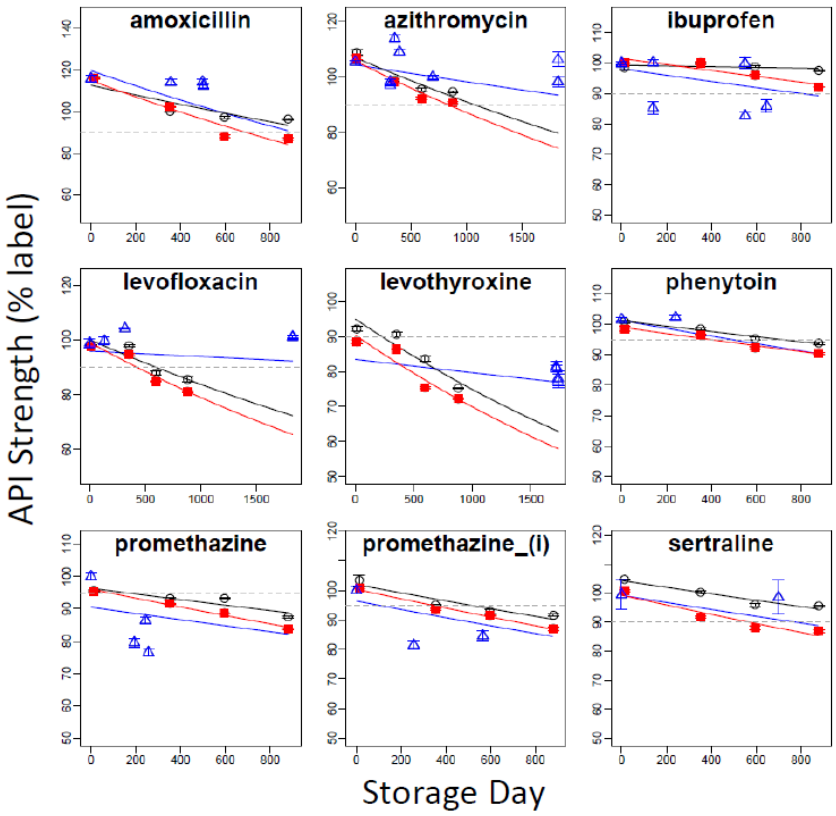

Figure 3. Least squares degradation trends for 8 active pharmaceutical ingredients (API) (9 formulations) based on testing data from all available spaceflight studies. The blue solid line is the overall trend for all available spaceflight data, including results from Du et al. (2011) and sui generis results from opportunistic studies. Triangles are mean ± one standard deviation API potency from these opportunistic studies. Black and red data points correspond to mean ± one standard deviation API potency in control (black) and spaceflight (red) samples from Du et al. (2011) with superimposed least squares trend lines for Du and colleagues' plotted data only.

mean API levels (± standard deviation) for the 9 drugs products (8 APIs) that were assessed in an opportunistic study and by Du and colleagues. A trend line incorporating all available data for each medication (blue line) is plotted to illustrate the overall pattern of API loss. A key observation from these composite plots is the large variability in measured API content across studies.

API levels in 5 of the 9 drugs that were common across studies contained more API in the follow-up studies than were reported by Du et al. (2011) at similar or earlier time points. The API level of ibuprofen in the opportunistic studies bracket levels reported by Du et al. (2011). Wu et al. (2016) reported lower levels of API at all time points, whereas Wotring et al. (2015) and Cory et al. (2016) reported higher levels. The level of API in both the oral and the injectable dosage forms of promethazine reported by Wu et al. (2016) were lower than the levels reported by Du et al. (2001). When the data from the opportunistic studies are

included in the analyses, spaceflight degradation of 5 common drugs are estimated to be slower than the degradation rate reported by Du et al. (2011); only phenytoin exhibited an increase in estimated rate of degradation (Reichard, et al., 2023). The spaceflight degradation rates for amoxicillin, ibuprofen, and injectable promethazine (the latter being the only drug maintained its original manufacturer's packaging) are similar when estimated with the Du et al. (2001) study data or when the data from the opportunistic studies are included, despite large variations in the data.

Cory (2017) and Khan (2014) analyzed equivalent medications, but differently formulated drug products. That is, equivalent products (i.e., pseudoephedrine 30 mg tablets) were analyzed but they had different NDC numbers and different formulations. Although all samples were analyzed using USP compendial methods, assessing different products in the same experiment is problematic. A compendial method can be applied to equivalent drug products that are composed of different ingredients; however, when comparing different product formulations, the USP method may require adjustment to account for differences in matrix and should be supported by method validation and verification. This fact is discussed in USP chapters <1225> and <1226>, as well as the FDA Guidance for Industry titled *Analytical Procedures and Methods Validation for Drugs and Biologics* (U.S. Food and Drug Administration (FDA), 2015; United States Pharmacopeia, 2019a; United States Pharmacopeia, 2022). Specifically, as stated in USP <1226>:

> …the excipients in a drug product can vary widely among manufacturers and may have the potential to directly interfere with the [compendial] procedure or cause the formation of impurities that are not addressed by the compendial procedure. In addition, drug products containing different excipients, antioxidants, buffers, or container extractives may affect the recovery of the drug substance from the matrix. (United States Pharmacopeia, 2019a)(USP <1226>)

Hence, although USP methods are validated, the method must still be verified under conditions of use. If this is not done, assay results may underestimate content. We have verified this through direct discussion with the U.S. FDA Office of Product Quality (personal communication).

NASA-supported studies have measured drug potency after various periods of spaceflight. All these studies have focused on solid oral drugs that have been repackaged[6] into uncharacterized or non-protective

[6] Repackaging is defined as "the act of taking a finished drug product from the container in which it was distributed by the original manufacturer and placing it into a different container without further manipulation of the drug" (U.S. Food and Drug Administration (FDA), 2017; United States Pharmacopeia, 2021b)

packaging, meaning that these packages are not rated as USP “tight” or “well-closed” based on vapor transmission rate (United States Pharmacopeia, 2021b). Such studies provide a worst-case estimate of drug stability under spaceflight conditions.

D. DEGRADATION IMPURITIES

This section evaluates the formation and the safety of pharmaceutical impurities. Impurities can cause adverse health effects if present at sufficiently high levels and with an adequate duration of exposure. All pharmaceutical products contain impurities, the levels of which are regulated by the U.S. FDA. The formal process to evaluate the safety of impurities, and the regulatory context of safety evaluations, is discussed in Appendix 6 (Assessment of Impurity Toxicity). Evidence regarding the role of spaceflight exposure on the formation of drug impurities is presented below.

1. CONTEXT: FORMATION OF IMPURITIES

All pharmaceuticals contain impurities that can originate from several sources. Impurities are frequently introduced during the production or synthesis of the API (i.e., “process-formed impurities”), or they can be contaminants of the excipients used in compounding the drug product. Drug manufacturers typically outsource excipient production to other chemical manufacturers; hence, impurities levels vary depending on the quality of the materials purchased (Waterman, et al., 2002; Waterman, Adami and Hong, 2004). Impurities can also accumulate over time due to the chemical reactions that mediate degradation. Such reactions frequently require the presence of environmental factors such as moisture (i.e., relative humidity) and oxygen. In some instances, excipients, or chemical contaminants in excipients, can react with the API (often in the presence of oxygen or moisture) to mediate API degradation. Contamination attributable to biological organisms and metals are excluded from this discussion.

Impurities can act as reaction substrates to mediate chemical degradation of a drug API, and, if present at sufficiently high levels, they can pose a risk for adverse health effects. Nitrosamines are an example of one class of impurities that can originate during the synthesis of drug substances, as contaminant of excipients and as products of chemical degradation (U.S. Food and Drug Administration (FDA), 2020b). Nitrosamines are classified as possible human carcinogens and the recent identification of nitrosamine impurities in several drug products has compelled the FDA to issue industry guidance to control sources of nitrosamine contamination and improve quality testing. Nitrosamines are the reason Ranitidine

(Zantac®) was withdrawn from the market and the reason for multiple recalls of drugs, such as benazepril (lotensin®).

Many of the drug products on the ExMC exploration candidate formulary[7] have well-established safety profiles. However, the safety of these medications is based on use within their established shelf life, and exploration space missions may require use of some medications well beyond their expiration date. Furthermore, most of the SODF will likely be repackaged for long-duration space missions to reduce mass and volume of the medical kits, and manufacture expiration dates are nullified when medications are removed from the sealed manufacturer container.

2. TOXICITY OF IMPURITIES

Significant misconceptions exist concerning the acceptability of toxic impurities in pharmaceuticals. Fundamentally, all pharmaceuticals contain impurities, many of which present a risk to human health if the quantities reach a critical level. This discussion is pertinent to the use of pharmaceuticals beyond their established shelf life, as would be expected for exploration space missions, *especially* if medications are repackaged. Appendices 2 and 6 discuss how acceptable impurity levels in pharmaceuticals are established. Consistent with industry guidance and accepted chemical risk assessment principals, the objective for assessing impurities is *not* to ensure spaceflight medications do not accumulate "toxic" impurities; instead, the objective is to ensure that impurities do not exceed levels that pose a health hazard (i.e., they are "qualified") or, that impurities with genotoxic potential or potential to be immune sensitizers, do not exceed default limits.

3. EVIDENCE: NASA SUPPORTED IMPURITY STUDIES

a. *Summary of Available Spaceflight Study Results*

Four studies have evaluated how spaceflight affects the levels of drug impurities. These studies, which are summarized above and in Table 1 (Cory, et al., 2016; Cory, James and Mangiaracina, 2017; Khan, M. A. and Wotring, 2014; Wotring, 2016), were all opportunistic studies that analyzed pharmaceuticals from the ISS medical kits that were returned near or shortly after their expiration dates.

[7] The ExMC exploration candidate formulary is an evolving list of medications for exploration space missions developed by ExMC. Medications derive from several different sources, including the current operational formulary on board the ISS, Condition Resource Trace medications derived from Clinical finding forms, the IMPACT (Informing Mission Planning via Analysis of Complex Tradespaces) tool, a historical list of drugs from flown ISS Medical Accessory Kit, and medications previously evaluated in spaceflight studies.

Wotring (2016) evaluated potency and impurities in 9 SODF that were flown on board ISS for 550 days. Because this was an opportunistic study, no terrestrial controls were included to measure relative effects of spaceflight or to perform hypothesis testing. An objective was simply to evaluate if unusual impurities might be observed, which might be a health hazard. This study design has several limitations that should be considered when interpreting the results:

- Without corresponding terrestrial control samples, the study does not provide any insight on whether (or not) spaceflight conditions affect drug stability any differently than would be expected for the same drug stored under similar terrestrial conditions.
- The study is a cross sectional design and did not evaluate the temporal effects of spaceflight on drug quality. Therefore, the results represent a snapshot at a single point in time. A temporal design would have been able to determine drug degradation rates and the rates of impurity formation.
- The mass balance of each medication was not reported, so it is impossible to determine if the major degradation products were quantified; the author acknowledged this limitation.
- Baseline impurity content was not measured for any of the drugs prior to spaceflight storage. In the absence of a baseline measurement, it cannot be determined if degradants observed after spaceflight are different from or at greater levels than those present at the start of the experiment.

Of the 9 medications, 3 (ibuprofen, loperamide and modafinil) were still within their expiration dates at the time of analysis, while the remaining 6 medications were expired, ranging from 151 (acetaminophen) to 334 days (pseudoephedrine) beyond their expiration dates at the time of analysis. The strength of several of the drugs was less than the labeled strength, including aspirin (96% of labeled strength), melatonin (90% of labeled strength) and acetaminophen (97% of labeled strength). The change in API content for drugs in this experiment are discussed in the Opportunistic Spaceflight Studies of Drug Content section of this report.

Two of the tested drugs, loperamide and melatonin, had impurity levels slightly exceeding USP quality standards but the impurities were not identified. A third drug, acetaminophen, contained an unidentified impurity that, if determined to be paraaminophenol, would also have exceeded the USP quality limit. In the absence of terrestrial controls or baseline testing, the relative effect of spaceflight exposure on impurity content cannot be determined from these results. Qualitatively, the results suggest that a spaceflight exposure of up to 550 days does not pose a concern for the formation of unusual or excessive accumulation of degradation products or premature drug failure.

Cory and colleagues evaluated drug impurities in 2 separate unpublished spaceflight studies. The first study evaluated the quality of 5 SODF that were repackaged at JSC and stored on board ISS for various durations from 132 to 700 days (Cory, et al., 2016). Each drug was evaluated at a single time point and spaceflight samples were compared to *unmatched* terrestrial samples of recent lots of the same medication from the same manufacturer (Appendix 10). It appears that all spaceflight samples were analyzed at least 1 to 3 years after return from orbit, which introduces some uncertainty regarding how much degradation is attributable to spaceflight, and how much is attributable to terrestrial storage. Despite using highly sensitive LC-MS chromatography, and the fact that 4 of 5 medications were well past their expiration dates, API potency (% of label strength) and impurity levels for all medications remained within USP acceptable limits. No unusual degradants were observed in spaceflight samples.

In the second study, Cory et al. (2017) evaluated 3 medications stored on board ISS for different periods of time and compared to a single representative terrestrial control maintained in the JSC pharmacy under ambient conditions (Cory, James and Mangiaracina, 2017). Medications for each treatment condition (i.e., control and spaceflight) were from the same manufacture, however, the terrestrial JSC controls were 2–4 years newer than the spaceflight samples: all spaceflight samples had expiration dates that were circa 2013–2016, whereas terrestrial samples expired circa 2017 or 2019; analysis was performed mid-2017. The interval of several years before the spaceflight samples were analyzed contributes additional variability and uncertainty to the results. At the time of analysis, all the flight samples were past their manufacturer's expiration dates, whereas the terrestrial samples were not expired. The authors reported that the amount of degradation impurities did not correlate with the duration of spaceflight exposure. Both studies by Cory and colleagues indicate that spaceflight exposure did not produce any unusual change in medications, despite the lack of lot-matched matched controls.

A fourth (unpublished) study (Khan, M. A. and Wotring, 2014) evaluated the content of 3 drugs previously reported by Du et al. (2011). This again was an opportunistic study rather than a designed study and therefore the sample selection appears somewhat ad hoc. Three drugs were tested, azithromycin 250 mg tablet, levofloxacin 500 mg tablet, and levothyroxine 0.025 mg tablet (Appendix 10).

- Azithromycin included 2 samples from Sandoz and 3 from Greenstone Pharmaceuticals, of which one Sandoz and 2 Greenstone samples were terrestrial comparators ("controls"). The Sandoz control and one Greenstone control remained in the manufacturer's packaging. The corresponding Sandoz sample and Greenstone samples were exposed to spaceflight for either 316 or 880 days, respectively.

- Levofloxacin samples were all Janssen products and were all repackaged by the JSC pharmacy. Two samples were exposed to spaceflight for either 316 or 880 days and the third sample served as a terrestrial control. The control sample of levofloxacin was lot-matched to the 880-day spaceflight sample but was of a different lot from the 316-day spaceflight sample.
- Levothyroxine consisted of 2 sets lot-matched control and spaceflight samples. (i.e., each flight sample had a lot of matched terrestrial control). The spaceflight samples spent either 13 or 880 days on board ISS. All samples were approximately 1600 days past expiration.

Most of the spaceflight samples were several years past their manufacturer expiration dates. Despite the age of these samples, no significant differences in impurity content were detected for any of these samples and all samples were within USP specifications. Interestingly, some of the process-formed impurities of the Sando and Greenstone azithromycin tablets were different, which may have been related to different synthesis processes or formulation ingredients used in the manufacturing of these products. This observation stresses the importance of brand selection for experimental studies and operational use.

b. *Conclusions from spaceflight drug degradation studies.*

The spaceflight drug degradation studies were all opportunistic studies that were not designed to assess time-dependent changes in the levels of degradation impurities. These studies cannot demonstrate an association between spaceflight exposure and emergence of degradation impurities because samples were not punctually analyzed after spaceflight return and were not paired with lot-matched terrestrial controls. In most cases, the spaceflight samples were substantially older than the corresponding controls, meaning that the effect of aging cannot be distinguished from the effects of spaceflight. Regardless of these changes, spaceflight had no clear effect on the degradation of SODF and spaceflight was not associated with the appearance of unusual impurities.

E. EFFECT OF SPACEFLIGHT ON PHYSICAL STABILITY OF DRUG SUBSTANCES

1. CONTEXT: FACTORS INFLUENCING PHYSICAL DRUG STABILITY

Physical drug stability contributes directly to pharmacokinetic and pharmacodynamic risks, both of which influence therapeutic efficacy and safety of medications. Physical attributes of a drug are classified by 2 broad testing categories: product quality tests and product performance tests. Product quality tests ensure continuity of manufacturing and storage; product performance standards, when applicable, ensure the functional requirements are met. Product quality tests include both “universal” tests and dosage form-specific tests. Universal tests are often termed “appearance” by USP specifications and are subjective

qualitative descriptions of the dosage form. Physical appearance attributes include the color, texture, and general appearances of the medication (United States Pharmacopeia, 2013; United States Pharmacopeia, 2019b). For example, the specifics of a tablet could be white, round, biconvex, film-coated tablet, imprinted with 400 on one side. As an example, the appearance of an injectable powder could be described as "white to off-white and as cake or powder; free from particles or foreign matter."(Skwierczynski, 2013). Qualitative universal test-results are the predominant type of data currently available from NASA-supported spaceflight studies.

Dosage form-specific tests, as the name suggests, depend on the specific dosage form. For example, product quality tests applicable to injectable solutions include pH, particulate matter, sterility, bacterial endotoxin, and product uniformity; no product performance tests exist for injectable solutions. For tablets, quality tests include product uniformity, weight, tablet friability, force required to break the tablet, and water content, among others. The excipients in the formulation can significantly influence several of these factors. For example, hygroscopic ingredients can adsorb moisture from the environment resulting in increased weight and water content, and decrease the force required to break a tablet (Waterman and MacDonald, 2010). Adsorbed moisture can also influence chemical stability (Asafu-Adjaye, et al., 2011; Carstensen, 1988; Chen, et al., 2012; Szakonyi and Zelkó, 2012). Tests of tablet performance include dissolution rate and disintegration tests. Dissolution rate governs the release of the API from solid dosage forms. When dissolution rate increases, the active ingredient may be released too quickly, resulting in elevated concentrations of API in the blood and an increased risk of side effects. Conversely, if the API is released too slowly then blood concentrations are reduced and the time to reach peak blood concentration will be longer or bioavailability will decrease, which increases the risk of therapeutic failure. Drug aging can induce changes in the molecular structure of drug ingredients, and this can slow dissolution. Such changes include time-dependent crosslinking of polymers (i.e., cellulose, polyethylene glycol [PEG]) that are commonly used in the formulation of many medications (Waterman and Adami, 2005), and polymer crosslinking can also be increased by exposure to ionizing radiation (Sarcan and Ozer, 2020; Sintzel, et al., 1997). A recent NASA-supported pilot study assessed dissolution performance of 4 irradiated and aged medications; these results are currently being prepared for publication.

2. EVIDENCE: NASA-SUPPORTED STUDIES OF PHYSICAL STABILITY

Two studies investigated the longitudinal changes in physical drug stability: Du et al. 2011, and an unpublished study of drug stability after simulated space radiation exposure performed in conjunction with

NASA Space Radiation Laboratory (NSRL) at Brookhaven National Laboratories (BNL) and University of Baltimore Maryland.

Du et al. (2011) reported that some physical changes occurred in spaceflight-exposed medications but did not provide a detailed discussion or tabulation of those changes. Furthermore, the report lists the spaceflight drugs that exhibited physical changes (but not the type of change), but did not discuss physical changes in the terrestrial samples. Hence, the results should *not* be interpreted to mean that the controls samples did not have physical changes. Rather, this is a typical form of omission bias because the authors *suggest* that changes were only observed in the terrestrial samples although the changes were not discussed. The report states

- "Discoloration of amoxicillin/ clavulanate (Augmentin®) tablets and liquefaction of ciprofloxacin ophthalmic ointment were noticed in control samples corresponding to payload"
- "The number of formulations with physical changes was higher in-flight samples from all payloads than in controls"

Although Du et al. (2011) summarized physical changes of spaceflight medications in Table II of their report, they did not provide an equivalent summary of physical changes in corresponding controls. The authors' presentation does not allow easy comparison of drugs that exhibited changes over time; therefore, the information provided by Du et al. (2011) is presented here in a revised format (Table 3). Additionally, corresponding API content (as the percent of labeled strength) is provided to enable comparison of physical changes with chemical changes. Mupirocin is reported to have undergone phase separation by the 880-day time point; however, this change is omitted in the authors' tabulated summary of physical changes.

Two observation that can be drawn from Table 3. First, there is no consistent dose-effect relationship between duration of spaceflight and physical changes; i.e., physical changes do not progress with increasing duration of spaceflight. Several samples have early changes that are not observed at later timepoints, despite substantially longer exposure to spaceflight (Table 3). Correlation of exposure and effect is one of the key criteria for causal relationships (Fedak, et al., 2015). Second, the presence of physical changes (or absence of physical changes in controls) is not associated with chemical changes: several instances of physical changes occurred in the absence of significant changes in API content, and in other cases, significant changes in potency occurred in the absence of corresponding physical changes. The fact that physical and chemical changes do not necessarily coincide is not unusual, but what is difficult to reconcile are instances where physical changes are associated with a clear loss of potency *at an earlier*

timepoint (i.e., Amoxicillin / clavulanate, Dextroamphetamine, Levothyroxine) but no physical changes were observed at a subsequent timepoint despite clear progression of API loss over time. The investigators also performed dissolution assays on 12 of the solid drug formulations, however, values were similar for control and flight samples of all 12 drug products at all timepoints.

It is well recognized that drug products deteriorate over time, especially when they are removed from the manufacturer's protective packaging. What remains unclear from the Du et al. (2011) report is whether the conditions of spaceflight accelerate (or inhibit) the normal degradation process. Du et al. (2011) explicitly state they collected weight, physical appearance, color, odor, hardness, friability, and drying data, however, these data are not presented in the text nor provided as supplementary information. Color change is briefly discussed, but the methods used to assess the subjective change are not provided, even though discoloration was reported as "the most frequently observed physical change in flight samples." Color changes in spaceflight samples were not provided along with corresponding changes in controls, which could have yielded greater insight into how spaceflight affects physical stability of drugs.

Table 3. Summary of Physical Changes in Spaceflight Samples Reported by Du et al. (2011) and corresponding API content.

Sample	Characteristic		13 days	353 Days	596 days	880 Days
Promethazine suppository	**Physical Changes**		✓	**X**	**X**	**X**
	API Content:	Control	99.3±0.15	97.3±0.4	95.7±0.62	93.9±0.54
		Flight	97.7±0.16	92.4±0.1	89.7±0.41	84±0.76
Triamcinolone Cream	**Physical Changes**		✓	**X**	**X**	**X**
	API Content:	Control	98.6±0.59	97.9±1.12	96.4±0.83	94.8±0.31
		Flight	98.3±0.54	93.8±0.94	93.1±0.02	92.3±0.36
Acyclovir Tablet	**Physical Changes**		**X**	✓	**X**	**X**
	API Content:	Control	107.2±0.31	106±0.29	102.3±0.44	100.1±0.53
		Flight	104.7±0.06	101.5±0.1	96.9±0.44	92.4±0.94
Amoxicillin & clavulanate tablet	**Physical Changes**		**X**	✓	**X**	**‡ Color change**
	API Content:	Control	116.2±0.35	100.1±0.05	97.2±0.37	96.4±0.47
		Flight	116±0.14	102.3±0.33	88±0.68	87±0.41
		Control	93.3±0.59	12±0.43	6.6±0.16	3.3±0.31
		Flight	91±0.79	36.7±0.33	21.1±1.1	9.1±2.07
Ciprofloxacin Tablet	**Physical Changes**		**X**	✓	**X**	**X**
	API Content:	Control	104.8±0.87	92.9±0.15	91.5±0.03	90.9±0.3
		Flight	101.5±0.31	92.1±1.19	90.6±0.34	84.4±0.49
Ciprofloxacin ophthalmic ointment	**Physical Changes:**		**X**	✓	**X**	**‡ Liquefaction / phase separation**
	API Content:	Control	95.4±0.96	NA	93.2±0.62	88.5±0.47
		Flight	94.7±0.92	NA	90.3±0.27	83.4±0.46
	Physical Changes:		**X**	✓	✓	**X**

Table 3. Summary of Physical Changes in Spaceflight Samples Reported by Du et al. (2011) and corresponding API content.

Sample	Characteristic		13 days	353 Days	596 days	880 Days
Dextro-amphetamine tablet	API Content:	Control	98.1±0.83	98.3±1.07	97.5±0.14	87.3±0.03
		Flight	98.3±0.6	89.5±1.09	88.8±1.46	84.5±0.34
Levothyroxine Tablet	**Physical Changes**		**X**	✓	✓	**X**
	API Content:	Control	92.3±0.66	90.7±0.8	83.7±0.78	75.3±0.14
		Flight	88.6±0.51	86.5±0.13	75.4±0.29	72.3±0.3
Metronidazole Tablet	**Physical Changes**		**X**	✓	**X**	**X**
	API Content:	Control	97.5±0.42	95.6±0.31	93.9±0.22	93.3±0.49
		Flight	96±0.28	94.4±0.46	92±0.46	90±0.85
Imipenem & cilastatin Inj. Powder	**Physical Changes:**		**X**	**X**	✓	✓
	API Content:	Control	97.6±1.43	103±0.73	102.6±0.31	96±0.75
		Flight	103.4±0.88	100.5±1.31	92.8±0.22	90.6±0.24
		Control	107±0.4	111.5±0.56	109.6±0.5	107.7±0.96
		Flight	98.5±2.02	103.1±0.75	99.6±0.25	98.3±0.11
Silver sulfadiazine cream	**Physical Changes**		**X**	**X**	✓	✓
	API Content:	Control	97.5±1.33	93.5±0.28	90.5±0.36	88.3±0.15
		Flight	96±1	92.6±0.51	89.8±0.61	83.9±0.05
Sulfamethoxazole & trimethoprim tablet	**Physical Changes:**		**X**	**X**	**X**	✓
	API Content:	Control	101 ±0.01	100±0.3	96.8±0.1	90.3±0.91
		Flight	98.9±0.54	96.9±0.26	90.9±0.06	80.7±0.64
		Control	102±0.1	97.9±0.14	96.4±0.36	88.8±1.45
		Flight	99.6±0.64	94.7±0.13	90.7±0.72	79.1±0.51
Fluconazole Tablet	**Physical Changes:**		**X**	**X**	**X**	✓
	API Content:	Control	96.3±0.51	96±0.09	91.7±0.4	89.9±0.84
		Flight	96±0.27	94.2±0.39	90.2±0.69	88.2±0.6

Physical changes do not appear to correspond with a reduction in API content for most drugs.□□= Physical changes in the spaceflight samples without changes in the corresponding control sample (highlighting added for clarity); X = No physical change reported in the spaceflight sample; ‡ = Similar physical changes in both the control and flight samples (highlighting added for clarity). API content = the active ingredient potency as a percent of labeled strength.

The second study that investigated physical changes was initiated in 2017 and includes an assessment of drug dissolution. The results of this study are currently being analyzed for potential publication. The study assessed how exposure to simulated galactic cosmic radiation (GCR) affects the stability of 4 solid drug formulations: acetaminophen 500 mg tablets, amoxicillin 500 mg capsules, ibuprofen 400 mg tablets, and promethazine 25 mg tablets. Each medication was evaluated for drug identity, potency, impurities, and tablet performance. Samples were placed on a foam backing material and irradiated with either 0.5 Gy or 1.0 Gy of mixed energetic ion beams that collectively simulate the GCR field (See Figure 4). A more complete discussion of the methods and conditions for this experiment is provided in the Irradiation Study with Long-term Post-irradiation Storage section of this report. The dissolution rates of the irradiated samples and lot-paired unirradiated controls were analyzed at 2 timepoints after irradiation (a later third

timepoint did not have enough sample to analyze dissolution rate). These data are currently being analyzed, although preliminary inspection of the results indicate that no medications showed a substantive change in dissolution rate.

In summary, available evidence does not support an association between length of time pharmaceuticals are exposed to the spaceflight environment and physical change in drug appearance or function. However, physical changes have not been either comprehensively studied and/or comprehensively reported by existing studies. It is plausible that long-term exposure to low dose-rate radiation could facilitate crosslinking reactions between some medication ingredients, which might slow dissolution and impact physical stability; however, this hypothesis has yet to be tested at spaceflight-relevant radiation doses.

F. PACKAGING AND DRUG STABILITY

1. CONTEXT: ROLE OF PACKAGING AND REPACKAGING ON DRUG DEGRADATION

This section addresses how the pharmaceutical industry and regulators use packaging to ensure the safety and efficacy of drug substances. Evidence from NASA-supported studies related to the effect of drug packaging and repackaging and relevant scientific literature is discussed. Pharmaceutical packaging is one of the most important factors that affect the stability of drugs, and packaging will be critical for maintaining safe and effective medications during long-duration exploration spaceflights. As noted above, the investigators of the only controlled study of spaceflight medications observed a very high premature failure rate of repackaged terrestrial control medications. The basic principles pertaining to NASA's repackaging of medications for long-duration space missions are given in Appendix 7.

a. *Atmospheric oxygen*

It is well established that atmospheric factors, such as oxygen and moisture, mediate degradation of many medications. For example, solid formulations of aspirin (tablets) degrade by hydrolysis, the rate of which correlates with atmospheric vapor pressure (Carstensen, 1988; Leeson and Mattocks, 1958).Similarly, furosemide, a potent diuretic, becomes unstable when exposed to moisture and is susceptible to changes in pH and oxygen in aqueous solutions (Asafu-Adjaye et al. 2011).

Oxygen not only contributes to the chemical degradation of many drugs in terrestrial conditions, it also contributes to radiolytic degradation of some drugs (Jacobs, 2022; Silindir Gunay and Ozer, 2009; Wilczyński, et al., 2012). The presence of oxygen during radiation exposure (Jacobs, 2022) increases radiation-induced oxidative degradation of many APIs because the oxygen reacts with intermediates or directly with ionized medicinal substances containing O_2 molecules (Sintzel, et al., 1997; Wilczyński, et al.,

2012). For example, solutions of propyl gallate, butylated hydroxyanisole, or o-tocopherol irradiated under vacuum with 20 kGy of gamma radiation degraded 16%, 8%, and 90%, respectively; whereas the same radiation exposure in the presence of O_2 caused the solutions to degrade 89%, 90%, and 100%, respectively (Jacobs, 1985). The presence of oxygen can also increase radiation-induced degradation of polymers (Shulman and Ginell, 1970). Wide arrays of polymers are commonly used to formulate both solid and non-solid formulations of drugs. Nisar et al. (2016) irradiated diclofenac solutions with 145–1015 Gy of gamma rays under different atmospheric conditions: air, N_2O, and N_2. At the lowest dose of gamma radiation tested (145 Gy) the loss of potency in the presence of O_2 and N_2O, both of which can form reactive oxygen intermediates, was substantially greater than in the presence of N_2,which does not form reactive oxygen species (Nisar, et al., 2016). Consequently, for some drugs there is a possibility that protective packaging can have an indirect role in protecting drugs from radiation by insulating drugs from oxygen and reducing the formation of reactive oxygen intermediates.

b. *Water vapor*

It is well established that moisture facilitates chemical degradation and physical deterioration of pharmaceuticals. Water reacts with solid drugs by several mechanisms of which water adsorption, capillary condensation, deliquescence are among the most important. Deliquescence is the process by which a substance sorbs (i.e., adsorption and absorption) water vapor from the atmosphere until it dissolves to form a solution. Capillary condensation draws adsorbed moisture into micropore spaces within a solid drug until the spaces become filled with condensed liquid from the vapor. Deliquescence and capillary condensation, lead to the formation of condensed or bulk water, which can dissolve water-soluble components of a pharmaceutical product. Crystal hydrates are formed when water molecules penetrate into the crystal lattice of a drug substance, which can disrupt the organized crystal structure to form an amorphous solid (Ahlneck and Zografi, 1990; United States Pharmacopeia, 3013). Amorphous or partially amorphous solids can absorb significant amounts of water because they have enough molecular disorder to permit penetration, swelling, or dissolution. These hygroscopic substances are particularly susceptible to hydrolysis (Waterman, et al., 2002). For example, solid formulations of aspirin (tablets) degrade by hydrolysis at a level that correlates with atmospheric vapor pressure (Leeson and Mattocks, 1958). Moisture is adsorbed at the surface of aspirin particles resulting in a film of water surrounding the aspirin particles. The water film is rapidly saturated as aspirin molecules are removed from the solid aspirin particle, and undergo hydrolytic decomposition, and as a molecule of aspirin hydrolyzes, it is almost instantaneously replaced by another aspirin molecule from the solid phase particle. The kinetic

principals underlying aspirin degradation have been documented in great detail, however, because some level of moisture is always present, the degradation rate is pseudo-first order with respect to aspirin concentration and pseudo zero-order with respect to water adsorption (Carstensen, 1988). Similarly, furosemide, a potent diuretic, becomes unstable when exposed to moisture and is additionally susceptible to changes in pH and oxygen in aqueous solutions (as cited in (Asafu-Adjaye, et al., 2011).

The science surrounding moisture ingress and rates of gas permeation into (and out of) pharmaceutical packaging is known, and rigorous models are available to predict how packaging configurations will perform (Nelson, Eric D. and Huang, 2011; Waterman, et al., 2002). Pharmaceutical manufacturers reduce the effects of environmental factors on medications primarily by selecting packaging materials with barrier properties corresponding to the susceptibilities of the drug product. Repackaging pharmaceuticals into non-protective containers significantly increases exposure to atmospheric water vapor and oxygen. Consequently, repackaging some drugs into non-protective containers (including Ziplock bags) increases the environmental exposure of the drug products and nullifies the manufacturer's experimentally determined shelf life. All the spaceflight drug stability studies have focused on testing repackaged drugs.

c. *Current NASA Repackaging Process*

NASA's practice of drug repackaging is essential to reduce the mass and volume of drug resources. The effect of drug repackaging on drug stability is not a concern for LEO missions because the ISS can be readily resupplied; however, for exploration space missions, resupply will be much more limited if not impossible. Therefore, to ensure drug stability throughout the full duration of an exploration mission, the materials used for repackaging will need to be far more protective than those used for the ISS. Additionally, although current drug repackaging is acceptable for near-Earth missions, improved repackaging (or use of the original manufacturer's packaging) could reduce the frequency of resupply, and hence the costs associated with resupply for the ISS or future near-Earth missions.

At present, the NASA Operational Pharmacy repackages SODF into polymeric plastic, zip-lock closure bags that are purchased from Healthcare Logistics (Circleville, OH) or from Consolidated Plastics (Stow, OH). These packaging products are permeable to gases and vapors, and do not meet the USP standards for protective multiple-unit packaging, which "must be at least as protective or more protective than the original container–closure system in terms of moisture vapor transmission rate, oxygen transmission, light transmission, and compatibility … with the drug product." (United States Pharmacopeia, 2020e). Likewise, these repackaging products do not meet USP performance standards, which apply to pharmacists and institutions (United States Pharmacopeia, 2020a). Because polymeric zip-lock bags are highly permeable to

oxygen and moisture, the current repackaging practices likely expose medications to atmospheric factors at concentrations that are equivalent to, and in equilibrium with, ambient atmosphere in the spacecraft (Putcha, et al., 2016; Waterman, et al., 2002). Atmospheric moisture and oxygen are known to reduce the shelf life of drugs (Roy, et al., 2018; Waterman, et al., 2002; Waterman, Adami and Hong, 2004), therefore repackaging into low-barrier packaging products will likely compromise the long-term reliability and safety of susceptible pharmaceutical resources (Putcha, Taylor and Boyd, 2011).

2. EVIDENCE: PACKAGING AND SPACEFLIGHT DRUG STABILITY

To date, no NASA-supported study has directly assessed how repackaging spaceflight medication affects drug stability relative to the stability of the same medications in their sealed manufacturer's packaging. The study by Du et al. (2011), is the only NASA-supported investigation that has included a range of drug formulations that were not repackaged (14/36 drugs); however, these were not matched to the same repackaged formulations. Ten of the drugs that were not repackaged were assorted non-solid formulations that included solutions, ointments, creams, and a suppository; the remaining 4 were combination products: imipenem with cilastatin (lyophilized powder for injection) and ethinyl estradiol with norethindrone (blister pack oral tablets) (see Table S3 of Du et al. 2011). Du et al. (2011) described the medication containers used for repackaging as custom manufactured "cylindrical polypropylene containers" without further elaboration. These containers are not consistent with current spaceflight operational procedures for SODF repackaging, which use re-closable zip-lock bags as discussed above. Because the repackaging products used for spaceflight SODF are not protective, the environment within the bag equilibrated with the external environment within a few days to weeks. Reichard et al. (2023) used the results from the Du et al. (2011) study to calculate degradation rates for both repackaged terrestrial and spaceflight samples. These rates are likely faster than the rate of degradation in the manufacturer's packaging because of the prolonged exposure to atmospheric factors (e.g., humidity, CO_2, oxygen)(Waterman and Adami, 2005). The difference in relative degradation rates for spaceflight and terrestrial samples reported by Du et al. (2011) is probably attributable, at least in part, to differences in atmospheric factors between the 2 storage environments, including different levels of CO_2 and possibly peak temperatures. The hypothesis that the current NASA drug repackaging process could contribute to accelerated degradation of some SODF has not been experimentally tested.

The Du et al. (2011) study, which is the only controlled study of repackaged and non-repackaged medication, shows a profound effect of repackaging on SODF. Of the 34 drugs in the terrestrial *control* group, 11 had API content below USP specifications (i.e., failed) *before* the manufacturer's label expiration date. Of

the 11 failed medications, 9 were repackaged orals drugs and 2 were non-solid topical medications. Nine of 22 SODF in the terrestrial *control* group failed to meet USP API content specifications before their labeled expiration date, which represents a striking failure rate of 41% in the control group. This result is incredibly consequential because the manufacturer guarantees that the product meets quality specification before the expiration date is reached. Because the control group was exposed only to terrestrial environmental conditions consistent with label storage requirements, the conclusion is that repackaging contributed to the exceptional number of premature failures. The mean time until failure[8] for non-repackaged drugs that failed during the 880-day storage period was 707 days (n = 8): most were non-solid formulations (the one exception was ethinyl estradiol). Whereas the average failure time was 633 days for repackaged drugs (n = 12), all of which were either capsules or tablets. This difference is unexpected because non-solid drugs typically have shorter shelf lives than comparable solid formulations of the same drug substance. Because repackaging can adversely affect stability (Bokser and O'Donnell, 2013; U.S. Food and Drug Administration (FDA), 1999; U.S. Food and Drug Administration (FDA), 2017; U.S. Food and Drug Administration (FDA), 2020a) the more frequent and earlier failure of repackaged solid formulations in both the terrestrial and spaceflight samples suggest that repackaging contributes to the drug degradation reported in these studies. For these reasons, NASA needs to investigate the effect of repackaging on drug stability and, if necessary, develop and test protective repackaging options for long-duration space missions (e.g., Mars-length mission).

G. THE EFFECTS OF IONIZING SPACE RADIATION ON DRUG STABILITY

1. CONTEXT: RADIOSTABILITY OF DRUGS

Speculation exists that exposure to ionizing radiation during long-duration space missions will compromise the stability of some pharmaceutical products (Blue, R. S., et al., 2019; Mehta and Bhayani, 2017; Putcha, et al., 2016; Wotring, 2012): this was driven by the pilot study of lot-controlled drug products (Du, et al., 2011), and by terrestrial radiosterilization studies of drug products and drug substances at absorbed doses of ionizing radiation that are much greater than those expected for crewed space missions (Gopal, 1978; Jacobs, 1985; Jacobs, 1995; Jacobs, 2022; Marciniec and Dettlaff, 2008). Du et al. (2011) concluded that "[c]umulative low-dose radiation and dispensers [containers] used for solid dosages in space appear to influence stability of pharmaceuticals in space", however, this study was not designed to

[8] Failure is an API content (i.e., potency) less than the acceptance threshold specified in the USP monograph for each drug.

determine how various environmental factors contribute to the failure of medications. The assumption that the dose of spaceflight radiation that is acceptable for occupational exposure and human habitation will influence drug stability is not supported by studies using analog GCR, in silico models, or radiostability studies in the literature. The evidence for each source of information is discussed below, as are data gaps and uncertainties. The effect(s) of ionizing radiation on drugs is discussed in Appendix 9.

2. EVIDENCE: NASA-SUPPORTED DRUG RADIATION STABILITY STUDIES

a. *Scope of Studies*

To date, no spaceflight studies have tested the effect of ionizing radiation on drug stability. No NASA-supported study of drug radiostability has been peer reviewed or published. Several pilot analog studies have been performed; however, all these studies have significant limitations that include study design issues, poor method transparency, and limited data availability. Therefore, despite engaging significant time and resources, substantial uncertainty persists.

In the sections below, studies are grouped into 3 categories: spaceflight studies, terrestrial analog studies, and *in silico* models. As discussed above, NASA has supported 6 spaceflight investigations of drug stability (Table 1). Of these studies, only Du et al. (2011) collected radiation exposure data. Three studies used terrestrial radiation exposure or simulated GCR to evaluate how ionizing radiation affects drug stability. Only one of these studies has a comprehensive record of methods and results; the remaining studies have methods and results available only in abstract format. One study used *in silico* modeling to evaluate aqueous medications exposed to ionizing radiation at fluences characteristic of exploration spaceflight.

b. *Studies of Spaceflight Radiation Exposure*

To date no dedicated studies have investigated the effects of spaceflight radiation on the long-term stability of drug products. Du et al. (2011) collected cumulative data on environmental factors, including radiation exposure, and suggested an association between radiation exposure and drug stability. Unfortunately, because of the experimental design, the effects of radiation cannot be isolated from other environmental variables acting on the medications. Most of the SODF evaluated in the study were re-packaged into non-protective zip-lock baggies. This type of repackaging exposes medications to atmospheric factors in the surrounding environment, as discussed in the PACKAGING AND DRUG STABILITY section. Du and colleagues noted the limitations of designing spaceflight studies, stating that "…constraints associated with conducting research in space limit the opportunity for robust experimental design and adequate statistical rigor." Study design limitations and the absence of method transparency, as discussed in the

EFFECT OF SPACEFLIGHT ON DRUG CONTENT and PACKAGING AND DRUG STABILITY sections, precludes causal inference for any environmental factor. The multitude of variables associated with testing spaceflight drug stability will make it difficult to perform well-controlled spaceflight studies.

To our knowledge 3 NASA-supported drug radiostability studies have been performed. All 3 have used the BNL NSRL facilities.

c. *Irradiation studies without post-radiation storage*

In 2006, the Humans Research Project's (HRP) Pharmacotherapeutics Discipline conducted 2 ground-based radiation experiments using the NSRL. These pilot studies were performed to test the hypothesis that high dose-rate ionizing radiation causes degradation of the API in some medications. However, neither study has been published nor are data available from either study for further analysis.

The first study exposed 5 drug products to 2 doses of gamma rays (9.36 kGy or 35.8 kGy) or a single dose of titanium ions (^{48}Ti, 17 Gy) (Table 4). Medications were evaluated for API content, which was expressed as a percentage of label strength. No additional details are available for this experiment.

Table 4. Results of the 2006 Gamma /Titanium Study API Content (% label strength) Remaining After Irradiation.

RADIATION SOURCE		Control		Gamma				Nucleon Titanium	
IRRADIATION DOSE (Kgy)		0		9.36		35.8		0.017	
DRUG PRODUCT		%	Std	%	Std	%	Std	%	Std
Augmentin ® Tablets	Amoxicillin 875 mg	111.5	0.16	104.8	1.49	101.5	NR	109.1	NR
	Clavulanate 125 mg	96.9	0.1	88.1	0.09	83.3	NR	94.5	NR
Promethazine 25 mg tab		96.2	NR	94	NR	NR	NR	96.3	NR
Promethazine 50 mg/mL Inj		98.3	0.26	96.8	NR	90.3	1.08	93.7	NR
Promethazine 25 mg PR		97.6	0.53	95.8	NR	89.5	0.08	95.6	NR
Bactrim® Tablets	Sulfamethoxazole 800 mg	97.9	1.27	94.2	NR	93.1	0.37	96	NR
	Trimethoprim 160 mg	96.8	1.81	97.9	NR	81.4	3.17	93.6	NR

NR = No results provided, PR = suppository, tab = tablet, inj = injectable solution
Data obtained from Putcha 2006 Stability Summit presentation, as cited in (Daniels 2019). Unpublished results.

High doses of gamma rays (35.8 kGy) and titanium ions (17 Gy) appear to marginally reduce API content. The most notable effects of gamma radiation were on trimethoprim and clavulanate. For the other drugs, 3.8-fold increase in gamma dose is associated with an apparent decrease in API content of about 5-6%. However, available records provide only the arithmetic mean API levels for most drugs and no associated measure of variability (e.g., standard deviation); therefore, it is not possible to statistically test the hypothesis that irradiated samples have lower API content than unirradiated matched control drugs. It is also

noteworthy that 9 kGy dose is approximately 9000-times greater than the cumulative dose estimated for a 3-year Mars mission, which is in the range of 1 Gy (National Academies of Sciences, Engineering, and Medicine, 2021). The API content of samples exposed to 17 Gy of titanium ions appears to be only slightly different than the API content of the matched controls, indicating that the medications are not sensitive to radiation at this dose—a dose that is much lower than the dose of gamma radiation (9,300 Gy and 35,800 Gy) and much less than the minimum dose of gamma radiation (25,000 Gy) used for radiosterilization of drugs during manufacturing, and far above the dose of ionizing radiation expected for spaceflight (approximately 1 Gy).

One major concern with this study is that it is unclear whether the experiment included independent replicates. Variance is required to make statistical inferences about whether experimental conditions have an effect. No statistical analysis is possible using the limited data available for this study. Furthermore, no additional details are available on how the experiment was carried out, including the experimental conditions (e.g., number of units treated, number of replicates, analytical procedures) or the irradiation parameters (gamma ray source, conditions of irradiation, drug packaging, or duration of exposure). It is possible that apparent differences reported in this small pilot study are due to experimental variability. This supposition is supported by other NASA-sponsored drug stability studies where independent replicates were definitively tested and the median standard deviation was ±1.5% (interquartile range = 1.1%) (Cory, et al., 2016; Cory, James and Mangiaracina, 2017; Wotring and Smith, 2020; Wu, L. and Chow, 2016). The reported experimental variability for most of the drugs in this 2006 radiostability study is much less than in other drug stability studies, indicating that replicate samples are not independent but were likely technical replicates of the same sample. This method was also used in the 2019 study discussed below. Considering the lack of experimental details, these results should be regarded as exploratory pilot research results and interpreted with caution.

A second radiostability study was also performed in 2006. An abstract this study was published as a part of the NASA HRP Investigators Work Shop (IWS) meeting in 2018 conference proceeding[9] that suggested some modest degradation changes were observed, but this cannot be confirmed (Daniels, et al., 2017). The objective of this second study was to assess the correlation between radiation dose and API content for a broader range of medications at radiation doses more relevant to spaceflight. This experiment

[9] The study was performed in 2006, but study results were not available until provided to the ExMC element in a 2019 study proposal (Daniels, 2019).

assayed 20 APIs contained in 18 drug products (2 drugs contained 2 APIs, Augmentin® and Bactrim®) at a single timepoint after irradiation (Daniels, 2019) The drugs were exposed to 0.1, 10, or 50 Gy of either 1000 MeV/n protons or 1000 MeV/n iron particles, or were unirradiated (Table 5). The tabulated results do not exhibit a dose-response relationship between radiation exposure and loss of API content, even for the highly sensitive aqueous formulations of ciprofloxacin (Tegze, et al., 2019) and promethazine (Bahnemann, Asmus and Wilson, 1983). The lack of a dose-response—a key Bradford Hill consideration for causal associations (Fedak, et al., 2015)—indicates the spaceflight-relevant doses were too low to elicit a measurable loss of API content. A radiation dose-response relationship was previously reported for damage to a wide range of polymers at gamma radiation doses greater than 10 kGy (Shulman and Ginell, 1970) and for drugs in the range of 10 to 100 kGy (Gopal, 1978; Jacobs, 1985; Jacobs, 1995; Jacobs, 2022).

The absence of a dose response in this study is likely the result of the low dose of ionizing radiation used. The highest radiation dose used in this study was 50 Gy, which is approximately 500- to 1000-fold less than the doses used for pharmaceutical radiosterilization, which range from 25 to 50 kGy. The selected drugs are not unusually resistant to the effects of ionizing radiation. Although this study did not observe a dose dependent change in the 3 mg/mL ciprofloxacin solution, related fluoroquinolones, including 2 mg/mL solutions of moxifloxacin and levofloxacin, lose 10% and 20% of their potency after gamma radiation exposures of 5 kGy and 15kGy, respectively (de Oliveira, Serro and Saramago, 2016). Low concentration ciprofloxacin (0.033 mg/mL) loses 66% of its potency after exposure to 500 Gy of gamma rays (Tegze, et al., 2019). A study of a selection of drugs known to be highly sensitive to ionizing radiation could confirm the susceptibility of solid-state drugs and aqueous solutions in this radiation dose range. It is recommended that future experiments should irradiate medications over a range of doses covering several orders of magnitude, from spaceflight-relevant doses to a dose shown to induce radiochemical effects. This will enable the shape of the dose effect curve to be determined. Inclusion of electronic spin resonance spectra measurements of the treated samples would confirm the ionizing effect, as well as the persistence of drug ions.

Table 5. Mean API content (% label strength) for the 18 drug products (20 APIs) tested in the 2006 NSRL study

RADIATION SOURCE		Control	Iron			Proton		
IRRADIATION DOSE (Gy) / DRUG PRODUCT		0	0.1	10	50	0.1	10	50
Acetaminophen 325 mg Tab		98.8	96.2	94.7	94	96.7	95.2	94.8
Atorvastatin 10 mg Tab		100.2	100.4	97.8	98.6	97.3	98.5	96
Augmentin® Tablets	Amoxicillin 875 mg	116.1	116.2	109.8	115.8	115.6	112	114.4
	Clavulanate 125 mg	93.5	88.6	79.4	83.4	88.1	48	78.2
Ciprofloxacin 3 mg/mL Sol		96.9	96	95.9	96.1	96.1	94.5	96.4
Ciprofloxacin 0.3% Oint		99	96.4	94.6	95	94.8	91.7	94.8
Ciprofloxacin 500 mg Tab		99.1	100.9	100.1	100.2	100.3	99.3	99.5
Clotrimazole 1% Cream		99.5	98.6	98.8	98.7	98.8	98.9	98.2
Ibuprofen 400 mg Tab		101.4	102.3	102.3	102.6	102.5	102.6	102.8
Levothyroxine 25 mcg Tab		94.1	96.6	93.5	95.3	93.4	94.2	94.4
Muprocin 2% Oint		100.5	99.6	100.2	100.3	100.3	99.7	99
Phenazopyridine 100 mg Tab		98	96.2	94.2	92.5	96.6	94.5	93.9
Promethazine 25 mg Tab		97	96.2	96.1	95.3	97.3	93.9	96.3
Promethazine 50 mg/mL Inj sol		99.2	99.6	97.3	98.7	97.8	98.4	98.8
Promethazine 25 mg Supp		103.5	102.3	103.1	103.3	102.1	102.9	103.6
Riboflavin 100 mg Tab		100.8	99.6	98.7	96.9	100.4	98.8	97.7
Silver Sulfadiazine 1% Cream		98.6	97.7	96.8	95.9	98	97.1	96.5
Temazepam 15 mg Cap		100.5	100.4	100.2	100.2	100.1	99.8	99.8
Bactrim® Tablets	Sulfamethoxazole 800 mg	100.7	97.5	95.9	96.2	100.5	97.5	96.5
	Trimethoprim 160 mg	101.5	98.2	96.5	97.1	101.3	98.5	97.3

API = active pharmaceutical ingredient, NSRL= NASA Space Radiation Laboratory, Supp = suppository, Cap = capsule, Tab = Tablet, Sol = Solution, Oint = Ointment, Inj = Injectable
Results are from the NxPCM Pharmaceutical Flight Stability Study Status Report, Lloyd, Putcha et al, 2007 as cited in (Daniels 2019) and as presented at the HRP Investigators' Workshop, 2018.

d. *Irradiation study with long-term post-irradiation storage.*

A follow-up radiation study was initiated in 2018 to evaluate the longitudinal effects of single dose ionizing radiation on 4 SODF. Mixed-species beam exposures were used to simulate the shielded radiation environment that would be encountered by an astronaut in a typical exploration vehicle. The 4 medications were selected based on apparent stability profiles in previous studies and relevance for spaceflight: acetaminophen 500 mg tablets, amoxicillin 500 mg capsules, ibuprofen 400 mg tablets, and promethazine 25 mg tablets. All medications were lot-matched and repackaged as they would be for spaceflight.

The 2 samples of each of the 4 different SODF were exposed to 0.5 Gy or 1.0 Gy of a simulated GCR-like field (GCRsim) consisting of ^{1}H, ^{4}He, ^{12}C, ^{16}O, ^{28}Si, ^{48}Ti, and ^{56}Fe beams. The detailed profile of the NSRL GCRsim is presented in Figure 4. Low-linear energy transfer (LET) (<5keV/µm) radiation provided 86.7% of

the total GCRsim dose, whereas the high-LET (>5keV/µm) radiation contribution was 13.3%. The 0.5 Gy and 1.0 Gy doses are within the range of the expected cumulative exposures for a round-trip Mars mission (the dose rate, however, is very much higher than expected during a Mars mission). After irradiation, on experimental day 0, the treated samples, along with matching untreated controls, were stored in a chamber at controlled room temperature and humidity (20 °C/30% relative humidity). One set of samples was used to assess potency, dissolution (API release) and impurities at 2, 18, or 34 months[10] (2018, 2019 and 2021 respectively) after irradiation.

Ion	Energy (MeV/n)	Range (cm)	LET (keV/µm)	Dose (mGy)
^{1}H	100	*Polyethylene degrader to*		
^{1}H	150	15.9	0.54	35.0
^{1}H	250	38.1	0.39	68.9
^{1}H	1000	326.6	0.22	123.6
^{4}He	100	*Polyethylene degrader to*		
^{4}He	150	16.0	2.17	7.5
^{4}He	250	38.3	1.56	16.4
^{4}He	1000	327.8	0.88	24.9
^{12}C	1000	110.1	7.95	11.7
^{16}O	350	17.0	20.8	15.4
^{28}Si	600	22.7	50.2	8.1
^{48}Ti	1000	32.5	109.5	4.5
^{56}Fe	600	13.1	175.1	4.1
Total				***500.0***

Ion	Energy (MeV/n)	Range (cm)	LET (keV/µm)	Dose (mGy)
^{1}H	20.0	0.43	2.59	30.4
^{1}H	23.3	0.56	2.29	6.7
^{1}H	27.2	0.75	2.02	7.4
^{1}H	31.7	0.98	1.79	8.0
^{1}H	37.0	1.30	1.58	8.7
^{1}H	43.2	1.72	1.39	9.3
^{1}H	50.3	2.26	1.23	10.0
^{1}H	58.7	2.99	1.09	10.6
^{1}H	68.5	3.95	0.97	11.1
^{1}H	79.9	5.20	0.86	11.2
^{1}H	100.0	7.76	0.73	**27.2**

Ion	Energy (MeV/n)	Range (cm)	LET (keV/µm)	Dose (mGy)
^{4}He	20.0	0.43	10.34	**11.0**
^{4}He	23.3	0.57	9.14	**2.1**
^{4}He	27.2	0.75	8.06	**2.2**
^{4}He	31.7	0.99	7.12	**2.3**
^{4}He	37.0	1.31	6.29	**2.5**
^{4}He	43.2	1.73	5.56	**2.6**
^{4}He	50.3	2.28	4.92	**2.7**
^{4}He	58.7	3.01	4.36	**2.7**
^{4}He	68.5	3.97	3.86	**2.7**
^{4}He	79.9	5.23	3.43	**2.7**
^{4}He	100.0	7.81	2.90	**6.1**

Figure 4. The composition of the NASA Space Radiation Laboratory Galactic Cosmic Ray simulation "high-LET" (>5keV/µm) dose contribution to the total GCRsim dose was only 13.3%. Image provided by R. Gaza, "SRAG Radiation Dosimetry Report", June 2018, courtesy of Dr. Tony Slaba, NASA Langley.

[10] Analysis of the 34-month time point was delayed by about a year due to the Covid19 pandemic

Preliminary analysis of the results (Figure 5) suggests that none of the measured parameters were altered in the irradiated samples relative to the parameters in the matched control samples, although final analysis is presently ongoing. A literature review indicates that none of the 4 medications tested are considered to be particularly susceptible to ionizing radiation in the solid form, according to information in the drug information database or other supporting information (Jacobs, 1985). Three of the 4 medications tested in this study (ibuprofen, amoxicillin, and promethazine) were evaluated previously by Du and colleagues (Du et al. 2011), and the authors reported that only amoxicillin showed a degradation rate greater than the pair-matched control, and ibuprofen and promethazine tablets were not substantially changed relative to controls. The study did not include medications that are known to be highly sensitive to ionizing radiation and did not expose drugs to a dose of radiation known to achieve a detectable effect on potency, which would have enabled failure risk analysis relative to mission parameters.

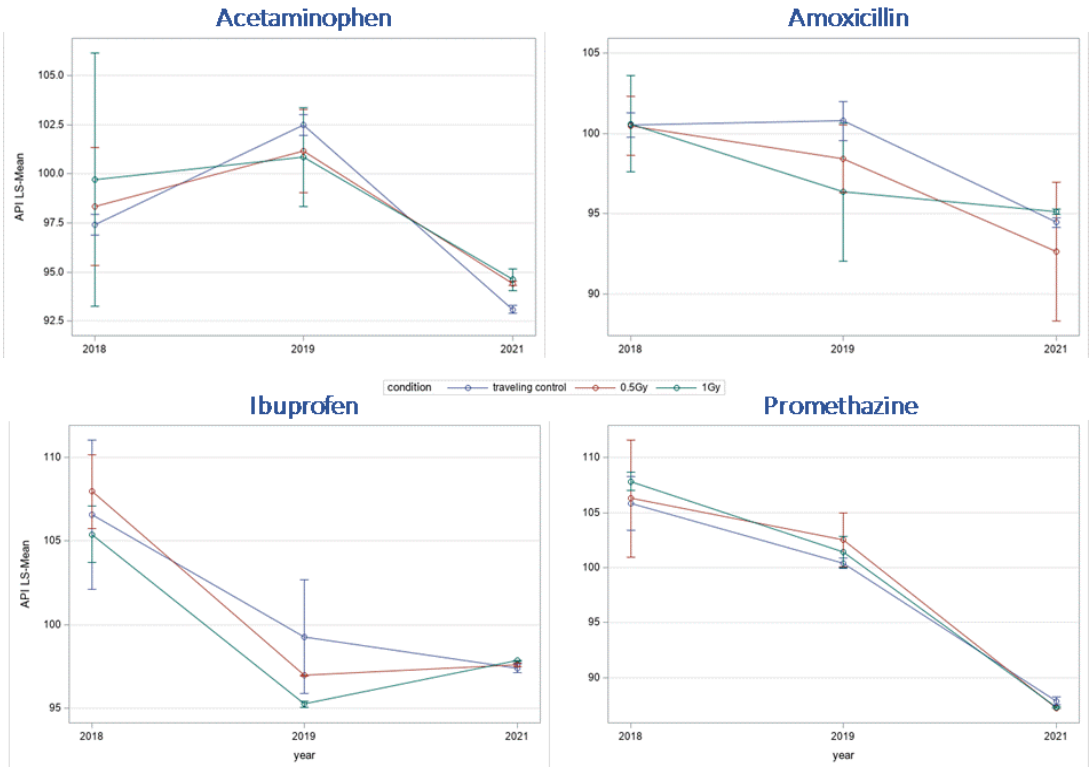

Figure 5. Longitudinal effects of storage time on API content. Four solid oral medications were exposed to ionizing radiation at 0.5 Gy (orange), 1 Gy (green), or control (blue) then stored for up to ~36 months. API = active pharmaceutical ingredient. Points and error bars are expected marginal mean ± 95% confidence limits

3. IN SILICO MODELING OF THE EFFECT OF SPACEFLIGHT RADIATION ON DRUG STABILITY

In silico modeling is an alternative approach to predict radiation effects that avoids the many challenges associated with measuring the effects of ionizing radiation during actual spaceflight. Well-developed theoretical models for predicting radiation transport through spacecraft shielding (O'Neill, 2010; O'Neill, Golge and Slaba, 2015; Wilson, et al., 1994) have been used to predict radiation exposures in deep space (Cucinotta, Kim and Chappell, 2012; Naito and Kodaira, 2022; Simonsen, et al., 2020). Although evaluating radiation transport models is beyond the scope of this report, this *in silico* approach has been used to predict how ionizing radiation affects drugs during a 3-year exploration mission.

A publicly available NASA technical report describes the modeled the effects of radiation in dried food, frozen food, and water (Kim and Plante, 2015) and the investigators predicted that the worst-case scenario would produce nanomolar concentrations of radiolytic radicals ($OH^{\bullet}$, $H^{\bullet}$, H_2, H_2O_2 and e^{-}_{aq}) in aqueous drug formulations. The report concluded that the low concentration of these metastable species, produced slowly over a 3-year mission, are unlikely to have a significant impact on drug stability. For example, the expected worst-case frequency for water molecule "hits" per mole of water during a 3-year mission is 7.8×10^9 hits from the core track of charged particles, which is insignificant compared to the number of molecules in a mole of water ($6.02 \times 10^{23} – 7.8 \times 10^9 = 6.02 \times 10^{23}$). Including secondary delta rays modestly increases the predicted number of hits without any substantive effect on the number of radiolytic products.

The approach used by Kim and Plante can be applied to drug solutions by considering the direct and indirect effects separately. Direct effects are the interactions of radiation with the drug substance, whereas indirect effects result from radiolysis of water in the drug formulation. Most drug products contain much less than one mole of active ingredients. For example, promethazine[11] 25 mg/mL injectable solution contains 8.8×10^{-05} moles/mL of API (5.29×10^{19} molecules of drug). Assuming an annualized radiation dose of 0.2 Gy/year inside the space vehicle, the number of hits on the drug substance over a 3-year mission is insignificant relative to the number of drug molecules in a 1 mL vial (Table 6). Likewise, the quantity of metastable radiolytic species produced is insignificant compared to amount of drug substance (approximately 685 nMol/L). A similar analysis that modeled the effects of radiation on a 10 ml vial of Epinephrine 0.1 mg/mL gives similar results—effectively no change in drug content, even though the

[11] molecular mass = 284.4191 g/mole

concentration of this epinephrine solution is much lower than promethazine. These are likely to be conservative estimates because they assume all incidence radiation interacts with the drug substance and all the radiolytic react with drug substance. In reality, radiation can pass through a target without interacting, and radiolytic species formed in water are transient and the reaction of these species with drug substance is inefficient; much less than 1:1. Furthermore, Kim and Plante (2015) noted that the model assumes a worst-case scenario based on peak ion fluence. Antioxidant excipients that manufacturers include in some aqueous drug formulations can increase the margin of error by increasing the stability of the drug substance (Sarcan and Ozer, 2020; Sintzel, et al., 1997). *In silico* predictions confirm that ionizing radiation at fluences anticipated during exploration spaceflight will have no significant effect on drug stability. Furthermore, because the effect is so small, these predictions should permit a very large margin of error, which increases the level of confidence in the conclusion that the risk is small.

Table 6. Molar quantity of drug remaining after exposure to 0.61 Gy of charged particle radiation for a 3 year mission

Drug product	Amount	Moles of drug or diluent	Molecules	Total mean hit frequency	Yield of water radiolysis species	Total hits direct hits + radiolytic species per drug volume	Moles of drug molecules remaining (Percent potency)
	mg	mol		Total hits	Moles/L	Total hits	
Promethazine Water	25 1	8.79E-05 5.55E-02	5.29149E+19 3.34161E+22	4.39E06 4.78E08	0 6.85E-10	4.39E+06	8.79E-05 (100%)
Epinephrine Water	0.01 10	5.46E-08 5.55E-01	3.28595E+16 3.34161E+23	1.85E+03 1.79E+10	0 6.85E-10	1.85E+03	5.46E-08 (100%)

Input values for calculations taken from Tables 4, 5, and 6 of Kim and Plante, 2015.

VII. RISK IN CONTEXT OF EXPLORATION MISSION OPERATION SCENARIOS

Drugs degrade over time and therefore the risk of degradation is greater for the Mars design reference mission (DRM) (Table 7) than the other DRMs. This contrasts with the risk(s) associated with

Table 7. Official HSRB Design Reference Mission (DRM) Categories (Antonsen, 2020).

DRM Categories	Mission Type and Duration	Gravity Environment	Radiation Environment	Vehicle/Habitat Design	Distance from Earth		EVA
					Evacuation	Communication	Frequency
Low Earth Orbit	Short (<30 days)	Microgravity	LEO-Van Allen (<5-15 mGy)	Mid-sized volume, resupply	1 day or less	Real time	1-4 EVAs
	Long (30 days-1 year)	Microgravity	LEO-Van Allen (5-150 mGy)	Mid-large optimized volume, resupply	1 day or less	Real time	1-10 EVAs
Lunar Orbital	Short (<30 days)	Microgravity	Deep Space-Van Allen (15-20 mGy)	Small volume, self contained, resupply	3 – 11 days	Real time	Contingency EVA only or very few EVA
	Long (30 days-1 year)	Microgravity	Deep Space (175-220 mGy)	Mid-sized volume, self contained, limited resupply	3 – 11 days	Real time	Contingency EVA only or very few EVA
Lunar Orbital + Surface	Short (<30 days)	Microgravity & 1/6g	Deep Space-Van Allen (15-20 mGy)	Small volume, resupply	3 – 11 days	Real time	5 EVAs, some back to back
	Long (30 days-1 year)	Microgravity & 1/6g	Deep Space (100-120 mGy)	Mid-large sized optimized volume, limited resupply	3 – 11 days	Real time	3-4 EVA per week, 20-24 EVA hrs. per week
Mars	Preparatory (<1year)	Microgravity	Deep Space (175-220 mGy)	Midsized optimal volume, limited resupply, closed loop environment	Days – weeks	Controlled - Delayed	Contingency EVA only or very few EVA
	Mars Planetary* (730-1224 days)	Microgravity & 3/8g	Deep Space – Planetary (300-450 mGy)	Midsized optimal volume, no resupply, closed loop environment	Mission duration	No real time	2 crew x 8-hour EVA x 20 EVA days

changes in PK and PD, which apply to any DRM and are associated with human physiological changes, *not* changes in medication quality. PK and PD changes are not included as risk drivers in the Human Systems Risk Board likelihood by consequence (LxC) for shorter DRMs that are considered "green". A brief discussion for each DRM LxC risk is provided.

The risk of ineffective or toxic medication during long-duration exploration spaceflight as related to drug stability from (1) the loss of API resulting in loss of efficacy and (2) the accumulation of degradation impurities. One controlled study (Du et al. 2011) suggests that most spaceflight medications appear to lose API faster than those stored terrestrially. No other controlled studies have been performed to confirm these results or to investigate the mechanisms contributing to these changes in drug quality. But even if spaceflight is assumed to have no effect on drug stability, there is no doubt that many medications will expire during a multi-year Mars mission, i.e., some medications may become ineffective due to normal time-depended degradation processes. Irrefutable evidence from the fields of pharmaceutical science and medicinal chemistry demonstrate that drug degradation is a chemical reaction that is commonly facilitated by exposure to environmental factors such as oxygen, moisture, and light. Ensuring that repackaged drugs are not exposed to these conditions is a commonsense approach for extending the stability of SODF. Other countermeasures can also be implemented, such as storage at low temperature, which universally slows

chemical reaction rates and is an acceptable storage practice under USP guidance (United States Pharmacopeia, 2021a).

LEO DRMs (< 1 year). The LxC risk posture for short- and long-term LEO DRMs is "strong" (Table 8). The likelihood is very low to insignificant (green) that degraded medications will impact crewmembers' health or mission objectives. This likelihood is driven by the fact that LEO DRMs can be resupplied rapidly, and therefore, minimal-to-no anticipated decrements in medication quality are expected. The consequences for crewmembers' long-term health (LTH) and operational performance is considered insignificant.

Lunar Orbital DRMs (< 30 d). The LxC risk posture for short lunar orbital DRMs is moderate (green). The likelihood that degraded medications will impact crewmembers' health or mission objectives is low (Table 8). The consequence for crewmembers' health and operational performance is insignificant. The LxC risk posture for LTH is "strong". The Likelihood of LTH is very low and minimal-to-no LTH impacts are anticipated.

Table 8. Likelihood by consequence (LxC) matrix for Risk of Ineffective or Toxic Medications.

DRM Categories	Mission Type and Duration	LxC Ops	Risk Disposition	LxC LTH	Risk Disposition
Low Earth Orbit	Short (<30 days)	1 X 1	Accepted	1 X 1	Accepted
	Long (30 d-1 yr)	1 X 1	Accepted	1 X 1	Accepted
Lunar Orbital	Short (<30 days)	2 X 1	Accepted	1 X 1	Accepted
	Long (30 d-1 yr)	3 X 2	Accepted with Optimization	2 X 2	Accepted with Monitoring
Lunar Orbital + Surface	Short (<30 days)	3 X 1	Accepted with Optimization	2 X 1	Accepted with Monitoring
	Long (30 d-1 yr)	4 X 2	Accepted with Optimization	2 X 2	Accepted with Monitoring
Mars	Preparatory (<1 year)	4 X 3	Requires Characterization	3 X 2	Accepted with Monitoring
	Planetary (730-1224 days)	5 X 3	Requires Mitigation	5 X 3	Requires Mitigation

LTH: long-term health; DRM: design reference mission; Ops: operations.

Lunar Orbital DRMs (30 d <DRM <1 y). The LxC risk posture for long lunar orbital DRMs is “weak” (green). The likelihood of an impact on crewmembers’ health or mission objectives is moderate, as attributed to mission length and uncertain mission details. The consequence for crewmembers’ health and performance is insignificant. The LxC risk posture for LTH is "weak” (green). The likelihood of LTH is low and the impacts to LTH are considered to be minor and short-term, although precise information regarding lunar missions is limited (Table 8).

Lunar Orbital with Surface Operations (DRM <30 d). The LxC risk posture for short lunar orbital with surface operations DRM is "weak” (green). The likelihood disposition is moderate (green) that reduced medication quality will impact crewmembers’ health or mission objectives for short lunar orbital DRMs with surface operations, and the likelihood is low for LTH (Table 8). The likelihood disposition is driven by the possibility that some medications on the landing vehicle could be exposed to vacuum, extreme temperatures, and unshielded radiation exposure. The consequence of reduced drug quality is considered insignificant given convenient 2-way audio and video communications with medical experts, and availability of rapid crew return. The low likelihood of LTH effects is driven by minimal consequences of inflight medication changes. Minimal-to-no consequences are anticipated on LTH.

Lunar Orbital with Surface Long operations (30 d <DRM <1 y). The LxC risk posture for long lunar orbital with surface operations DRM is “weak” (yellow). The likelihood disposition is high that reduced medication quality will impact crewmembers’ health or mission objectives for long lunar orbital DRMs with surface operations. The likelihood disposition is driven by the possibility that some medications on the landing vehicle could be exposed to vacuum, extreme temperatures, and unshielded radiation exposure. The consequence of reduced drug quality is considered insignificant given convenient 2-way audio and video communications with medical experts, and availability of rapid crew return. The LxC for LTH is “weak” (green). The likelihood that reduced medication quality will impact crewmembers’ LTH is low is driven by minimal consequences of changes in inflight medication (Table 8). Consequences are expected to be minor, short-term impacts on LTH.

Mars Preparatory mission (< 1 y). The LxC risk posture for a Mars preparatory DRM is “weak” (yellow). The likelihood disposition is high that reduced medication quality will impact crewmembers’ health or mission objectives for a Mars preparatory DRM. The likelihood disposition is driven by the length of mission, the spaceflight environmental conditions, and the lack of ability for resupply, as well as unknown technical details for this DRM. The consequence of reduced drug quality is possibly significant due to lack of mission details and potentially limited ability for crew return. The LxC for LTH is “weak

(green) (Table 8). Likelihood that reduced quality of medication will impact crewmembers' LTH is moderate is driven by mission duration and limited ability for crew return. Consequences are expected to be minor, short-term impacts on LTH.

Mars Planetary DRM (> 2 y). The LxC risk posture for a Mars preparatory DRM is "speculative" (red). The likelihood disposition is very high that reduced medication quality will impact crewmembers' health or mission objectives for a Mars planetary DRM. The likelihood disposition is driven by length of mission, spaceflight environmental conditions, and lack of ability for resupply, as well as unknown technical details for this DRM. The consequence of reduced drug quality is possibly significant due to lack of mission details and potentially limited ability for crew return. The LxC for LTH is "speculative" (red). The likelihood that reduced medication quality will impact crewmembers' LTH is very high is driven by mission duration and limited ability for crew return (Table 8). Consequences are expected to be moderate but treatable effects on LTH.

A. COUNTERMEASURES

1. Protective packaging/repackaging.

Available evidence and first principals suggest that some drugs that are repackaged into non-protective containers will not remain stable throughout the full duration of an exploration spaceflight. The risk that any drug will fail to meet compendial specifications is time dependent. For drugs stored in manufacturer's packaging, the risk of degradation should remain low until the manufacturer's expiration date is reached. For repackaged drugs in non-protective packaging, the time-dependent probability of failure increases at the time the original container is opened. If drugs are placed into packaging that is at least as protective as manufacturer's packaging, then the shelf life of these repackaged drugs would be equivalent to their shelf life in the manufacturer's container. (U.S. Food and Drug Administration (FDA), 1985; U.S. Food and Drug Administration (FDA), 1999; U.S. Food and Drug Administration (FDA), 2004a). Repackaging into containers that are resistant to oxygen and water vapor transmission will help mitigate the risk of drug failure due to loss of API content, impurity accumulation, and physical changes. Some drugs may require additional protective countermeasures that may include purging the containers with inert gas or including oxygen and/or moisture scavenging materials into the packaging. The effectiveness of protective packaging should be confirmed in experimental studies

2. Drug product selection.

Because the shelf life of drugs is proprietary information in the U.S., it is not possible to compare shelf life of different brands of equivalent drugs and to purchase the most stable brands (longest shelf life) for planetary DRMs. Equivalent drug products from different manufacturers can have very different ingredients (Table A2), some of which affect drug stability. Although selecting the product with the longest shelf life is not a major concern for DRMs of a few months to one year, it will be necessary for longer missions. Variability in brand shelf life may be a significant issue for Mars missions because the medications listed in the ExMC Exploration Candidate Formulary are marketed by nearly 700 different U.S. drug manufacturers/labelers, and more than 70 drug products are marketed by 30 or more manufacturers. Drugs with shelf lives that are close to the duration of the DRM must be carefully evaluated to characterize medication quality because missions beyond LEO cannot be resupplied. Judicious selection of drug brands formulated without hygroscopic (sorbitol, PEG) and other problematic ingredients is encouraged.

3. Pragmatic Storage Conditions.

Drug degradation is a chemical reaction, and all chemical reactions are temperature dependent. This dependence is described by the Boltzmann distribution that relates the rate constant for a chemical reaction as a function of temperature. As temperature increases, reaction rate increases, as described quantitatively by the Arrhenius law. This law applies to all pharmaceuticals such that exposure to increased temperature increases chemical reaction rates—i.e., drug degradation. Conversely, reaction rates slow proportionally with reduced temperature. Storing pharmaceuticals at low temperatures, unless directed otherwise by the drug label, will therefore extend shelf life for most medications. Generally, low temperature has no adverse effect on most pharmaceuticals and can be protective because physical and chemical changes are reduced, gas and vapor transmission through packaging is slowed, and the rate and extent of water sorption is inhibited, the last of which limits deliquescence formation of hydrates and mesophases. For drugs formulated as aqueous solutions, low temperature storage slows reaction rate chemistry (according to the Arrhenius Law as above) and significantly decreases drug degradation caused by ionizing radiation. Therefore, storage at sustained low temperatures is an effective countermeasure to prolong shelf life of pharmaceuticals with significant stability concerns. However, low temperature storage is not universally protective; some aqueous medications may not tolerate freezing or may precipitate and form insoluble complexes at low temperatures. Freezing and subsequent thawing of emulsions could cause formulations to crack or separate; and some solutions may precipitate. When room temperature storage is directed for medications, these medications may be stored and shipped in a

cool place or refrigerated, unless otherwise specified by the drug monograph or on the label (United States Pharmacopeia, 2021a)

B. OPERATIONAL PERSPECTIVE

- **Drug Repackaging.** It is expected that Mars missions will require many medications to be removed from the original manufacturer's packaging and repackaged to reduce mass and volume. Implementing protective packaging will require operational changes in repackaging materials, equipment, and processes. Because some drug products have unique vulnerabilities, customized countermeasures may be necessary to ensure stability of some drugs. Depending on repackaging needs for a Mars mission, a contract repackaging service may be required to provide better assurances of packaging integrity, consistency, and reliability than the current in-house process. For medications with unique vulnerabilities or packaging needs (i.e., packaging incompatibilities), retaining medications in the manufacturer's packaging may be the most effective method for storing them during spaceflight.

- **Bulk packaging of drugs.** Once a package containing multiple units of a medication is opened, all the medications in that package are exposed to the ambient atmosphere. For some drugs, this exposure could accelerate degradation of the dosing units remaining in the package. The problem could be worse if the package is repeatedly reopened over time or if the package is not tightly resealed. Medications that will be repackaged into multiple-unit packaging should be divided among several multiple-unit packages so that only a fraction of the total number of units provided are exposed when the package is opened. This will limit exposure of an acceptable portion of the medication to the atmosphere, while protecting the remaining units until they are needed later in the mission. Decisions regarding the number of dosing units in each multiple-unit package should be guided by information on the susceptibility and stability of individual drug products.

- **Low temperature storage.** Some drugs deemed essential for the treatment of medical conditions may have inadequate shelf life for the full duration of a Mars mission (Appendix 2). Such drugs may lose API at an unacceptable rate or may degrade in ways that makes the medication unacceptable for clinical use (i.e., high concentrations of a hazardous impurity), even when highly protective packaging is used. For example, drugs with formulation incompatibilities, reactive impurities, or metastable drug substances may not retain sufficient potency to ensure clinically efficacy throughout the duration of a Mars planetary

mission. Such drugs can be stored at low temperature to slow the chemistry of degradation and prolong shelf life of most drugs.

- **Drug Formulation.** The importance of formulation is discussed in Appendix 2, section D. Equivalent drug products from different manufacturers commonly contain different ingredients. Selecting drug products that contain favorable ingredients and no unfavorable ones may increase the stability of the drug substance. For example, if a drug API is susceptible to hydrolysis, it may be reasonable to select formulations that contain excipients such as sucrose rather than sorbitol, which readily takes up water when exposed to humidity. Likewise, antioxidants are sometimes incorporated into formulations of drugs that are sensitive to oxidation, and antioxidants have been used to protect aqueous formulations from ionizing radiation. Drug ingredients are publicly available through the National Libraries of Medicine database Drug Bank.
- **Direct drug purchasing.** Pharmacies typically purchase drugs from a distribution wholesaler, and these drugs typically spend a long period of time in the supply chain (Shah, N., 2004). Purchasing drugs directly from the manufacturer or labeler, shortly after they are manufactured, may extend the functional shelf life of these drugs during spaceflight.

VIII. DIRECTED ACYCLIC GRAPH (DAG) REVIEW AND INTEGRATION WITH OTHER RISKS

A. DAG REVIEW:

The risk of ineffective or toxic medication during long-duration exploration spaceflight centers on pharmaceutical effectiveness. Three basic factors contribute to this: (1) actual shelf life, (2) physiologic changes in the pharmaceutical, and (3) antibiotic resistance. This evidence report focuses on actual shelf life, as highlighted by the red rectangle in the DAG (Figure 6).

The actual shelf life of a medication is affected by the storage conditions, e.g., refrigeration, packaging, etc., whereas the expected shelf life is the shelf life the medication would have without the effects of the spaceflight environment or without repackaging. Evidence presented in this report shows that some uncharacterized aspect(s) of spaceflight increases the rate of degradation of some pharmaceuticals, particularly SODF. These studies, however, have several important limitations that reduce the level of confidence in the results, and issues with study design that preclude direct comparison of results across studies. No radiostability studies have provided evidence that ionizing radiation increases degradation of SODF, although it cannot be ruled out that drugs in aqueous dispersions (e.g., solutions, suspensions, creams) may be more susceptible to ionizing radiation than solid-state formulations at radiation doses expected for exploration spaceflights. Drug packaging strongly affects the shelf life of drugs, and the current operational procedure is to repackage SODF into plastic zip-lock bags to reduce the mass and the volume of the medical kit. This practice removes medications from the manufacturer's protective packaging thereby exposing the medications to oxygen and water vapor, which are common co-reactants for many chemical reactions involved in degradation. Repackaging accelerates degradation reactions both terrestrially and during spaceflight, and protective packaging would be expected to inhibit such reactions.

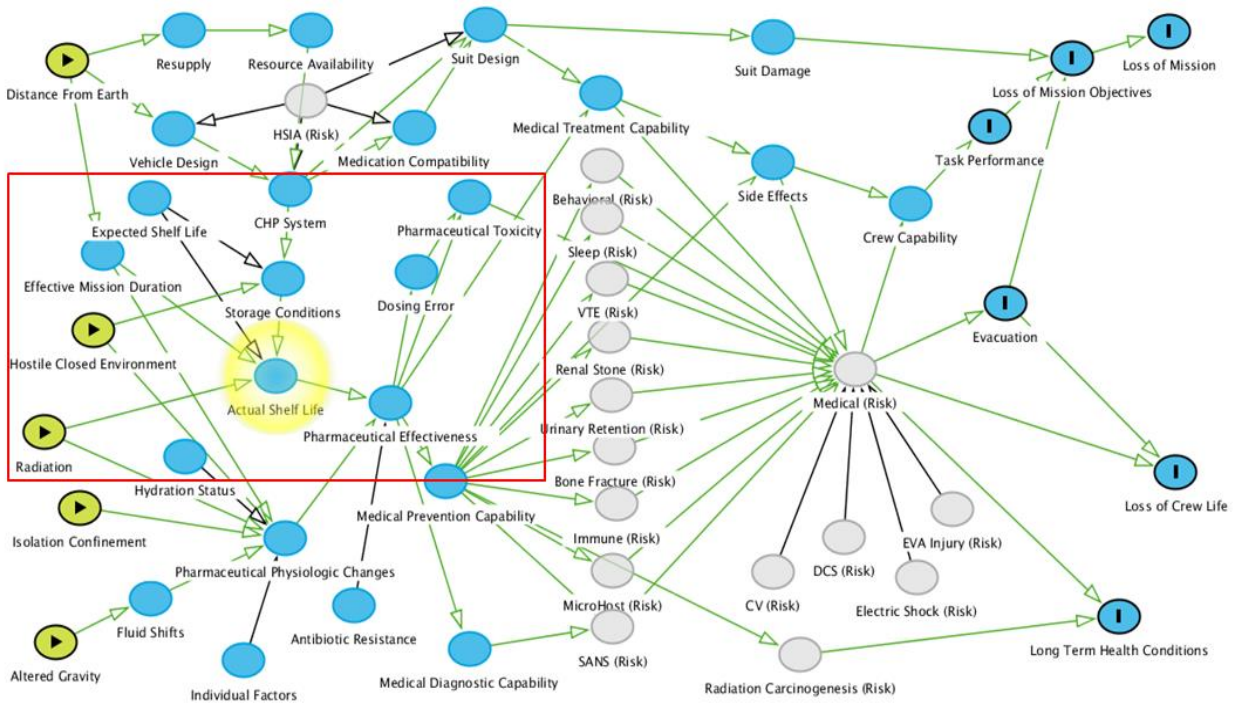

Figure 6. Directed acyclic graph (DAG) for the risk of ineffective or toxic medication during long-duration exploration spaceflight. The evidence in this report is focused on the actual shelf life vertex with a single edge directed to pharmaceutical effectiveness.

In the DAG, *Resupply and Resource Availability* lies upstream of *Actual Shelf Life:* An inability to resupply can lead to a risk of inadequate medications for some DRMs. If pharmaceutical effectiveness is lessened through degradation, crewmembers may use more medications than originally planned and potentially run out sooner.

Pharmaceutical Effectiveness lies upstream of *Pharmaceutical Toxicity*: Dosing errors can occur that result in either under-dosing or overdosing of a given medication. Underdosing would be expected if degradation of the active pharmaceutical ingredient leads to a loss of drug potency. Underdosing may also occur if a drug product is rendered unusable by physical changes such as phase separation of topical creams or ointments, or tablet disintegration due to moisture absorption by hygroscopic ingredients. Overdosing of medication can lead to life-threatening toxicities such as suppression of breathing in the case of opioid overdose, or liver damage with acetaminophen overdose. Overdosing can occur as a result of physical deterioration of medications such as extended-release formulations: degradation can lead to "dose dumping" of the active ingredient, resulting in shorter absorption time and a higher peak plasma concentration of the drug. Appropriate dosing is a function of both the amount of the API present (actual shelf life) and how the body processes the medication (PK and PD).

Not captured in the DAG is the toxicological risk of the degradation impurities. When drug products degrade, impurities are formed and accumulate. When the amount of impurities exceeds established standards, the quality of the drug is adversely affected. Impurities may have toxicodynamic activity that could pose a health risk when a sufficient dose is consumed. Daily exposure limits are required for any impurity that exceeds FDA qualification limits. The spaceflight evidence discussed in this report is inadequate for testing the hypothesis that spaceflight affects the safety of pharmaceuticals.

INTEGRATION WITH OTHER RISKS

Pharmaceutical Effectiveness lies upstream of *Medical Prevention Capability*, *Medical Diagnostic Capability*, and *Medical Treatment Capability*. Pharmaceutical Effectiveness also affects the severity of side effects and adverse effects. Medications constitute the largest component of the medical system in terms of number of items, mass, and volume.

The risk of ineffective or toxic medications during long-duration exploration spaceflight is also relevant to other human health risks that involve pharmaceutical countermeasures, and therefore the risk of ineffective or toxic medications extends across a range of human system risks. Some of the planned

countermeasures are biotechnology products that have not been tested in any NASA-supported study. This limitation is highlighted as Gap 1 in subsection titled REMAINING GAPS

B. GAPS IN KNOWLEDGE:

1. Link to the current gaps on the Human Research Roadmap:

HRR - Risk - Risk of Ineffective or Toxic Medications During Long-Duration Exploration Spaceflight (nasa.gov)

https://humanresearchroadmap.nasa.gov/Risks/risk.aspx?i=177

C. STATE OF KNOWLEDGE AND FUTURE WORK

NASA has chosen to follow the FDA and the state of Texas rules for determining the expiration of repackaged drugs. The drug products on LEO missions are replaced annually, which will be problematic for some long-duration missions and will be impossible for Mars preparatory and planetary missions. Radiation-induced effects on the stability of medication during long-duration and deep space missions are not fully characterized. How, and to what extent, the spaceflight environment and resultant alterations of human physiology may affect drug PK and PD is unclear. The potential for increased drug instability that is compounded by altered drug response poses a significant risk to crews of exploration spaceflights. Research efforts are underway in the ExMC Element to determine a safe and effective drug formulary for exploration spaceflight that can maintain a ≥ 3-year shelf life. The proposed ExMC strategy will validate the chemical and physical stability, the toxicity of degradation products, and the drug safety profiles of these pharmaceuticals, and better characterize PK, PD, and pharmacotherapeutic properties of drugs stored in the exploration spaceflight environment. The current drug repackaging methods will be evaluated in accelerated drug stability studies to quantify the effect of nonprotective packaging on drug stability. If it is demonstrated that current repackaging practices are detrimental to the stability of medication, protective packaging will be identified and tested.

D. REMAINING GAPS:

Several plausible risks and data gaps should be addressed before planning begins for space exploration missions away from LEO. These include

- Gap 1 – Sensitivity of biotechnology (biotech) drugs to the spaceflight environment. Biotech drugs are a subset of drugs that are of biological origin, including peptides, proteins, enzymes, and various nucleic acid-based technologies. Biotech drugs are a rapidly growing class of drugs used to treat common health disorders, and these drugs will represent a growing part of the

spaceflight drug formulary in the future. Biotech drugs may be used to counter the physiological effects of prolonged weightlessness, ionizing radiation exposure, or other effects. Biotech drugs include proteins and peptides, antisense oligonucleotides, small inhibitory RNAs, and other technologies. The stability of biotech medications has not been evaluated in spaceflight.

- Gap 2 – Radiostability. Drug substances in aqueous solution are typically far more susceptible to degradation from exposure to ionizing radiation than the same drug substance in a solid formulation. The radiostability of the aqueous solutions in the spaceflight drug formulary need to be evaluated over a dose and energy range that is near and well above that anticipated for Mars mission.

- Gap 3 – Drug repackaging. NASA currently repackages SODF in non-protective zip-lock bags that may expose medications to ambient oxygen and humidity (water vapor). This type of packaging likely permits unacceptable levels of degradation of susceptible medications. The effect of the current repackaging process needs to be evaluated relative to manufacturer's packaging, and, if necessary, alternative protective repackaging solutions must be identified.

- Gap 4 –Formulation selection. Inactive ingredients can have a profound effect on drug stability of both solid and non-solid formulations. The effect of differences in excipients in equivalent drug formulations should be tested to determine the extent to which brand selection affects the probability of drug failure or the extent of degradation over time.

- Gap 5. –Drugs that are susceptible to the spaceflight environmental. It will not be possible to test the stability of every drug in the spaceflight formulary during spaceflight because studies of drug stability are slow and very expensive. The drugs that are likely to be the most sensitive to spaceflight environmental conditions must be identified and tested to determine whether their stability is compromised during prolonged storage in space. The results of the tests on susceptible medications will provide evidence for other medications that may be similarly susceptible. Key characteristics that need to be evaluated for medications include identifying drugs with the shortest shelf lives; identifying APIs or formulations that are highly sensitivity to ionizing radiation; identifying drugs most sensitivity to oxidation or hydrolysis (esp. acid hydrolysis); identifying drugs with ingredients that shorten shelf life such as hygroscopic excipients or amorphous APIs; and identifying APIs that degrade to produce highly potent health hazards.

Safety of medications resulting from changes in PK and PD are excluded in this evidence report and will be addressed separately in a future evidence report.

IX. CONCLUSION

Decreased therapeutic efficacy of some medications during spaceflight has led to speculation that some drugs may degrade faster with exposure to spaceflight, resulting in less effective medications. Several studies have investigated this hypothesis. However, design limitations in all NASA-supported studies that have investigated spaceflight drug stability have consistently yielded inconclusive results. The most comprehensive study performed to date was an 880-day longitudinal study with multiple timepoints and matched terrestrial controls (Du, et al., 2011). Although this study provides some qualitative evidence that unidentified factors associated with spaceflight have a modest long-term effect on drug stability, the study's method and data are not transparency. Several opportunistic studies provide anecdotal evidence that spaceflight has no unusual effect on API content or accumulation of impurities. Together, these studies and first principles of drug chemistry signify that physical and chemical changes in medications do not contribute to the apparent therapeutic failures during short-duration space missions, as has been previously suggested (Mehta and Bhayani, 2017; Wotring, 2011). However, long-duration exploration spaceflight presents a different set of challenges: the processes and procedures used to supply medications to the ISS will be unlikely during long-duration exploration missions, and some medications inherently have shelf lives that are inadequate for these types of mission.

The studies discussed in this report are not adequate to characterize the risk that the spaceflight environment poses to medications. Several of the common design limitations in these studies should be avoided going forward. Future studies must include the following fundamental design characteristics:

- Matched controls. All studies that test a hypothesis must include matched controls for each treatment condition (i.e., spaceflight).
- Multiple time points. If a temporal effect is suspected, then multiple timepoints enable the slope of change to be evaluated over time. Ideally, the experimental design should include a 0-day timepoint to baseline the initial condition (i.e., amount of API in the medication at the start of the experiment).
- Prompt sample analysis. Several of the anecdotal studies, and one that is currently ongoing, have not promptly evaluated drug products after sample collection. For a spaceflight time course experiment, the samples need to be analyzed immediately after return of each sample, not after all sample have been collected. The lack of prompt analyzes of medications confounds the data

and introduces substantial biases for type II statistical errors (false negative result). Uncertainty regarding false negatives contribute to the inconclusive results presented in the report.

- Independent replicates and statistical testing. A fundamental assumption of statistical tests used for hypothesis testing is that replicate samples are independent. Independent samples are essential for characterizing experimental variability and for determining the statistical power that correctly rejects the null hypothesis (i.e., no difference between control and treated samples) with a pre-defined level of confidence.
- Data availability. Raw and summary data must be maintained and archived for future review and analysis. Data from pharmaceutical studies must be accessible to investigators.
- Transparent methods. Descriptions of methods must be complete and sufficiently comprehensive to enable other investigators to understand how the experiment was performed and whether the results are reliable.
- Focus on the physiochemical characteristics of drugs. Past studies have focused on testing drugs that subject matter experts deemed to be operationally important. This subjective approach does not consider pharmaceutical chemistry or other physiochemical properties as evidence to prioritize medications for testing. This subjective approach is biased by previous experience that may not be pertinent to exploration missions. Because testing drug quality is time consuming and expensive, testing pharmaceuticals that are known to be stable wastes time and resources, and is likely to yield no observed treatment-related effect. Future studies should focus on drug substances that are known to be sensitive to chemical changes such as oxidation or hydrolysis. Measures that protect the most sensitive medications from conditions that cause degradation will also be effective for prolonging the shelf life of other less-sensitive medications.
- Drug formulation. Equivalent drugs can have very different formulations that affect stability. The brand and formulation must be considered as part of the study design of future studies.

Many drugs currently used during spaceflight, as well as others on the exploration candidate formulary, will expire over the course of an interplanetary exploration mission, i.e., extend beyond the shelf life determined by the manufacturer. NASA does not have the resources to perform extended stability tests to empirically ensure stability of its formulary drugs throughout the duration of long-term space missions. Because every drug substance is a unique combination of chemicals, it is very unlikely that every drug product will meet USP quality specifications throughout the duration of an exploration spaceflight.

Nevertheless, long-term stability studies conforming to scientific and industry standards will be extremely important to inform a risk/benefit analysis.

X. REFERENCES

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XI. APPENDIX 1. DRUG DEGRADATION KINETICS

In the presence of abundant substrates, a chemical reaction will proceed at a rate dictated by temperature and thermodynamic constants for that reaction. The key variable that governs the rate of reaction is temperature. This relationship between reaction rate and temperature is described by the Arrhenius equation, which shows that reaction rate is proportional to the negative exponent of temperature. The Arrhenius equation is given as

$$rate\ (k) = Ae^{-Ea/RT}$$

where k is the rate of reaction, Ea is thermodynamic energy of activation established for a reaction (e.g., hydrolysis, oxidation), R is a constant and T is temperature, and A is an empirical factor expressed in terms of the entropy of activation of the reaction. This correlation of rate and temperature means that reaction rate and temperature are positively correlated, i.e., as temperature increases the reaction rate increases, and vice versa. In part, this is the reason the U.S. FDA recommends thermal stability testing only at elevated temperatures; reduced temperature will universally slow chemical reactions, hence, refrigerated drugs have low stability (U.S. Food and Drug Administration (FDA), 2003).

Drug degradation reactions are commonly second order chemical reactions, which means that the reaction rate depends on 2 co-reacting substances. For example, the hydrolysis of a saturated aqueous solution of ethyl acetate is a second-order reaction because the rate depends on the concentrations of both water and ethyl acetate, and the rate of the reaction decreases as the concentrations of co-reactants are depleted. Second order chemical reaction kinetics with respect to substrate A are represented by the formula

$$\text{rate} = -\frac{d[A]}{dt} = -k[A][B] = -k[A]^2$$

where the reaction rate k is dependent on the concentrations of reactants $[A]$ and $[B]$ as a function of time, t.

The co-reactant contributing to the degradation of the drug substance is commonly in excess and the drug substance is limiting. This is often the case when medications are removed from the manufacturer's packaging, exposing them to *unlimited* amounts of atmospheric factors, particularly humidity and oxygen. Under this scenario, the concentration of the co-reactant(s) is in vastly greater supply than the drug substance and this remains constant over the course of the reaction. That is, if [A] is the

concentration of drug substance and [B]t is a co-reactant, then [B]0 >> [A]0 and [B]0 ≈ [B]t, where the subscript "0" indicated initial concentration and the subscript "t" is some point in time during the reaction. Under these environmental conditions the second-order decay of API (A) simplifies to linear first-order kinetics, which is referred to as pseudo-first order kinetics, and is simplified to

$$\text{rate} = -\frac{d[A]}{dt} = -k[A]^1$$

In a dilute solution of ethyl acetate water is more abundant than ethyl acetate: this is an example of a pseudo-first order reaction because the rate is governed by the remaining concentration of ethyl acetate. Such reactions are one important reason drug products degrade faster when removed from the manufacturer's packaging than when they are sealed in the manufacturer's container. Inside the sealed container, access to the co-reactant is extremely limited (discussed below); once the sealed package is opened, the supply of co-reactant becomes unlimited.

Drug containers are used by pharmaceutical manufacturers as a barrier to limit environmental exposure of drug products and to ensure quality standards are met throughout a drug's shelf life. In fact, USP sets standards for the rate at which moisture penetrates packaging. Other atmospheric gases also penetrate packaging, although oxygen is generally considered easier to control than humidity, and regulatory standards only pertain to moisture (United States Pharmacopeia, 2020a). The rate at which water vapor and gas permeate containers and packaging are well understood and depends largely on the materials the container is made from and its thickness. The relationship between vapor and permeation can be calculated as

$$Amount\ of\ water\ = \frac{Transmission\ rate\ x\ Surface\ area\ x\ Time}{Thickness}$$

A paper published by Pfizer Global Research and Development used this relationship to determine that a 60-cc high density polyethylene bottle with a surface area of 100 cm^2 and a wall thickness of 0.9 mm will have a vapor transmission rate of 1.3 mg of water/day, assuming no permeation through the cap, a starting interior RH of 0%, and an external RH of 90% at 38°C (Waterman, et al., 2002). Even at a more nominal 40° C/75% RH, the permeation rate is still about 1 mg/day, and the RH inside the bottle will rise to over 50% RH *within about one day*. Because plastic polymers are permeable, conditions inside the container equilibrate over time to the ambient atmosphere, which is why drug manufacturers often include silica gel packs inside these sealed containers to scavenge moisture. The vapor transmission rate of other substances can range over several orders of magnitude, as shown in Table A1.

Table A1. Water Vapor Transmission Rate for Common Packaging Materials	
Material	Water Vapor Transmission g mm/(m^2 day) at 38°C and 90% Relative Humidity
Polyvinyl chloride (PVC)	1.8
Polypropylene	0.54
High Density Polyethylene (HDPE)	0.12
Aclar UltRx	0.006
Aclar 22A	0.011
Cold Formed Foil Blister	0.005
Source: (Waterman, et al., 2002)	

Barrier protection limits the rate that atmospheric factors permeate packaging. When the permeation rate is less than the rate of the chemical reaction, i.e., when availability of co-reactants limits the chemical reaction, the rate of reaction can only proceed at the rate the reactant enters the container. As a result, the chemical reaction rate (k) depends on the permeation rate (i.e., diffusion rate) and is independent of the drug substance. Because diffusion under a given set of conditions is driven by the concentration difference of the co-reactant (e.g., oxygen, humidity) inside and outside the container (Δ[B]), the reaction rate is constrained to the rate of gas permeation of the container. Such a reaction is referred to as a zero-order. Hence, with respect to the drug substance (A),

$$rate = -\frac{d[A]}{dt} = -k[A]^0 = -k = constant$$

The ideal scenario for long-term medication storage is to maximize the protection of susceptible drugs using packaging materials that restrict permeation of oxygen, moisture vapor, or other factors that contribute to drug reactions. This can be accomplished by using layered polymers or other high barrier packaging. For spaceflight, this might include repackaging some drugs in blister packages, high-barrier bulk repackaging, or overpackaging. A multitude of considerations come into play, and the most suitable packaging for NASA flight operations may not necessarily be the most protective. Nevertheless, protective packaging is essential for many drug products, especially when those medication must be repackaged to conserve mass and volume.

The kinetics of API degradation are important because shelf life and retest period [12] are determined based on regression analysis. The drug content must be assessed at multiple time points during a stability test, and these data can be used to determine the reaction rate that establishes the shelf life or retest period (U.S. Food and Drug Administration (FDA), 2004b). Hence, if degradation rates are controlled using high-barrier protective packaging, the new shelf life can be predicted based on empirical degradation kinetics, and this may qualify drugs that have insufficient shelf life for long-duration space missions. There are, however, important limits to this approach. For example, drug substances that undergo reactions with excipients are problematic—a manufacturer's choice of excipients can in some cases significantly affect the stability of the API and product shelf life. The kinetics of chemical reactions are also important for modeling time-dependent API loss. For example, an analysis of the summary data reported by Du et al. (2011) compared the overall performance of zero-order and first order reaction kinetics and determined that a first-order model provided the best fit to the data (Reichard, 2023).

[12] The period of time during which the drug substance is expected to remain within its specification and, therefore, can be used in the manufacture of a given drug product

XII. APPENDIX 2. DRUG SHELF LIFE

A. REGULATION OF DRUG STABILITY AND SHELF LIFE.

1. Drug potency (i.e., API content)

USP drug quality specifications (i.e., quality standards) for small molecule drugs are acceptance criteria that help to ensure the identity, strength, quality, and purity of a drug product [13]. Acceptance criteria for drug content permit limited variability of API amounts relative to the labeled strength of the medication due to variations in manufacturing process control, analytical measurement, and drug deterioration over time (United States Pharmacopeia, 2021c). The allowable error is based on practical considerations of "acceptable", hence, USP specifications for API are *not* based on drug pharmacology or health-based effects. Rather, USP specifications are practical, consensus quality-assurance thresholds. This ensures that official products are "*formulated with the intent to provide 100% of the quantity of each ingredient declared on the label"*, while also allowing for analytical error, unavoidable variations in manufacturing and compounding, and a limited level of deterioration that is considered acceptable under practical conditions (United States Pharmacopeia, 2021c). Appropriate drug packaging is one key factor for ensuring potency of a drug during long-term storage (see APPENDIX 7. DRUG PACKAGING) and can be used in conjunction with storage of medications at refrigerated temperatures below controlled room temperatures (United States Pharmacopeia, 2021a), which slows degradation reactions. Acceptance criteria for API content are consistent with good manufacturing practices or good pharmaceutical practices (United States Pharmacopeia, 2021c), but do not have direct health-based implications and should not be treated as such.

2. Organic Impurities

Impurities are always present in drug products and acceptable limits are established under guidance from the ICH and as promulgated by the U.S. FDA. Impurities in drugs originate from multiple sources including the manufacturing process ("process impurities"), impurities from excipients, and impurities resulting from degradation. In the U.S., ICH guidelines have been adopted by the U.S. FDA as impurity standards Q3A, Q3B, Q3C, and M7, among others (U.S. Food and Drug Administration (FDA), 2006; U.S. Food and Drug Administration (FDA), 2008; United States Pharmacopeia, 2021c). In addition, the USP has several General Chapters that address the control of organic impurities, most notably General Chapter ‹476› Control

[13] Biotechnology drugs have separate guidance that are not currently coved in this document.

of Organic Impurities in Drug Substances and Drug Products and General Chapter ‹1086› Impurities in Drug Substances and Drug Products. It is important to understand that not all drug products will have the same impurity profile: differing synthetic routes and the unique chemical composition of different drug product formulations may mean that different manufacturers' products can have different impurity profiles. With respect to USP specifications, NASA will need to consider both 'degradation product' and 'total degradation products' as noted the drug product monographs, rather than 'impurity' and 'total impurities', which are listed in drug substance (API) monographs. The USP defines degradation products as impurities resulting from a chemical change in the API. Total degradation products in a formulated drug product represent the sum of all specified and unspecified degradation products above the FDA reporting threshold, which is lower than the qualification threshold, described below.

For NASA, degradation products and total degradation are the most pertinent guidance; process impurities are outside NASA's control, aside from the potential impact on product selection. U.S. FDA guidance establish criteria for setting acceptance thresholds for impurities in drug products. The lowest threshold is the reporting threshold. Impurities that exceed the reporting threshold are reported to the FDA as part of the marketing application. When impurities exceed the qualification threshold, the safety of the impurity must be established, which must be based on a combination of chemical safety data, intended use, applicable guidance, and scientific rationale. Qualification thresholds are sliding scale limits for acceptable levels of impurities that depend on the maximum daily dose of the drug substance (API). Higher or lower qualification thresholds may be appropriate based on scientific rationale and level of concern (i.e., toxicology testing), such as historical precedent or risk assessment analysis. In short, identified degradation impurities below the qualification limit are generally acceptable, while impurities above the qualification threshold can be acceptable contingent on safety data or health-based exposure limit (HBEL) risk analysis (U.S. Food and Drug Administration (FDA), 2006; U.S. Food and Drug Administration (FDA), 2008; U.S. Food and Drug Administration (FDA), 2018; U.S. Food and Drug Administration (FDA), 2021).

In contrast to FDA/ICH impurity limits, organic impurity acceptance criteria in USP drug substance and drug product monographs generally reflect FDA-approved products developed from sponsor submission(s). USP does not determine the acceptance criteria; rather, they are adopted from drug approvals that were approved by the FDA. The allowable error in drug API content is based on practical considerations of "acceptable". USP specifications for impurities are quality-based acceptance criteria reflecting FDA-approved products and are not based on pharmacology or health-based safety studies. Rather, acceptance criteria are consistent with good manufacturing practices or good pharmaceutical

practices (United States Pharmacopeia, 2021c). In short, USP specifications for the loss of API content or accumulation of impurities do not have direct health-based implications and should not be treated as such. For this reason, quality standards should *not* be used to infer health-related risk, which is distinctly different from product quality. Instead, USP specifications are benchmarks that NASA can use to evaluate the effect of spaceflight exposure on medications.

In this regard, USP acceptance criteria are similar to the ICH & FDA Q3A and Q3B quality guidance that set default impurity limits, but are different from Q3C guidance for deriving health-base impurity limits. Hence, it is reasonable and practical to recognize that deterioration of some drugs will occur over time during exploration spaceflight, and the resulting loss of API or accumulation of impurities may exceed USP thresholds, but this does not necessarily mean the drugs are unusable or ineffective. It means we have reduced confidence in the safety and effectiveness of the medications; therefore, the risk of adverse health effects may be increased as medication degrades over time. NASA must consider the acceptable risk/benefit of using deteriorated medications during an exploration spaceflight when there is no other alternative.

B. SHELF LIFE VERSUS EXPIRATION DATE AND THE AVAILABILITY OF SHELF LIFE DATA

The U.S. FDA requires all approved drugs to be labeled with an expiration date, which is the final day the manufacturer guarantees full potency and safety of a medication when stored according to conditions on the medication's label. Because the *expiration date* is based on the day the drug was manufactured, it changes with each batch produced (i.e., manufacturing lot). Expiration dates are calculated based on the product shelf life, which is determined experimentally by the drug labeler (e.g., manufacturer, packager). Before the U.S. FDA allows the drug to be marketed, the shelf life must be determined in long-term and accelerated stability studies. Shelf life is the same for all batches produced and does not change based on when the drug is manufactured, unlike expiration date (U.S. Food and Drug Administration (FDA), 1985; U.S. Food and Drug Administration (FDA), 2004a). Stability testing is expensive, and the manufacturer does not benefit financially by guaranteeing shelf life beyond more than a few years, therefore the manufacturer typically underestimates the true shelf life of a drug when stored in sealed packaging under labeled storage conditions. Most drugs in their sealed packaging are stable well beyond their labeled expiration date, and many maintain potency for years to decades after expiration (Cantrell, et al., 2012; Lyon, et al., 2006; Stark, Fawcett and Tucker, 1997; Zilker, Sörgel and Holzgrabe, 2019).

It is common for a manufacturer to produce several lots (batches) of a drug product during a single manufacturing campaign and release the product slowly over time until the next campaign (Shah, N., 2004). Although alternative manufacturing processes such as continuous production are gaining acceptance,

campaign manufacturing remains the standard for most manufacturers. The distinction of shelf life from expiration date is important because no requirements exist for U.S. manufacturers to disclose shelf life of medications. In the U.S., drugs are required under federal law to provide an expiration date only; however, such dates do not reveal the product shelf life without knowledge of when the drug was manufactured. In the U.S., drug shelf life is treated as proprietary data and is not publicly available.

The European Union (EU), United Kingdom (UK) and other countries have different labelling requirements for shelf life than the U.S.: EU and UK manufacturers and labelers must disclose shelf life in the summary of product characteristics (SPC). The SPC is analogous to the package insert in the U.S., however, the shelf life information in the SPC does not apply to similar products marketed in the U.S. because products marketed in the U.S. do not need to be equivalent[14] to similar products approved in the EU. Furthermore, many of the medications marketed in the EU are not manufactured by companies that market products in the U.S. Consequently, similar drug products marketed in the U.S. and the EU cannot be assumed to be equivalent, and the SPC shelf life *could be* longer or shorter than the shelf life of a similar U.S. product. The SPC shelf life can be regarded as the approximate the shelf life of a comparable U.S. drug in lieu of specific U.S. manufacturer's data. It is noteworthy that both the EU and the U.S. have adopted ICH guidance for drug stability testing, so the requirements for demonstrating shelf life are the same (The International Council for Harmonisation (ICH) of Technical Requirements for Pharmaceuticals for Human Use, 2003; U.S. Food and Drug Administration (FDA), 2004b).

C. DRUG SHELF LIFE FOR EXPLORATION SPACESFLIGHTS

NASA does not have reliable information on the shelf life of exploration formulary drugs. In the current version of the ExMC drug data repository[15], shelf life is estimated based on the average expiration dates for drugs used on past space missions or on "equivalent" EU products listed in the European Medicines Compendium (emc®), a UK database maintained for the European medicines Agency (EMC). No shelf lives are available for U.S. products. Although shelf life is limited with respect to operational use, it is essential for identifying the most stable brand of equivalent products and formulations for long-duration spaceflights. Shelf life is also vital for prioritizing the drugs and the drug classes that require further investigation that will ensure available medications will be effective when needed during space missions.

[14] "Equivalence" has important regulatory meaning. Classification of equivalent in the U.S. depends on both USP specifications and FDA regulations and guidance.

[15] 08/31/2022

Without the manufacturer's shelf life, or better yet the data from stability testing studies, there is no reliable way to evaluate or prioritize U.S. drug products for exploration spaceflights. NASA has attempted to partner with the U.S. FDA to obtain the required information but to date these attempts have failed to provide information on any product.

The estimates of shelf life for the exploration formulary drugs indicate that many drugs will expire during a Mars mission. It will be important to determine if these drugs expire due to actual degradation of the drug or if the expiration reflects testing limitations or marketing choices of the manufacturer. One source of information that is likely to be very relevant is the Shelf life Extension Program (SLEP), which is maintained jointly by Department of Defense (DoD) and the FDA. SLEP monitors the quality of medications in the U.S. national stockpile to ensure that enough medications will be available for an immediate response to a natural or a man-made mass disaster. Stockpiled medications are continuously monitored and expiration dates periodically extended based on U.S. FDA analytical testing (Khan, S. R., et al., 2014; Lyon, et al., 2006). Of the 277 drugs on the current list of resources for exploration class missions (Lake, Harrivel and Reichard, 2023), 64 medications are included in the partial list of medications reported in the SLEP database as of March, 2006 (Lyon, et al., 2006). It is anticipated that more than 64 drugs of the exploration drugs are now listed in the SLEP database because the report by Lyons et al. (2006), which was used for the current assessment, was published over 16 years ago and the SLEP program has continuously added and changed drugs over time. SLEP focuses on medications commonly used for critical care and emergency medicine, and this covers an important fraction of exploration formulary. However, because different brands of drugs from different manufacturers are formulated and packaged differently, shelf life can vary significantly from one manufacturer's product to another.

D. DRUG STABILITY AND THE IMPORTANCE OF FORMULATION

Drug ingredients can interact and directly affect API stability. These interactions result from chemical reactions (incompatibilities) between the API and excipients, or from reactions between the API and impurities that may be present in the drug substance or the formulation excipients (Narang, Desai and Badawy, 2012; Waterman, Adami and Hong, 2004). Pharmaceutical excipients include many classes of chemicals that are important for the manufacturing process and the physical characteristics of the drug. Although excipients are therapeutically inactive ingredients, *they are not chemically inert* (Narang, Desai and Badawy, 2012; Waterman, Adami and Hong, 2004). Several commonly used pharmaceutical excipients contain trace levels of low molecular weight reactive aldehydes or peroxides (Waterman, Adami and Hong, 2004). For example, polymeric ethers (i.e., PEG, polyethylene oxides, polysorbates, etc.) and polyvinyl

pyrrolidone, which are commonly used classes of excipients, are associated with peroxide contaminates (e.g., povidone and crospovidone) (Waterman, Adami and Hong, 2004). Peroxides can be formed through oxidative degradation of the excipient (i.e., aging) and are especially damaging to susceptible drugs because trace amounts can initiate radical chain reactions and significant loss of API (Narang, Desai and Badawy, 2012; Waterman and Adami, 2005). Such interactions are well understood and can be predicted based on the chemical structure of the API and the properties of the excipients. Significantly, environmental factors can directly influence the rate and extent of many reactions between the drug ingredients. Selecting drug products that do not include some of the most problematic excipients may be one way to help ensure the stability of some drug products for long-duration space missions.

Because drug formulation can significantly affect drug stability, and because drug manufacturers use different excipients when formulating equivalent drug products[16], brand selection can be an important consideration in planning a pharmaceutical formulary for long-duration space missions. Excipient ingredients can have significant effects on the stability of the finished drug product. SLEP[17] showed large variation in shelf life extension times for some drugs, such as Ciprofloxacin tablets (242 lots tested with a range of 12 to 142 months) or morphine sulfate (13 lots tested with a range of 35 to 119 months). Similarly, Cory et al. (2010) investigated the stability of different brands of ibuprofen and demonstrated a dramatic effect of excipients on formulation stability. Detailed analysis showed that a sizable portion of the variation in stability was due to polymeric excipients (i.e., polyethylene glycol polysorbate 80). The brands containing polymeric excipients degraded 5% to 30% within 3 weeks under accelerated testing conditions, whereas, brands without these ingredients showed a negligible change from baseline (Cory, Harris and Martinez, 2010).

Different manufacturers of equivalent drug products typically use different ingredients when formulating their version of a drug product. For this reason, the FDA requires each manufacturer of a drug product to assess drug stability before the product can be marketed. The labeler (i.e., manufacture or drug packager) provides the "stability data package" to the FDA as part of a new drug application (U.S. Food and Drug Administration (FDA), 2003; U.S. Food and Drug Administration (FDA), 2004b) or abbreviated new drug application (U.S. FDA,2013). The labeler derives a shelf life period from stability studies that must be

[16] A single generic drug manufacturer may produce multiple equivalent products containing different ingredients and sell them under different trade names.

[17] SLEP is a joint effort between the U.S. FDA and Department of Defense (DoD), SLEP is a comprehensive testing and evaluation program designed to justify extending the shelf life of drug products through annual or biannual testing until products fail or are predicted to fail retest (Khan, S. R. et al. 2014).

performed using the “same formulation and packaged in the same container closure system (i.e., packaging) as proposed for marketing” (U.S. Food and Drug Administration (FDA), 2003). These shelf life data are submitted to the FDA as part of the overall application for marketing approval. However, it is known that many drugs have shelf lives that are much longer than the shelf life approved by the FDA (Abramowicz, Zuccotti and Pflomm, 2016; Cantrell, et al., 2012; Khan, S. R., et al., 2014; Lyon, et al., 2006; Stark, Fawcett and Tucker, 1997; Zilker, Sörgel and Holzgrabe, 2019). Recognizing that labelers have little incentive to seek shelf life extensions, the SLEP periodically evaluates a subset of national stockpile drugs and has shown that ~88% of the lots were stable for at least 1 year beyond their original expiration date, with an average extension time of 66 months (Lyon, et al., 2006). Since this 2006 report, drugs maintained by the program have increased and now far exceed the 122 drugs reported by Lyons et al. (per FDA SLEP administrator, personal communication). Furthermore, the FDA has now accumulated over 35 years of data, which is nearly twice that reported by Lyons et al. (2006). NASA should continue to seek a collaboration with FDA to obtain and analyze data on stability of the drugs on the exploration candidate formulary.

Formulation variability of a single medication (Ibuprofen 400mg tablet) from 12 different manufacturers is presented in Table A2. This medication has a high degree of variability in the ingredients, and none have the same composition. The combination of ingredients used to formulate drug products is known to affect drug stability (Waterman, Adami and Hong, 2004), and some ingredients dramatically affect degradation of ibuprofen (Cory, Harris and Martinez, 2010). Therefore, for those drugs with insufficient shelf lives for long-term exploration spaceflights it is important that the drug brands selected for exploration space missions are similar in formulation to the products tested by SLEP. Products maintained in the stockpile are only known to the U.S. FDA and the DoD.

NASA does not compound or repackage non-solid medications for space missions, preferring instead to use commercially available drug formulations. Improved drug stability may be achieved through judicious selection of commercial drug products in combination with protective packaging. More advanced countermeasures (i.e., low temperature storage) to prolong stability of drug substances can also be considered for drugs that are deemed medically essential and have stability issues that compromise efficacy or safety. Flight-based drug manufacturing remains a theoretical possibility, but the feasibility of the approach has yet to be demonstrated, and concerns about quality and safety of these drug products have not been addressed.

Table A2. Excipients used by representative manufacturers in the formulation of Ibuprofen 400mg

Inactive ingredient (Excipient)	Product: Manufacturer / Labeler as listed below											
	1	2	3	4	5	6	7	8	9	10	11	12
BUTETH-3							✓					
CARNAUBA WAX					✓			✓				
CELLULOSE, MICROCRYSTALLINE		✓	✓		✓	✓	✓			✓	✓	✓
COLLOIDAL SILICON DIOXIDE		✓										
COPOVIDONE K25-31	✓											
CROSCARMELLOSE SODIUM		✓	✓		✓		✓	✓	✓	✓	✓	✓
HYDROXYPROPYL CELLULOSE, UNSPECIFIED									✓			✓
HYPROMELLOSE 2910 (MPA.S 3,5,6)/				✓					✓			✓
HYPROMELLOSES					✓	✓		✓				
LACTOSE MONOHYDRATE				✓		✓						
LECITHIN, SOYBEAN										✓	✓	
MAGNESIUM STEARATE	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
MICROCRYSTALLINE CELLULOSE	✓			✓				✓	✓			
POLYDEXTROSE					✓			✓				
POLYETHYLENE GLYCOL (PEG), UNSPECIFIED		✓	✓	✓	✓	✓		✓				
POLYETHYLENE GLYCOL 1000										✓	✓	
POLYETHYLENE GLYCOL 400									✓			✓
POLYETHYLENE GLYCOL 20 SORBITAN STEARATE								✓				
POLYSORBATE 80	✓				✓							
POLYVINYL ALCOHOL		✓	✓				✓			✓	✓	
POVIDONE K90									✓			✓
SILICON DIOXIDE	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
SODIUM CITRATE				✓		✓						
SODIUM LAURYL SULFATE									✓			✓
SODIUM STARCH GLYCOLATE TYPE A POTATO	✓			✓		✓				✓	✓	
STARCH, CORN		✓		✓		✓	✓		✓	✓	✓	✓
STARCH, PREGELATINIZED CORN			✓									
STEARIC ACID							✓			✓	✓	
TALC		✓	✓	✓		✓	✓			✓	✓	
TITANIUM DIOXIDE		✓	✓		✓		✓	✓	✓	✓	✓	✓

Mfr.	Product NDC	Manufacturer / Labeler
1	55154-1380	Dr. Reddy's Laboratories Louisiana, LLC / Cardinal Health / Dist. by: Major® Pharmaceuticals
2	52605-121	Marksans Pharma Ltd. / Polygen Pharmaceuticals LLC / Dist. by: Polygen Pharmaceuticals LLC.
3	25000-121	Marksans Pharma Ltd. / Marksans Pharma Limited / Dist. by: Time-Cap Labs, Inc.
4	50090-5819	Uncertain / A-S Medication Solutions
5	12634-171	Dr. Reddy's Laboratories Louisiana, LLC / Apotheca Inc.
6	0615-8309	Vivimed Life Sciences Private Limited / NCS Healthcare Of KY, Inc Dba Vangard Labs / Dist. by: Strides Pharma Inc.
7	10544-030	Amneal Pharmaceuticals of NY / Blenheim Pharmaceutical, Inc. / Dist. by: Major Pharmaceuticals
8	58657-680	Anshi Pharmaceutical (Zhongshan) Inc / Method Pharmaceuticals, LLC
9	50090-2996	Granules India, Limited / A-S Medication Solutions
10	11788-008	Anshi Pharmaceutical (Zhongshan) Inc / Aiping Pharmaceutical, Inc.
11	51293-843	Shandong Xinhua Pharmaceutical Co., Ltd. / ECI Pharmaceuticals LLC
12	76282-712	Granules India Limited / Exelan Pharmaceuticals, Inc.

E. SHELF LIFE OF REPACKAGED DRUGS

Manufacturer's packaging is the gold-standard for benchmarking the stability of repackaged drugs. Before marketing a drug product in the U.S., manufacturers or packagers must assess the stability of the drug product in the same or similar packaging in which the drug will be marketed (U.S. Food and Drug Administration (FDA), 2003; U.S. Food and Drug Administration (FDA), 2017; U.S. Food and Drug Administration (FDA), 2020a).

After the drugs are removed from the sealed manufacturer's packaging they are exposed to atmospheric factors that frequently facilitate degradation (Khan, M. A., 2009; Khan, M. A. and Wotring, 2014; Khan, S. R., et al., 2014). Because the mass and volume of medications is expected to be constrained for exploration spaceflights, a significant fraction of solid pharmaceuticals, principally tablets and capsules, will likely be removed from the manufacturer's packaging and repackaged. NASA currently repackages only solid oral medications; other non-solid medications (e.g., solutions, ointments) are not repackaged.

The role that moisture and other atmospheric factors play in facilitating chemical degradation and physical deterioration of pharmaceuticals is well established. The science surrounding the rate of moisture ingress and gas permeation into (and out of) pharmaceutical packaging is known, and rigorous models are available to predict the performance of packaging configurations (Nelson, Eric D. and Huang, 2011). Manufacturers control for the effects of environmental factors on medications by selecting packaging materials with barrier properties that protect the integrity of the specific drug product, and by incorporating

protective excipients in the drug formulation. However, in most cases, the atmospheric content within most manufacturer's packaging changes slowly over time until it equilibrates with the external storage environment at a rate determined by the characteristics of the package and its contents.

Repackaging pharmaceuticals into non-protective containers significantly increases exposure to atmospheric factors, including moisture, oxygen, CO_2, and other gases or vapors. Consequently, repackaging facilitates degradation, resulting in increased risk of therapeutic failure of the drug and adverse events associated with impurities. All NASA spaceflight drug stability studies have focused on testing repackaged drugs. These SODF drugs were repackaged under ambient room air at JSC into either polypropylene containers or low-density polyethylene plastic bags with zipper-seal closures (i.e., "zip-lock bags"). Such non-protective repackaging, which is entirely suitable for short-duration spaceflights that can be regularly resupplied, exposes pharmaceuticals to ambient atmospheric conditions at the time of repackaging and throughout storage. Such repackaging methods may not be suitable for long-duration spaceflights.

XIII. APPENDIX 3. DIFFERENCE IN API POTENCY (%) BETWEEN SPACEFLIGHT AND CONTROL MEDICATIONS

Drugs where API content was significantly less ($p < 0.05$) in spaceflight samples than corresponding lot-matched controls in a one-tailed t-test within the total timeframe of the experiment. Values in table A3

Table A3. Difference in API potency (%) between spaceflight and terrestrial control drugs

API Name	Formulation	Timepoint (days)			
		13	353	596	880
Acyclovir	Tablet	2.5	4.5	5.4	7.7
Amoxicillin	Tablet	0.2	-2.2	9.2	9.4
Atorvastatin	Tablet	0.9	2.9	5.6	6.4
Azithromycin	Tablet	2.1	0.7	3.4	3.9
Cefadroxil	Capsule	-3	5.7	4.4	3.5
Cilastatin	Powder	8.5	8.4	10	9.4
Ciprofloxacin	Ointment	0.7	NA	2.9	5.1
Ciprofloxacin	Solution	2.2	NA	4.6	4.6
Ciprofloxacin	Tablet	3.3	0.8	0.9	6.5
Clotrimazole	Cream	0.3	1.2	2.2	3
Dextroamphetamine	Tablet	-0.2	8.8	8.7	2.8
Epinephrine	Injection	0.5	6.3	5.7	4.5
Fluconazole	Tablet	0.3	1.8	1.5	1.7
Furosemide	Tablet	5.2	3.7	4.7	6
Ibuprofen	Tablet	-1.7	0.2	2.9	5.5
Imipenem	Powder	-5.8	2.5	9.8	5.4
Levofloxacin	Tablet	0.7	3.3	3.1	4.4
Levothyroxine	Tablet	3.7	4.2	8.3	3
Metoprolol	Tablet	3.9	6.4	4.5	4.8
Metronidazole	Tablet	1.5	1.2	1.9	3.3
Mupirocin	Ointment	-0.8	NA	5	4.1
Norethindrone	Tablet	-2.1	1.3	1.1	3.9
Phenytoin	Capsule	2.4	2.1	3.1	3.4
Promethazine[1]	Injection	2.6	1.6	1.4	4.5
Promethazine[1]	Suppository	1.6	4.9	6	9.9
Promethazine	Tablet	0.2	1.6	4.5	3.8
Risedronate	Tablet	1.8	1.9	5.1	5.2
Sertraline	Tablet	4	8.6	7.9	8.7
Ag sulfadiazine	Cream	1.5	0.9	0.7	4.4
Sulfamethoxazole	Tablet	2.1	3.1	5.9	9.6
Temazepam	Capsule	0.1	3.3	2.7	3.4
Triamcinolone	Cream	0.3	4.1	3.3	2.5
Trimethoprim	Tablet	2.4	3.2	5.7	9.7

[1] In the Du *et al.*,2011 publication, panels b and c of Figure 4 (promethazine) are switched based on the accompanying published supplementary data.
NA = not available. API = Active Pharmaceutical Ingredient

are the relative potency of terrestrial drugs to the matched spaceflight equivalent in percent of content. Positive values indicate that the potency of the terrestrial control was greater than that of the spaceflight sample.

XIV. APPENDIX 4. RATE OF DEGRADATION OF DRUGS IN THE DU ET AL. (2011) STUDY.

Table A4. Estimates of degradation rate and predictions of shelf life during exploratory space missions

API	Control Degradation Rate (%/day)	Spaceflight Degradation Rate (%/day)	**Rate Ratio (flight/ control)**	Estimated Control Half-life (Years)	Estimated Spaceflight Half-life (Years)	Control, API Percent remaining after 3 years	Spaceflight, API Percent remaining after 3 years
imipenem_(p)#	-1.73E-05	-1.63E-04	**9.43**	109.8	11.65	98.12	83.65
ibuprofen	-1.56E-05	-1.10E-04	**7.02**	121.53	17.32	98.3	88.68
ciprofloxacin_(s)#	-1.97E-05	-5.68E-05	**2.89**	96.57	33.45	97.87	93.97
atorvastatin	-3.50E-05	-9.80E-05	**2.8**	54.22	19.37	96.24	89.82
cefadroxil	-4.80E-05	-1.23E-04	**2.57**	39.56	15.42	94.88	87.38
promethazine_(pr)#	-7.00E-05	-1.68E-04	**2.41**	27.11	11.27	92.62	83.15
risedronate	-5.64E-05	-1.11E-04	**1.97**	33.68	17.1	94.01	88.55
acyclovir	-7.27E-05	-1.43E-04	**1.96**	26.13	13.3	92.35	85.53
trimethoprim	-1.40E-04	-2.55E-04	**1.81**	13.52	7.46	85.74	75.68
norethindrone#	-8.70E-05	-1.48E-04	**1.71**	21.82	12.79	90.91	85
sulfamethoxazole	-1.38E-04	-2.28E-04	**1.65**	13.76	8.33	85.97	77.9
ciprofloxacin_(o)#	-8.63E-05	-1.40E-04	**1.63**	22.01	13.52	90.99	85.74
amoxicillin	-2.17E-04	-3.47E-04	**1.6**	8.77	5.46	78.88	68.35
mupirocin_(o)#	-1.28E-04	-2.05E-04	**1.6**	14.82	9.27	86.91	79.91
ethinyl_estradiol#	-8.59E-05	-1.36E-04	**1.59**	22.11	13.93	91.02	86.13
promethazine	-9.51E-05	-1.47E-04	**1.55**	19.97	12.91	90.11	85.12
sertraline	-1.12E-04	-1.75E-04	**1.55**	16.9	10.88	88.42	82.61
triamcinolone_(c)#	-4.54E-05	-6.88E-05	**1.52**	41.86	27.62	95.15	92.75
metronidazole	-4.94E-05	-7.27E-05	**1.47**	38.47	26.13	94.74	92.35
clotrimazole_(c)#	-9.77E-05	-1.36E-04	**1.39**	19.43	13.95	89.85	86.16
phenytoin	-8.37E-05	-1.11E-04	**1.33**	22.69	17.1	91.24	88.55
dextroamphetamine	-1.27E-04	-1.62E-04	**1.27**	14.9	11.73	86.98	83.75
lidocaine_(i)#	-5.42E-05	-6.91E-05	**1.27**	35.02	27.47	94.23	92.71
ciprofloxacin	-1.56E-04	-1.96E-04	**1.26**	12.16	9.68	84.28	80.66
levofloxacin	-1.79E-04	-2.25E-04	**1.26**	10.63	8.45	82.23	78.19
Ag sulfadiazine_(c)#	-1.16E-04	-1.46E-04	**1.26**	16.36	12.97	88.06	85.18
temazepam	-1.81E-04	-2.22E-04	**1.23**	10.5	8.57	82.03	78.45
azithromycin	-1.62E-04	-1.94E-04	**1.2**	11.76	9.78	83.79	80.85
epinephrine_(i)#	-2.17E-04	-2.59E-04	**1.19**	8.77	7.34	78.89	75.33
fluconazole	-8.63E-05	-1.00E-04	**1.16**	21.99	18.99	90.98	89.63
furosemide	-1.69E-04	-1.95E-04	**1.15**	11.25	9.75	83.13	80.8
promethazine_(i)#	-1.37E-04	-1.56E-04	**1.14**	13.88	12.16	86.08	84.28
metoprolol	-1.21E-04	-1.37E-04	**1.13**	15.73	13.88	87.61	86.08
levothyroxine	-2.45E-04	-2.55E-04	**1.04**	7.75	7.46	76.46	75.66
clavulanate	-3.80E-03	-2.62E-03	**0.69**	0.5	0.72	1.56	5.66
cilastatin_(p)#	9.73E-06	-9.89E-06	**-1.02**	-195.14	191.98	101.07	98.92

Abbreviations: o = ointment, c=cream, s = suppository, i = injectable solution, p = powder, pr = suppository, NA = not applicable

*The least-squared regression model for cilastatin exhibited no degradation resulting in a negative value.

Medications that were *not* repackaged

XV. APPENDIX 5. DRUGS TESTED IN OPPORTUNISTIC SPACEFLIGHT DRUG STABILITY STUDIES

Table A5. Summary of Drug Products Tested in Opportunistic Studies

Drug product	Manufacturer	Studies	Flight days	Percent label strength	Day past expiration date at testing	Significance Level (*p*-value)1
Amoxicillin (cap) 500 mg	Sandoz	Cory 2017	0 356 498 501	115.9 ± 1.8 114.1 ± 1.5 114.3 ± 1.4 112.4 ± 1.1	Not Exp. 28 18 8	0.740
Azithromycin (tab) 250 mg	NA	Wu 2016	NA	100.0 ± 0.8 114.0 ± 1.1 109.2 ± 1.1	NA	0.540
	Greenstone	Wotring 2014	316	98.3 ± 0.9	366	
	Sandoz	Wotring 2014	880	98.3 ± 2.0	1355	
Ibuprofen (tab) 400 mg	NA	Wu 2016	0 551 647 140	100.0 ± 0.6 82.7 ± 1.0 85.8 ± 2.0 85.2 ± 2.2	NA	0.188
	NA	Wotring 2015	550	99.9 ± 1.8	NA	
	Dr. Reddy's Lab	Cory 2016	0 140	100.1 ± 0.9 99.8 ± 0.8	12 Not exp.	
Levofloxacin (tab) 500 mg	Sandoz	Cory 2016	132 0	99.7 ± 1.4 98.8 ± 1.5	Not exp.	0.656
	Janssen	Wotring 2014	316 880	104.2 ± 0.22 101.1 ± 0.61	Not exp 1264	
Levothyroxine (tab) 0.025 mg	Sandoz	Wotring 2014	880	81.39 ± 1.47	1690	0.30344
Phenytoin 300 mg	Mylan	Cory 2016	0 (control) 241	101.5 ± 0.7 102.2 ± 0.5	12 8	0.28103
Promethazine (tab) 250 mg	NA	Wu 2016	0 256 193 432	100.0 ± 1.0 76.5 ± 1.3 79.5 ± 1.3 86.4 ± 1.1	NA	0.174
Promethazine (inj) 25 mg/mL	Mylan	Wu 2016	0 256 565	100.0 ± 1.1 81.5 ± 1.6 84.6 ± 1.7	NA	0.1294
Sertraline (tab) 50 mg	Greenstone	Cory 2016	0 700	99.5 ± 5.2 98.6 ± 5.8	Not exp. 43	0.0647

Significance is Flight versus control in the combined data regression model.

NA = not available, Not exp. = not expired, cap = capsule, tab = tablet, inj = injectable.

Full opportunistic data are available from Figshare via the DOI:10.6084/m9.figshare.19394252

XVI. APPENDIX 6. ASSESSMENT OF IMPURITY TOXICITY AND SETTING HEALTH-BASED EXPOSURE LIMITS.

All spaceflight medications are drug products that are commercially available in the U.S. and are therefore considered both safe and effective. The only uncertainty with regards to the drug product itself is whether or not some aspect of spaceflight accelerates the rate of degradation over time. Accumulation of degradation impurities resulting from chemical reactions of any ingredient (API or excipients) contribute to the uncertainty that a drug may become less safe over time. However, the presence of impurities, even at levels well above pharmacopeial specifications, do not necessarily mean that a drug is unsafe or that adverse reaction will occur. To understand the health risk of impurities in expired or failed medications (i.e., levels of impurities greater than specification limits), it is necessary to have a basic understanding of how impurity levels are set.

It is extremely rare for drugs marketed in the U.S. to accumulate levels of degradation products sufficient to elicit *documented* adverse health effects, even when well past their expiration date. In part, this is because the FDA requires *all* drug labelers (i.e., manufacturer or packager) to perform drug stability studies before marketing a drug product in the U.S. (U.S. Food and Drug Administration (FDA), 2003; U.S. Food and Drug Administration (FDA), 2013). Stability studies must be performed in the same packaging (or very similar packaging) in which the drug product will be marketed (U.S. Food and Drug Administration (FDA), 2003). This requirement ensures that all drug products meet quality requirements until their labeled expiration date. Stability studies for *all* medications include both long-term (≥ 1year) and accelerated (≥ 6 months) studies, the latter of which are conducted at elevated temperatures and humidity to accelerate drug degradation (40^{o}C/75% humidity). Drug products in the accelerated studies are subjected to much more severe and sustained environmental conditions than would be expected for a crewed Mars mission. The levels of API and of impurities are repeatedly sampled over the course of a stability study. When an impurity exceeds specification or qualification thresholds, the labeler must either make changes to lower the impurity level in the product or demonstrate the impurities are safe (U.S. Food and Drug Administration (FDA), 2008; U.S. Food and Drug Administration (FDA), 2010). The formal process for evaluating a health risk and setting a safe human exposure limit for an impurity (or impurity profile) is chemical risk assessment.

The determination of whether an impurity is “toxic” is *not* demonstrated by toxicity studies, clinical studies, or epidemiological studies; it is based on a weight of evidence analysis of all information that often (but not always) includes toxicity studies. Results from toxicological and clinical studies are assessed jointly with dose-response analysis, exposure assessment, and risk characterization to set HBELs for drug impurities

(ISPE, 2017; National Research Council, 1983). The risk assessment paradigm is a well-established field of practice and a fundamental tenent used worldwide to establish safe exposure limits for chemicals, including drugs and impurities (Boobis, et al., 2008; European Medicines Agency, 2014; ISPE, 2017; Sargent, et al., 2013; The International Council for Harmonisation (ICH) of Technical Requirements for Pharmaceuticals for Human Use, 2021; U.S. Food and Drug Administration (FDA), 2021)[18]. It is through this formalized risk assessment process that HBELs for drug impurities are set (Ball and Beierschmitt, 2020; International Programme on Chemical Safety, (IPCS), 2005; The International Council for Harmonisation (ICH) of Technical Requirements for Pharmaceuticals for Human Use, 2021; U.S. Food and Drug Administration (FDA), 2021). These exposure limits are meant to prevent adverse effects from a *lifetime daily* exposure.

The risk assessment process classifies chemicals, including drug impurities, as either genotoxic or non-genotoxic hazards, based on their mode of action (MoA). A drug with a non-genotoxic MoA has a threshold dose below which there is no adverse effect (Boobis, et al., 2008; Munro, Renwick and Danielewska-Nikiel, 2008). This dose is referred to as the threshold of toxicological concern (International Programme on Chemical Safety, (IPCS), 2005). In contrast, chemicals with DNA-reactive or mutagenic MoAs are considered to be genotoxic. Genotoxic chemicals have no threshold levels below which the exposure is safe (U.S. Food and Drug Administration (FDA), 2018; U.S. Food and Drug Administration (FDA), 2021). Exposure limits for genotoxic impurities are based on a linear no-threshold assumption (Boobis, et al., 2006), although this regulatory assumption is controversial and likely overly protective (Calabrese, 2013). The default acceptable limit for a daily lifetime exposure to genotoxic impurities in drug substances assumes a 10^5 (1 in 100,000) excess lifetime risk of cancer (Fiori and Meyerhoff, 2002; U.S. Food and Drug Administration (FDA), 2018). The cancer risk limit for pharmaceuticals is higher than the cancer risk limit for environmental genotoxic hazards, which assumes a 10^6 excess lifetime risk for cancer (e.g., Environmental Protection Agency). This 10-fold higher risk for pharmaceuticals is justified because pharmaceuticals have significant health benefits, whereas exposure to environmental chemicals has no health benefits.

FDA guidance stipulates that impurities in new drug products must be below qualification limits, which are based on the maximum daily medication dose and their content (U.S. Food and Drug Administration (FDA), 2008; U.S. Food and Drug Administration (FDA), 2010). For generic drug products

[18] For more detailed information on chemical risk assessment processes and procedures that are generally accepted internationally, see https://www.epa.gov/risk/risk-assessment-guidance (US), https://echa.europa.eu/guidance-documents/guidance-on-information-requirements-and-chemical-safety-assessment (EU).

(those marketed under an Abbreviated New Drug Application), it is "recommended" that impurities be below pharmacopeial specification limits or qualified as safe. Impurities at levels below their HBEL (i.e., "qualified") do not represent a human health risk for several reasons:

- Threshold dose. To elicit measurable biological effects, chemicals with non-genotoxic MoAs must exceed a minimum threshold dose. The adverse effect that occurs at the lowest tested dose is the "critical effect". The highest dose of a chemical that does *not* elicit the critical effect is the no adverse effect level (NOAEL). For most chemical risk assessments, the NOAEL is the basis for an exposure limit, and is referred to as the point of departure (POD; analogous to a benchmark dose). Hence, exposure limits for non-genotoxic chemicals begins with the POD, which is a dose of chemical that has no adverse effect. For genotoxic chemicals, a linear slope factor based on cancer risk is used to establish a POD, as discussed above. A safe exposure limit that is derived from the NOAEL observed in the most sensitive species is generally very protective for humans (ISPE, 2017; U.S. Food and Drug Administration (FDA), 2021).
- Uncertainty. The possibility exists that humans are more sensitive to a chemical than the animal species used in toxicology studies to assess the risk. To ensure adequate margin of safety "uncertainty factors" are applied to the POD, which reduce the exposure dose to *at least* 2 orders of magnitude below the toxicological NOAEL (benchmark dose), (ISPE, 2017; U.S. Food and Drug Administration (FDA), 2021)[19]. Consequently, impurities would need to accumulate to levels that are orders of magnitude greater than the HBEL in order to reach levels equivalent to the toxicological NOAEL (Boobis, et al., 2008; ISPE, 2017; Jacobson-Kram and McGovern, 2007). The applied uncertainty factors typically account for intra-species difference and human variability as well as critical data gaps, such as reproductive toxicity, study duration, and other uncertainties.
- Chronic Exposure. Exposure limits for impurities assume daily exposure for a lifetime. Most drugs (with many exceptions) are used only for a limited course of therapy and are not used

[19] Impurities with genotoxicity alerts or evidence of carcinogenicity have a somewhat different analysis approach that is similarly protective

for a full lifetime. No medication flown on a space exploration spaceflight will be used chronically for a lifetime, which will generally increase the margin of safety.

- Potency. Biologically active degradation impurities are usually much less potent[20] than the parent drug substance, either for the intended therapeutic effect or for adverse effects. Consequently, the amount of the parent drug in a formulation is typically too small to produce a dose of hazardous degradant that elicits an acute adverse effect. In part, this is because drug substances can degrade by more than one pathway and degradation products can undergo further degradation reactions resulting in an array of degradation products. Consequently, the stoichiometry of accumulated degradation impurities are almost always a fraction of the initial concentration of the parent compound (Waterman, Adami and Hong, 2004; Waterman and Adami, 2005). If the degradation product is a metabolite of the drug, then the FDA provides guidance on the acceptable limit of the degradation product.
- The HBEL is not a fine line separating safe levels from harmful levels. There is very high level of confidence that exposures below the HBEL are safe. Because HBELs have a very large margin of safety resulting from the cumulative protective assumptions listed above, exposures greater than the HBEL do not indicate harm will occur, only that the certainty of safety is reduced. Although exposures above the HBEL are not acceptable[21], exceeding the exposure limit is not a threshold for onset of adverse effects (Boobis, et al., 2006; Boobis, et

[20] Potency has different meanings depending on the scientific field. In the field of drug quality testing and pharmaceutics, potency refers to the amount of active ingredient (i.e., drug substance) in a formulated drug product. In the field of pharmacology and toxicology, potency is the amount of drug substance (drug dose) required to achieve a specified outcome, and potency is often used to compare different drug substance where a more potent drug achieves the specified outcome at a lower dose than a less potent drug. In this bullet point, the pharmacological/toxicological definition of potency is applied.

[21] Several regulatory agencies have set precedents for de minimis risk. This is particularly important for carcinogenic impurities because regulatory agencies have adopted the linearized multistage cancer model that assumes there is no safe threshold for carcinogenicity. The FDA uses a negligible risk for genotoxic carcinogen exposures for marketed drug products and less than life time use (≤10 years) with an upper bound (95% CI) risk level of one excess cancer per 100,000 people (i.e., 10^5) (U.S. Food and Drug Administration (FDA), 2018). Environmental Protection Agency has established a more stringent drinking water standard for carcinogen exposure based on lifetime risk (70 years) over background of one excess cancer death per 1 million people (10^{-6}) (Environmental Protection Agency Clean Water Act). The U.S. Supreme Court has affirmed the *de minimis* risk principle that "safe" does not mean "risk-free" (U.S. Supreme Court, 1980 https://supreme.justia.com/cases/federal/us/448/607/).

al., 2008; Fiori and Meyerhoff, 2002; U.S. Food and Drug Administration (FDA), 2018; U.S. Food and Drug Administration (FDA), 2020b; U.S. Food and Drug Administration (FDA), 2021).

Two concerns may not be addressed by the usual chemical risk assessment paradigm for drug degradants. The first is DNA-reactive genotoxic impurities. Genotoxic impurities have very low exposure limits (Fiori and Meyerhoff, 2002; ICH, 2017; Kroes, et al., 2004; Kroes, Kleiner and Renwick, 2005; Munro, Renwick and Danielewska-Nikiel, 2008). Given the elevated radiation environment anticipated for planetary mission, there may be a cumulative risk for the combined effects of radiation exposure and genotoxic impurities. Second, degradants (or drugs) that react with peptides, proteins, or other macromolecules can form a hapten-carrier complex capable of inducing immunologic sensitization. After sensitization, future elicitation results in exaggerated immunological responses, which may include anaphylaxis. Penicillin is an excellent example of a drug that forms a hapten-carrier complexes that cause immunologic reactions. *In silico* analysis of predicted degradants can be used to help screen for potential haptenizing molecules; however, there are no reliable *in silico* toxicological models for identifying immune sensitizing chemicals in humans. Evaluating candidate spaceflight drugs for potentially reactive degradation products should be considered.

XVII. APPENDIX 7. DRUG PACKAGING

A. REGULATORY CONTEXT FOR DRUG REPACKAGING

USP specifies protective standards for drug packaging that are intended to ensure that the container in which a drug product is packaged will be suitable to maintain potency until the drug's expiration date (United States Pharmacopeia, 2020a; United States Pharmacopeia, 2020b; United States Pharmacopeia, 2020d; United States Pharmacopeia, 2021a). FDA regulations require drug manufacturers to conduct stability testing of drug products in the same packaging in which the product will be marketed (U.S. Food and Drug Administration (FDA), 1985; U.S. Food and Drug Administration (FDA), 2003). The results of these stability tests, along with the proposed expiration date, are submitted to the FDA when a manufacturer applies for market approval in the U.S. These stability tests provide confidence that the product will meet applicable standards of strength, quality, and purity throughout the drugs proposed shelf life. This means that the shelf life of a drug is an integrated measure of the drug's chemical and physical properties and its packaging properties. Hence, the "container closure system" (i.e., packaging) is important for determining the drug product's shelf life.

Removing drug products from their sealed manufacturer's packaging exposes them to atmospheric factors. This can change the characteristics of drug products in ways that are not evaluated during the FDA approval process and can affect the safety and efficacy of medications. Examples of physical changes are adsorption of atmospheric moisture that results in increased water content, decreased tablet hardness, and faster tablet dissolution (Asafu-Adjaye, et al., 2011; Yang, et al., 2010). Such changes can significantly increase (or decrease) dissolution rate, resulting in shorter time to peak plasma concentration, and possibly adverse effects associated with elevated levels of the drug in the blood (Dello Russo, et al., 2022). Manufacturers typically do not submit data on the effects of direct atmospheric exposures to the FDA when requesting approval to market a drug in the U.S. Instead, manufacturers often include technologies in packaging that compensate for the transmission of atmospheric factors through the packaging. One example is silica gel, which has very high adsorption energy for binding and sequestering moisture that prevents moisture from interacting with drug products (Perrier and Kesselring, 1983). Generally when drugs are repacked such protection is removed, although there is no reason why NASA repackaging processes could not provide protection equivalent to, or in excess of, the protection afforded by the manufacturer's container system, thereby enabling the shelf life of some drugs to meet or exceed (when supported by the necessary stability data) the shelf life established by the manufacturer (U.S. Food and Drug Administration (FDA), 2003; U.S. Food and Drug Administration (FDA), 2004a).

The FDA regards repackaging as "the act of taking a finished drug product from the container in which it was distributed by the original manufacturer and placing it into a different container without further manipulation of the drug" (U.S. Food and Drug Administration (FDA), 2017). To illustrate, FDA gives the example of "tablets and capsules that are repackaged from large containers into smaller containers". This is exactly what NASA is doing when providing oral medications for spaceflight. The FDA recognizes that "[w]hen a drug product is repackaged, its characteristics may change in ways that have not been evaluated during the FDA approval process and that could affect the safety and efficacy of the drug product". NASA must make this concern its highest priority because, unlike the uncharacterized effects of the spaceflight environment, the effects of improper packaging are well documented.

When non-sterile SODF are repackaged, only a few acceptable options are available for assigning a beyond use date[22] (BUD) to the repackaged drug. In the absence of stability studies for the drug in the new packaging, the options are the follows:

- For non-sterile, FDA-approved drug products without an in-use time, BUD cannot not exceed 6 months, or assign the expiration date of the drug product being repackaged, whichever is shorter (U.S. Food and Drug Administration (FDA), 2017; U.S. Food and Drug Administration (FDA), 2020a).
- Repackage into containers that are comparable with the manufacturer's packaging. "It is the policy of the Center for Drugs and Biologics to allow repacking into container-closure systems that can be demonstrated to be at least as protective or more protective than the original system (USP Chapter <797>,) without performing new stability studies prior to marketing" (U.S. Food and Drug Administration (FDA), 1985; U.S. Food and Drug Administration (FDA), 2017; United States Pharmacopeia, 2020b). Container-closure systems may be compared by several methods, i.e., reviewing literature of permeation properties of different container materials; testing moisture permeation; or comparing the properties of the original container-closure system to a new system by stress testing.
- Perform stability studies to establish the shelf life of the repackaged drug. It can be presumed that if the manufacturer's shelf life is insufficient for the mission duration, and if this shelf life is based on the limits of the manufacturer's testing and not the inherent chemical or physical stability of the drug, then the drug stability studies can be conducted to determine if the drug meets USP specifications for API content, and/or qualification limits for degradation impurities. Such studies must be performed in the packaging that will be used for space missions and must demonstrate that the packaging is at least as protective as the original manufacturer's packaging (U.S. Food and Drug Administration (FDA), 1985; U.S. Food and Drug Administration (FDA), 2003; U.S. Food and Drug Administration (FDA), 2006; U.S. Food and Drug Administration (FDA), 2020a).

B. DRUG EXPIRATION DATES AND PHARMACEUTICAL PACKAGING

By law, every drug product sold to consumers is required to have a label that includes an expiration date (21 code of federal regulations Part 211.137). An expiration date represents the medication's shelf life, which is based on the date the drug was manufactured. For this reason, expiration dates change with each batch of drug manufactured, whereas a shelf life does not change from batch to batch and is the same across all batches of a specific drug product.

[22] Beyond use date (BUD) is the FDA term for the date beyond which a drug product should not be used after repackaging or compounding.

A report commissioned by the ExMC Element summarized the opinions of several subject matter experts in the field of pharmaceutical packaging. According to these industry experts, shelf lives are not accurate predictions of when a drug will no longer meet USP specifications; rather, they are the period during which the manufacturer will guarantee the identity, strength, quality, purity, and potency of their specific drug product. These opinions are supported by several assessments of pharmaceutical products that were aged well past their expiration dates (reviewed in (Zilker, Sörgel and Holzgrabe, 2019). The manufacturer's shelf life is much shorter than the actual stability of most drug products. In part, this is a result of the regulatory process for bringing a drug to market in the U.S., as well as profit-driven business decisions on the part of the manufacturer. The manufacturer's determination of a drug's shelf life is only partially based on the actual stability of the drug under a defined set of conditions. Also critical to the process are essential business decisions, including market strategy, supply chain, manufacturing capabilities, warehousing, and distribution plans, as well as the lifecycle of the product.

The drug packaging is integral to the shelf life of many drugs. In FDA parlance, packaging is referred to as the "container closure system," which is defined as "the sum of packaging components that together contain and protect the dosage form." This can include the bottle, cap, and any added materials that contribute to the packaging, such as a silica gel packet. As discussed above, the packaging is integral to guaranteeing that the stability of a drug product meets the desired shelf life. However, there is little incentive for pharmaceutical manufacturers to innovate and/or test packaging to preserve pharmaceuticals past the proposed expiration date, in part because performing long-term stability studies beyond the desired shelf life adds to production costs, and because expired medication will be discarded ensuring the purchase of new medications.

The bottom line for NASA is that packaging that ensures adequate drug stability for exploration spaceflights cannot be overlooked and needs to be evaluated. The study by Du et al. (2011) suggests that drug repackaging contributes to the increased rate of drug degradation during spaceflight relative to matched terrestrial controls (Reichard, 2023). According to the U.S. FDA, this concern can be mitigated "based on literature reference to permeation properties of different container materials performance of moisture permeation testing" (U.S. Food and Drug Administration (FDA), 1985) or by directly comparing stress tests of the properties of the original container-closure system and a new system. Although manufacturer's packaging is the de facto gold standard for assuring drug stability throughout its expected shelf life; it is not necessarily the most protective because it is, by necessity, a pragmatic compromise between the regulatory requirements assuring drug stability and a wide range of business-related decisions.

A highly protective packaging system could be one strategy to extend the shelf life of drugs that are deemed essential for exploration spaceflights but have a manufacturers' shelf life that is inadequate for the full mission duration.

XVIII. APPENDIX 8: PUBLICLY AVAILABLE SOURCES OF RADIOSTABILITY DATA

Because it is not possible to physically shield drugs to reduce all radiation exposure (see MECHANISMS OF IONIZING RADIATION-MEDIATED DRUG DEGRADATION section of this report), it is desirable to identify which drugs are sensitive to the effects of ionizing radiation and other spaceflight factors. Unfortunately, evaluating the radiosensitivity of each formulary drug is not viable due to cost and technical limitations of this approach. The gold standard for evaluating radiostability of drug substances would likely be the drug master file, which is confidential information that the drug labeler (e.g., manufacturer, packager) submits to the U.S. FDA. If drug products are radiosterilized during manufacturing, this process is described in the drug master file along with stability testing and quality control information. Unfortunately, most drug master file data are not publicly available.

To our knowledge only 2 sources of information on radiostability of drugs are publicly available. One is the FDA-required storage instructions that indicate if a drug should be protected from light, which is based on ultraviolet (UV) photostability testing of drug substances. The second is scientific literature that reports the results drug radiostability tests. Photostability data and literature-based radiostability data both have important limitations for predicting radiostability during spaceflight, as discussed below.

A. LABEL "PROTECT FROM LIGHT" STATEMENT

Classifying the radiostability of a drug using on the manufacturer's "protect from light" storage instruction is likely to misclassify the radiostability of many drugs, resulting in both type I errors (classifying the drug as sensitive when it is not) and type II errors (classifying the drug as not sensitive when it is) because: (a) Label precautionary statements are nonspecific; (b) FDA-required stability testing excludes electromagnetic wavelengths with sufficient energy to cause ionization; and (c) photochemistry is not the same as radiochemistry.

The storage instruction "protect from light" is a precautionary statement that is used inconsistently, resulting in misclassification. Inconsistent use occurs for the following reasons:

- Photostability testing is not the same as standardized testing processes of other environmental testing conditions. The sensitivity of any drug to photochemistry depends on not just the period of exposure, but also the wavelength range, intensity of light, surface

area of sample, and concentration of material tested (Hjorth Tønnesen, 1996). Hence, the meaning of light sensitivity can be subjective.

- Each manufacturer is responsible for determining light sensitivity of their products, but there are no specific standards for testing, so it is up to each manufacturer to judge the results. Consequently, recommendation from different labelers may not be comparable. In part, this is why USP specifications for a drug substance, the manufacturer's package inserts, and the package labeling are often inconsistent (Hjorth Tønnesen, 1996; Perkins, Evans and King, 2020).
- Ambiguous terminology used on manufacturer labels and package inserts can denote light sensitivity and are open to interpretation with regards to the photostability of the drug. For example, "must be protected" vs "should be protected". Some product labels state medications be dispensed in a "light-resistant" container or the "original container" (Perkins, Evans and King, 2020).
- Manufacturer recommendations for drug photostability are not likely to predict drug degradation due to radiation. The confirmatory FDA test for photostability requires exposing the drug substance to not less than 200 watt hours per square meter of UV light (U.S. Food and Drug Administration (FDA), 1996), which 720,000 joules/m^2. Over the course of a Mars mission, the expected dose of radiation inside the spacecraft is about 1 Gy, which is 1 joule/Kg. This means that the power required in the FDA photostability test is 5-orders of magnitude greater than the amount of energy absorbed by a 1 kg mass over a Mars-length mission. For this reason, photostability results are expected to be poor predictors of drug degradation; however, if the drug does not degrade in the photostability test, it is likely to be stable after exposure to GCR radiation[23].

Photochemistry and radiochemistry are different: Photostability studies using non-ionizing UV irradiation are not adequate surrogates for evaluating the radiostability of drug substances. The U.S. FDA and the EMA require that photostability testing of drugs substances be performed at electromagnetic wavelengths *greater* than 320 nm (European Medicines Agency, 1998; U.S. Food and Drug Administration (FDA), 1996). This cutoff wavelength falls within the range of UV radiation and equates to an energy of 3.9 electron volts (eV), which is *less* than the minimum energy required to eject electrons and ionize atoms. This

[23] Conversions: 1 Gy = 1 joule/kg; 1 watt = 1 joule/second = 3600 joules/hour.

means photostability testing uses electromagnetic radiation that can excite atoms but cannot ionize them. For radiation to be ionizing it must have a minimum ~10 (eV) to eject an electron from an atom, although other thresholds, such as the ionization energy for water (33 eV) are also used (Carron, 2007). Because wavelength is inversely proportional to energy (per Planck's equation), 10 eV equates to a wavelength of approximately 125 nm. In terms of electromagnetic radiation 10 eV is a considerably shorter wavelength than the cutoff mandated by U.S. FDA or EMA standards. Consequently, the FDA- and the EMA-compliant photostability tests specifically exclude wavelengths with ionization potential. This difference has important implications for drug chemistry.

A fundamental law of photochemistry is the Grotthuss–Draper law, which says that light must be absorbed to produce a chemical effect. According to this law, a drug is affected by a particular wavelength of non-ionizing electromagnetic radiation *only* if the wavelength is absorbed by the atom or molecule, and *only* if the energy exceeds an energy threshold that facilitates a chemical reaction (Bokser and O'Donnell, 2013; Moore, 2004). The molecular structure of the atom or molecule determine the specific wavelengths of non-ionizing radiation that are absorbed, a fact that is commonly used in spectrometry to identify chemical substances. An absorbed photon can transiently excite an electron to a higher energy state (i.e., orbital). The extra quanta of energy is subsequently dissipated in one of 3 ways; as heat (i.e., kinetic energy), light (i.e., emission of a photon) or both. Electronically excited molecules are also more chemically reactive than their corresponding ground state analogs, and therefore can undergo photochemical reactions (Moore, 2004). Photochemistry is the mechanism through which non-ionizing radiation mediates degradation of pharmaceuticals. The FDA and the EMA photostability guidance is intended to help ensure that appropriate packaging is used to prevent degradation of drug products by visible and near UV wavelengths that are present in terrestrial sunlight (Carron, 2007; U.S. Food and Drug Administration (FDA), 1996).

Ionizing radiation consists of particles and electromagnetic waves (photons) that have sufficient energy to remove electrons from atoms and molecules (as mentioned above). Ionizing electromagnetic radiation includes gamma rays, X-rays, and a portion of the high-energy UV spectrum, inclusive of wavelength equal to or shorter than germicidal UV-C. Ionizing particles include alpha particles (helium nuclei), beta particles (electrons or positrons), neutrons, a wide range of charged nuclei and subatomic particles.

Space radiation, which is predominantly charged accelerated nuclei, interacts with pharmaceuticals through 2 mechanisms: radiochemistry (i.e., ionization, excitation), and stochastic atomic displacement collisions with drug molecules (Shulman and Ginell, 1970). Radiochemistry is the most applicable to

spaceflight stability of drugs because it includes both mechanisms of drug interaction. Whereas ionizing radiation includes excitation similar to that of photochemistry, what sets it apart are a wide range of chemical changes, notably a cascade of ejected electrons, (parent) ion fragmentation, ion-molecule reactions, non-uniform distribution of reaction intermediates, and non-selective chemistry (stochastic) leading to the production of multiple reaction products (Carron, 2007). It can be concluded that FDA "protect from light" storage recommendations are not sufficient to infer that a medication either *is* or *is not* susceptible to ionizing radiation.

B. LITERATURE STUDIES OF DRUG RADIOSTERILIZATION AND RADIOSTABILITY

A literature-based approach for evaluating drug radiostability relies on published gamma-ray and electron beam (e-beam)studies Many drug radiostability studies have been published, the review of which is beyond the scope of this report; however, there are several published reviews that have tabulated and summarized much of these data (Boess and Bögl, 1996; Bogi, 1985; Gopal, 1978; Hasanain, et al., 2014; Jacobs, 1985; Jacobs, 1995; Jacobs, 2022; Sarcan, et al., 2020; Sarcan and Ozer, 2020; Silindir and Ozer, 2012). It is reasonable to assume that such data could be used to classify the expected susceptibility of many of NASA's spaceflight formulary drugs to ionizing radiation. However, the irradiation treatments used in many of these published investigations have several important qualitative and quantitative differences from the radiological environment of spaceflight, including *the types of radiation, cumulative dose, dose-rate, and the energy spectrum.* Drug radiosterilization and radiostability testing usually involves irradiation with either gamma-rays or electron beam radiation. A radiation dose of 25 kGy is widely accepted as a suitable radiation dose for drug sterilization (Jacobs, 2021) and is typically delivered over a few hours. Most drug radiostability studies include doses in this range, and also include much lower doses (1–10 kGy) to characterize the dose-response curve for chemical stability. Using these dose response curves, it is possible to evaluate the effects of low doses of ionizing radiation and identify drug substances or formulations that may become unstable when exposed to radiation doses attainable during exploration spaceflight (~ 0.001 kGy).

Conclusion regarding literature data: Although ionizing radiation associated with spaceflight is quantitatively and qualitatively different from radiosterilization, radiosterilization study results may be useful for identifying drug products that may be sensitive to ionizing radiation exposure. Some drugs, especially those formulated in aqueous suspensions, are known to be more sensitive to ionizing radiation than solid formulations. Hence, it is reasonable to conservatively assume that drugs known to be sensitive to radiosterilization may also be susceptible to prolonged exposure to space radiation.

XIX. APPENDIX 9: MECHANISMS OF IONIZING RADIATION-MEDIATED DRUG DEGRADATION

A. SPACE RADIATION ENVIRONMENT

The 4 sources of ionizing radiation in space are GCR, solar particle events (SPE), trapped radiation, and neutrons and their secondary particles (Chancellor, et al., 2018; The National Council on Radiation Protection and Measurements, (NCRP), 1989). GCR consists of highly energetic, fully ionized nuclei that originate outside the solar system (see Table 4). In deep space the most abundant GCR particle types are protons (~87%) and helium (~12%) with the remaining ~1% composed of heavier ions. SPEs are created by magnetic disruptions on the solar surface, which create a highly energetic shockwave that accelerates solar particles out into the solar system in transient bursts. Trapped radiation is the energetic particles that are trapped in Earth's magnetic field. Two permanent radiation belts called the Van Allen Belts form toroidal rings around Earth. The inner belt is composed of mainly protons and the outer belt is composed of mainly electrons. Missions to the moon and to Mars may only experience transient exposure to trapped radiation when passing through the 2 belts, however, long-duration missions in LEO can receive a substantial dose from trapped radiation depending on the mission trajectory. Therefore, it is important to consider the source of radiation if medications are to be stored for extended durations without resupply. SPEs are composed primarily of protons with large and unpredictable variability in energy, fluence, and duration. Energetic SPEs are particle events that have an increased energy (>100 Mev) of protons that are capable of penetrating a spacecraft, and therefore can increase the radiation dose in the space vehicle if it is the path of the event. Generally, SPEs tend to be more frequent during the part of the solar cycle when the sun is more active (solar maximum), however, event intensity is independent of solar cycle (Cucinotta, Kim and Chappell, 2012). Only a small percentage of SPEs (<5%) represent a hazard to crewmembers' health even if astronauts are not protected by shielding (Cucinotta, Kim and Chappell, 2012). The sun's activity, which follows an approximately 11-year cycle, also plays a major role in modulating the intensity of GCR and trapped radiation. During solar maximum the sun's stronger magnetic activity and field redirects more GCR away from our solar system, effectively reducing the GCR exposure. GCR fluence can vary 3–4-fold depending on solar cycle parameters (Chancellor, et al., 2018; Simonsen, et al., 2020). The proton flux within the inner Van Allen Belt is also inversely correlated with solar activity (Nakano and Heckman, 1968).

The passive shielding used in current spacecraft designs provides a measure of protection from energetic particles because it absorbs relatively low energy particles and it fragments high-LET particles into lighter particles. In general, particles with energies < 30 MeV do not penetrate the spacecraft (Modisette, Vinson and Hardy, 1965). However, passive shielding does not attenuate a large portion of high-LET GCR (Blue, R. S., et al., 2019; Chancellor, et al., 2018; Cucinotta, Kim and Chappell, 2012; Naito and Kodaira, 2022;

National Academies of Sciences, Engineering, and Medicine, 2021). Rather, the radiation environment within a shielded spacecraft has a spectrum that is shifted toward lower HZE (high atomic number and energy) particles, compared to that of free space due to ionization and fragmentation events that occur as HZE particles pass through matter (Naito and Kodaira, 2022; Simonsen, et al., 2020). Particles at energy ranges within a spacecraft can be generated at the NSRL. Because protons constitute, by far, the most frequent GCR particles within a spacecraft, it is not necessary to expose medications to the full GCRsim to assess stability; drug radiostability can be reliably evaluated using proton irradiation alone. The effects of proton irradiation on medications can be adequately simulated with gamma radiation.

B. EVIDENCE OF HOW DRUG PRODUCTS ARE IMPACTED BY IONIZING RADIATION

1. Radiosensitivity of drugs versus radiosensitivity of organisms

Ionizing radiation affects drugs differently than it affects living systems, and many key assumptions that apply to organisms do not apply to drug products. These differences make drugs much less sensitive than organisms to ionizing radiation exposure.

Both drugs and biological systems can incur immediate molecular damage as a result of ionizations and collisions; however, in organisms, structural damage can perturb biological pathways required for homeostasis (e.g., membrane dysfunction, delayed cell cycle), and can result in delayed emergence of disorders (e.g., cancer, reproductive effects, immune dysfunction). Animals have cellular structures including nuclei, membranes, organelles, and biochemical pathways that are sensitive to the effects of ionizing radiation, and damage to these structures perturbs physiological homeostasis resulting in illness and disease. Drugs, by comparison do not depend on complex biochemical processes requiring homeostasis. Most ingredients constituting drugs are typically disbursed homogenously throughout the volume of a drug product (with some exceptions) and therefore ingredients are all similarly susceptible targets for penetrating radiation (Kim, Plante and Simonsen, 2014; Reid and Fairand, 2018). Because drugs do not require homeostasis, they are not susceptible to functional perturbations that increase the probability of acute or chronic adverse effects in living organisms, often well after the exposure.

The radiation dose-rate has more important consequences for biological organisms than for drug products. Cells have dedicated sensors and enzyme systems that detect and repair damage from ionizing radiation and other environmental stressors; drugs do not. An organism's capacity to repair radiation damage is limited, and the efficiency of these repair mechanisms is reduced when damage occurs rapidly. Ionizing radiation damages cells in many ways, including direct and indirect effects on membranes and DNA.

The “one hit” cancer risk paradigm assumes that any unrepaired DNA damage can result in a critical mutation that increases cancer risk, and that the risk of disease increases linearly with dose[24]. In comparison, a drug cannot “fail” if a critical “hit” damages a molecule of drug substance. Drug products possess high concentrations of API that are homogenously dispersed in the excipient matrix; therefore, an incredibly large number of hits is required to produce measurable changes in drug content on a molar scale (Crucq, et al., 2005)(also see discussion of Kim and Plante in the *In Silico Modeling of the Effects of Spaceflight Radiation* section of this report). Consequently, organisms can be adversely affected by radiation at doses and dose-rates well below those that affect drug products, and organisms manifest damage in many ways that are inapplicable to inanimate materials such as drugs.

2. Drug degradation pathways and products are not unique to radiation

Food and pharmaceutical stability studies have shown that degradation products produced by radiolysis are not unique to irradiation. Instead, degradation impurities are similar to those produced when the same drug is subjected to other sterilization procedures (Kane and Tsuji, 1983; Jacobs, 1985; Jacobs, 1995; Bozdag, et al., 2010; Jacobs, 2022). Furthermore, the concentrations of radiolytic degradation impurities generated in food substances from irradiation at doses of up to 10 kGy pose no toxicological hazard to consumers (United Nations World Health Organization (WHO) Joint Food and Agriculture Organization (FAO) and International Atomic Energy Agency (IAEA) Expert Committee, 1981). This inference from irradiated food studies would likely also apply to pharmaceuticals (Jacobs, 2022). This evidence supports the conclusion that prolonged exposure to a spaceflight environment may facilitate degradation of susceptible drugs, and the degradation pathways and reaction products will be the same as those observed in FDA-compliant stability studies. The mechanism of drug degradation is essential for identifying susceptible drugs.

3. Sensitivity of drugs to ionizing radiation

Drug products are composed of API(s) dispersed in a matrix of excipients. Although each chemical entity in a drug product has a characteristic susceptibility to radiolytic decay, unlike animals, drugs do not have sensitive target sites. The effects of radiation exposure on pharmaceutical products are immediate and measurable ionized species, dissociated and excited molecules, and thermal processes. Recombination processes also begin to occur in the same time frame; however, long-lived species (i.e., certain free radicals)

[24] linear no-threshold model of carcinogenesis is controversial and accumulating evidence questions its application by regulatory agencies as a basis for chemical and radiation risk assessment (Calabrese, 2013).

may be chemically active for hours or days (Reid and Fairand, 2018). Some formulations, such as solid drug products, are, however, much more resistant to radiolytic chemistry than are other formulations, such as aqueous solutions. It should be understood that therapeutically inactive ingredients (i.e., excipients) are *not* chemically inert and can potentially modulate stability of the formulation, either positively or negatively.

A drug's formulation determines the drug's stability after ionizing radiation exposure. Approximately 45% of drugs on the exploration candidate formulary are non-solid drug formulations in an aqueous matrix (i.e., solutions, creams). Aqueous drug formulations are much more susceptible to ionizing radiation than solid formulations because ionization of water produces reactive intermediates that can diffuse from the site of formation and react with drug ingredients (Gopal, 1978; Marciniec and Dettlaff, 2008). Solid formulations do not form such reactive intermediates; when solid drug ingredients are ionized, they are locked in a matrix that substantially inhibits diffusion. For this reason, solid state drugs are far less stable than liquid drugs to the effects of ionizing radiation (Kane and Tsuji, 1983; Jacobs, 1985; Boess and Bögl, 1996; Juanchi, Albarran and Negron-Mendoza, 2000; Guo, et al., 2017; Jacobs, 2022).

Irradiation of pure liquid water leads to the formation of many radiolytic species, some of which are potent oxidative (e.g., $^{\bullet}OH$, H_2O_2) or reductive (e.g., H_O, H_2, $O_2^{-\bullet}$,and e_{aq}^-) moieties (Crucq, et al., 2005; Crucq, Deridder and Tilquin, 2005; Marciniec and Dettlaff, 2008). Although most reactive oxidative species decay very quickly, some react to form meta-stable species (e.g., $^{\bullet}OH + {}^{\bullet}OH \rightarrow H_2O_2$), while others diffuse and can directly react with drug ingredients (Kim and Plante, 2015; Marciniec and Dettlaff, 2008). These meta-stable species can permit reactive intermediates to persist for days after irradiation and contribute to degradation of medications (Gopal, 1978; Jacobs, 2022; Waterman and Adami, 2005). Water is a more abundant in liquid formulations than in solid formulations, and reactive intermediates readily diffuse in solutions and have greater freedom to interact with drug molecules. Freezing a susceptible solution at-80^{o}C is known to *significantly* increase the stability of susceptible drugs because the frozen matrix limits diffusion of reactive species and their subsequent interaction with drug molecules (Gopal, 1978; Jacobs, 1995; Sarcan and Ozer, 2020). As shown in Figure 4, the content of some solid-state drugs with known resistance to radiolytic degradation decreased a few percent after irradiation with 60 kGy of gamma radiation, whereas water solutions of these same drugs decomposed 20–50% after a lower dose of 25 kGy (Marciniec and Dettlaff, 2008). Importantly, the radiation doses used in these studies are orders of magnitude larger than any radiation exposure anticipated for human spaceflight (Doarn, et al., 2019; National Academies of Sciences, Engineering, and Medicine, 2021). It is reasonable to assume that absorbed doses of ionizing radiation that

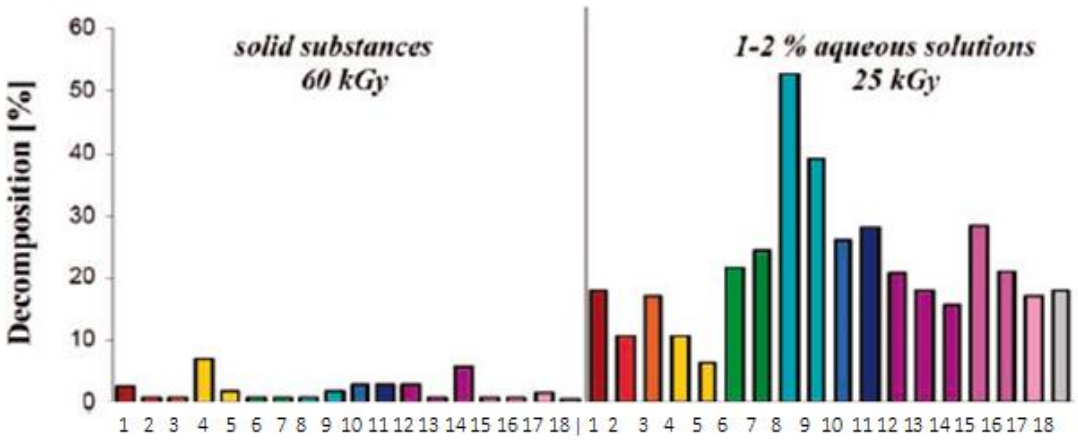

Figure A1. Comparison of the decomposition of solid substances and aqueous solutions. Repeated colors are results from independent studies. From left to right: 1) atropine sulphate, 2) cocaine hydrochloride, 3) codeine phosphate, 4 & 5) ephedrine hydrochloride (x2), 6) hydrocodone hydrochloride, 7) hydrocodone hydrogentartrate, 8 & 9) hydromorphone hydrogentartrate (x2), 10) levomethadone, 11) methadone hydrochloride, 12- 14) morphine hydrochloride (x3), 15 & 16) oxycodone hydrochloride (x2), 17) pilocarpine hydrochloride and 18) scopolamine hydrobromide. (Boess and Bögl 1996)

are thousands of times lower will have much less of an effect on drug stability than shown in Figure A1, particularly for solid state drugs that don't degrade much.

C. DILUTE DRUG SOLUTIONS MAY BE MORE SUSCEPTIBLE TO DEGRADATION THAN CONCENTRATED SOLUTIONS

Drug degradation is inversely related to solution concentration when irradiated at the same cumulative radiation dose. i.e., low concentrated drugs exhibit more change that high concentrated drugs (Bogi 1985; Gopal 1978; Marciniec and Dettlaff 2008). Figure A2 shows that, for 6 drug solutions, as concentration decreases the proportional loss of potency increases after irradiated with 25 kG of gamma radiation.

D. THE DOSE-RATE OF IONIZING RADIATION IMPACTS DRUG DEGRADATION

Degradation increased with decreasing radiation dose-rate in aqueous solutions of atropine (0.1% solution), benzalkonium chloride (0.3% solution), morphine (1% solution), or lidocaine (2% solution) that were irradiated with 10 kGy of gamma radiation at rates from 0.01–10 Gy/s (Gopal, 1978). A 10 kGy dose delivered at 2.5 kGy/h caused atropine sulfate (1.0% solution) to decompose by 28%, whereas the same radiation dose delivered at 0.1 kGy/h caused the same solution to degrade by 62% (Boess and Bögl, 1996; Marciniec and Dettlaff, 2008). Similarly, a 0.3% aqueous solution of benzalkonium chloride was almost entirely degraded after exposure to 30 kGy (^{60}Co gamma irradiation, 1 Gy/s) but had little change after the

Table A6. Concentration-dependent drug decomposition in aqueous solutions. Drug formulated at lower concentrations exhibit more extensive degradation (Radiation dose of 25 kGy of gamma radiation) (Marciniec and Dettlaff 2008).

Substance	Concentration (%)	Decomposition (%)
Chloramphenicol	0.1/0.05	42/62
Dihydrocodeine hydrogen tartrate	0.5/0.2/0.1/0.05	9/15/27/49
Ephedrine HCl	0.5/0.2/0.1/0.05	18/38/63/95
Glucose	50/40/20/10/5	1.5/1.6/1.8/2.8/3.3
Lidocaine HCl	0.5/0.2/0.1/0.05	16/27/39/81
Morphine HCl	0.5/0.2/0.1/0.05	30/42/43/80

same dose delivered at 10.13 Gy/s. Hence the dose rate of irradiation can have an effect on the stability of the solute in aqueous dispersions, and radical-to-radical reactions are more predominant than radical-to-solute interactions after high dose rates of ionizing radiation (Gopal, 1978).

Mechanistically, reactive species in water have a very short half-life and for this reason must form near a target molecule to react with the drug substance. It has been suggested that at these extremely high dose-rates, the number of radicals formed as a function of time is also high, and, in the local vicinity, such as ionization spurs where a reactive species is formed, they recombine without producing any effect on the drug molecules. At lower dose-rates, the number of radicals produced is proportionally lower and, because both recombination and reaction with drug substance are stochastic events, the likelihood of recombination is reduced relative to the likelihood that the radicals will diffuse and react with susceptible drug substance (Navarro, et al., 2018; Sintzel, et al., 1997). Hence, proportionally speaking, high dose-rates appear to cause less degradation than lower dose-rates.

XX. APPENDIX 10: EXPERIMENTAL DETAILS FOR MEDICATIONS TESTED IN ALL OPPORTUNISTIC SPACEFLIGHT STUDIES

Study	Date	INN	Dose	Dose Units	Dosage Form	Treatment	Mfr.	Lot	NDC	N	Repacked	Mfr exp. date.	Launch Date	Landing Date	Days in space	Analysis date	Percent content	Percent St. dev
Wu	2016	Promethazine	25	mg	tablet	control	N/A	N/A	N/A	3	N/A	not avail	N/A	NA	0	1/30/2016	100.0	1.0
Wu	2016	Promethazine	25	mg	tablet	flight	N/A	N/A	N/A	3	N/A	11/1/2013	N/A	3/26/2013	256	1/30/2016	76.5	1.3
Wu	2016	Promethazine	25	mg	tablet	flight	N/A	N/A	N/A	3	N/A	11/30/2014	N/A	5/18/2014	193	1/30/2016	79.5	1.3
Wu	2016	Promethazine	25	mg	tablet	flight	N/A	N/A	N/A	3	N/A	9/30/2015	N/A	5/25/2015	243	1/30/2016	86.4	1.1
Wu	2016	Promethazine	25	mg/mL	injection	control	N/A	N/A	N/A	3	N/A	not provided	N/A	NA	0	1/30/2016	72.3	1.1
Wu	2016	Promethazine	25	mg/mL	injection	flight	N/A	N/A	N/A	3	N/A	10/31/2013	N/A	3/26/2013	256	1/30/2016	82.5	1.6
Wu	2016	Promethazine	25	mg/mL	injection	flight	N/A	N/A	N/A	3	N/A	2/28/2014	N/A	5/18/2014	565	1/30/2016	79.0	1.7
Wu	2016	Azithromycin	250	mg	tablet	flight	N/A	N/A	N/A	3	N/A	not provided	N/A	10/28/2012	699	1/30/2016	100.0	0.8
Wu	2016	Azithromycin	250	mg	tablet	flight	N/A	N/A	N/A	3	N/A	not provided	N/A	5/18/2014	356	1/30/2016	114.0	1.1
Wu	2016	Azithromycin	250	mg	tablet	flight	N/A	N/A	N/A	3	N/A	not provided	N/A	2/11/2015	399	1/30/2016	109.2	1.1
Wu	2016	Ibuprofen	400	mg	tablet	control	N/A	N/A	N/A	3	N/A	not provided	N/A	NA	0	1/30/2016	100.0	0.6
Wu	2016	Ibuprofen	400	mg	tablet	flight	N/A	N/A	N/A	3	N/A	11/30/2013	N/A	3/26/2013	551	1/30/2016	82.7	1.0
Wu	2016	Ibuprofen	400	mg	tablet	flight	N/A	N/A	N/A	3	N/A	not provided	N/A	5/18/2014	647	1/30/2016	85.8	2.0
Wu	2016	Ibuprofen	400	mg	tablet	flight	N/A	N/A	N/A	3	N/A	6/26/2015	N/A	2/11/2015	140	1/30/2016	85.2	2.2
Wotring	2015	Aspirin	325	mg	tablet	flight	N/A	N/A	N/A	5	N/A	7/31/2012	N/A	NA	550	4/30/2013	96.5	0.2
Wotring	2015	Acetaminophen	325	mg	tablet	flight	N/A	N/A	N/A	5	N/A	11/30/2012	N/A	NA	550	4/30/2013	97.0	1.0
Wotring	2015	Ibuprofen	400	mg	tablet	flight	N/A	N/A	N/A	5	N/A	11/30/2013	N/A	NA	550	8/30/2013	99.9	1.8
Wotring	2015	Loperamide	2	mg	tablet	flight	N/A	N/A	N/A	4	N/A	8/31/2013	N/A	NA	550	6/30/2013	100.0	30.0
Wotring	2015	Loratadine	10	mg	tablet	flight	N/A	N/A	N/A	4	N/A	8/31/2012	N/A	NA	550	4/30/2013	100.0	3.0
Wotring	2015	Pseudoephedrine	120	mg	ET Tablet	flight	N/A	N/A	N/A	4	N/A	9/30/2013	N/A	NA	550	6/30/2014	99.1	2.8
Wotring	2015	Melatonin	3	mg	tablet	flight	N/A	N/A	N/A	4	N/A	5/31/2012	N/A	NA	550	4/30/2013	90.0	3.3
Wotring	2015	Modafinil	200	mg	tablet	flight	N/A	N/A	N/A	5	N/A	9/30/2012	N/A	NA	550	7/30/2012	100.6	1.2
Wotring	2015	Zolpidem	10	mg	tablet	flight	N/A	N/A	N/A	5	N/A	9/30/2012	N/A	NA	550	6/30/2013	100.7	0.9
Cory	2016	Levofloxacin	50	mg	tablet	flight	Sandoz	EM0315	N/A	10	N/A	6/30/2016	1/10/2015	5/21/2015	132	6/15/2016	99.7	1.4
Cory	2016	Levofloxacin	50	mg	tablet	control	Sandoz	GA3487	N/A	10	N/A	1/31/2018	N/A	NA	0	6/15/2016	98.9	1.5
Cory	2016	Ibuprofen	400	mg	tablet	flight	Dr. Reddy's Lab	L-04201	N/A	10	N/A	6/26/2015	9/25/2014	2/11/2015	140	6/15/2016	100.1	0.9
Cory	2016	Ibuprofen	400	mg	tablet	control	Dr. Reddy's Lab	L-04415	N/A	10	N/A	10/31/2015	N/A	N/A	0	6/15/2016	99.8	0.8
Cory	2016	Phenytoin	300	mg	ER capsules	flight	Mylan	3048017	N/A	9	N/A	6/30/2015	9/23/2014	5/21/2015	241	6/15/2016	102.2	0.5
Cory	2016	Phenytoin	300	mg	ER capsules	control	Mylan	3063826	N/A	9	N/A	1/31/2017	N/A	N/A	0	6/15/2016	101.5	0.7
Cory	2016	Valacyclovir	1000	mg	ER capsules	flight	Actavis	1013120A	N/A	10	N/A	1/31/2016	1/9/2014	5/21/2015	498	9/15/2016	107.8	6.0
Cory	2016	Valacyclovir	1000	mg	ER capsules	control	Actavis	G34672	N/A	10	N/A	5/31/2015	N/A	N/A	0	9/15/2016	101.6	2.4
Cory	2016	Sertraline	50	mg	tablet	flight	Greenstone	V100436	N/A	10	N/A	11/30/2012	4/27/2011	3/26/2013	700	6/15/2016	98.6	5.8
Cory	2016	Sertraline	50	mg	tablet	control	Greenstone	NA	N/A	10	N/A	5/30/2018	N/A	N/A	0	6/15/2016	99.5	5.2
Cory	2017	Amoxicillin	500	mg	capsule	flight	Sandoz	CM3543	00781-2613-01	10	N/A	5/31/2015	5/28/2013	5/18/2014	356	9/30/2017	114.1	1.5
Cory	2017	Amoxicillin	500	mg	capsule	flight	Sandoz	DF6370	00781-2613-01	10	N/A	2/29/2016	1/9/2014	5/21/2015	498	9/29/2017	114.3	1.4
Cory	2017	Amoxicillin	500	mg	capsule	flight	Sandoz	EC3644	00781-2613-01	10	N/A	1/31/2017	4/14/2015	8/26/2016	501	9/30/2017	112.4	1.1
Cory	**2017**	**Amoxicillin**	**500**	**mg**	**capsule**	**control**	**Sandoz**	**GJ8058**	**00781-2613-01**	**10**	N/A	**6/30/2019**	N/A	N/A	**0**	7/30/2017	**115.9**	1.8

Cory	2017	Aspirin	325	mg	tablet	flight	Hospak	D026Y	66553-0001-01	10	N/A	3/31/2014	3/28/2013	5/18/2014	417	6/30/2017	97.7	2.3
Cory	2017	Aspirin	325	mg	tablet	flight	Hospak	C060Z	66553-0001-01	10	N/A	5/31/2015	1/9/2014	2/11/2015	399	6/30/2017	94.9	2.0
Cory	2017	Aspirin	325	mg	tablet	flight	Hospak	G063Z	66553-0001-01	10	N/A	8/31/2015	1/10/2015	5/11/2016	488	6/30/2017	93.9	2.2
Cory	**2017**	**Aspirin**	**325**	**mg**	**tables**	**control**	**Hospak**	**L028A**	**66553-0001-01**	**10**	N/A	**11/30/2017**	N/A	N/A	**0**	6/30/2017	**96.9**	2.0
Cory	2017	Pseudoephedrine	30	mg	tablet	flight	Major	A102Z	00904-5053-60	10	N/A	3/13/2016	11/7/2013	5/18/2014	193	7/13/2017	103.4	2.8
Cory	2017	Pseudoephedrine	30	mg	tablet	flight	Major	A103Z	00904-5053-60	10	N/A	3/13/2016	1/9/2014	5/21/2015	498	7/13/2017	107.6	6.4
Cory	2017	Pseudoephedrine	30	mg	tablet	flight	Major	K135Z	00904-5053-60	10	N/A	4/30/2017	7/7/2016	8/26/2016	51	7/30/2017	103.9	1.9
Cory	**2017**	**Pseudoephedrine**	**30**	**mg**	**tablet**	**control**	**Major**	**9102503**	**00904-6338-60**	**10**	N/A	**11/30/2019**	N/A	N/A	**0**	7/30/2017	**91.0**	2.0
Khan-Wotring	2014	Azithromycin	250	mg	tablet	Control	Sandoz	CA6971	NA	3	Mfr pack	4/30/2013	N/A	N/A	0	6/7/2012	105.5	0.5
Khan-Wotring	2014	Azithromycin	250	mg	tablet	flight	Sandoz	190919	00781-1496-68	3	6/7/2011	6/7/2011	9/8/2010	7/21/2011	316	6/7/2012	98.3	0.9
Khan-Wotring	2014	Azithromycin	250	mg	tablet	control	Greenstone	1B81002BA	NA	3	Mrf pack	12/31/2013	N/A	N/A	0	6/7/2012	97.1	0.2
Khan-Wotring	2014	Azithromycin	250	mg	tablet	flight	Greenstone	5HP059A	59762-3060-02	3	5/17/2007	8/31/2008	7/4/2006	11/30/2008	880	5/17/2012	98.3	2.0
Khan-Wotring	2014	Azithromycin	250	mg	tablet	control	Greenstone	5HP059A	59762-3060-02	3	5/17/2007	8/31/2008	N/A	N/A	0	5/17/2012	106.5	2.8
Khan-Wotring	2014	Levofloxacin	500	mg	tablet	flight	Janssen	OCG513	50458-0925-50	3	6/2/2011	1/31/2013	9/8/2010	7/21/2011	316	1/25/2012	104.2	0.215
Khan-Wotring	2014	Levofloxacin	500	mg	tablet	flight	Janssen	6AG613	00045-1525-50	3	5/17/2007	11/30/2008	7/4/2006	11/30/2008	880	5/17/2012	101.1	0.614
Khan-Wotring	2014	Levofloxacin	500	mg	tablet	control	Janssen	6AG613	00045-1525-50	3	5/17/2007	11/30/2008	N/A	N/A	0	5/17/2012	101.2	0.422
Khan-Wotring	2014	Levothyroxine	0.025	mg	tablet	control	Sandoz	C05T0861A4	600781-5180-01	3	5/1/2007	8/31/2007	N/A	N/A	0	1/26/2012	77.38	1.89
Khan-Wotring	2014	Levothyroxine	0.025	mg	tablet	flight	Sandoz	C05T0861A4	00781-5180-01	3	5/1/2007	8/31/2007	7/4/2006	7/17/2006	13	1/26/2012	78.12	1.99
Khan-Wotring	2014	Levothyroxine	0.025	mg	tablet	flight	Sandoz	C05T0861A5	00781-5180-01	3	5/17/2007	8/31/2007	7/4/2006	11/30/2008	880	1/26/2012	81.39	1.47
Khan-Wotring	2014	Levothyroxine	0.025	mg	tablet	control	Sandoz	C05T0861A5	00781-5180-01	3	5/17/2007	8/31/2007	N/A	N/A	0	1/26/2012	80.91	0.91