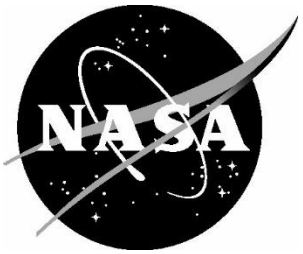
NASA/TM– 20240001489



# Exploration Medical Capability (ExMC) Strategy for Assuring Pharmaceutical Stability During Exploration Spaceflight

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May 2024

Available from:

NASA STI Program / Mail Stop 050
NASA Langley Research Center
Hampton, VA 23681-2199

Table of Contents

## LIST OF TABLES



## LIST OF FIGURES


*Figure 1. Hierarchical structure of the relational DDR.* 30
*Figure 2. Venn diagram illustrating some of the available data sources linked in the DDR.* 33
*Figure 3. Degradation of aqueous dispersion formulations in terrestrial and space flight conditions.* 53
*Figure 4. Comparison of the decomposition of solid substances and aqueous solutions* 57
*Figure 5. Study design for spaceflight drug stability testing.* 65
Appendix 3 Figure 1. Drug information decision tree. 95
*Appendix 3 Figure 2. Drug classification by Mission Duration.* 97
*Appendix 3 Figure 3. Decision logic to classifying drug stability to ionizing radiation.* 101

# I. *LIST OF ACRONYMS*

| Acronym/Abbreviation | Definition |
|---|---|
| API | active pharmaceutical ingredient |
| ANDA | abbreviated new drug application |
| BDDCS | Biopharmaceutics Drug Disposition Classification System |
| BMD | benchmark dose |
| CDER | [FDA] Center for Drug Evaluation and Research |
| CliFF | clinical finding form |
| CRT | condition resource trace |
| DDR | drug data repository |
| DoD | Department of Defense |
| DRM | design reference mission |
| ECF | exploration candidate formulary |
| EMA | European Medicines Agency |
| emc | Electronic Medicines Compendium |
| ESR | electron spin resonance |
| EU | European Union |
| ExMC | Exploration Medical Capability [HRP Element] |
| FAO | Food and Agriculture Organization |
| FDA | Food and Drug Administration |
| FOIA | Freedom of Information Act |
| GEE | Generalize Estimating Equation |
| Gy | Gray |
| HRP | Human Research Program |
| IAA | Interagency agreement |
| IAEA | International Atomic Energy Agency |
| ICH | International Council for Harmonisation |
| IMAK | ISS Medical Accessory Kit |
| ISS | International Space Station |
| JSC | [Lyndon B.] Johnson Space Center |
| kGy | kilogray |
| LET | linear energy transfer |
| LOAEL | lowest observed adverse effect level |
| LSDA | (NASA) Life Science Data Archive |
| MeV | megaelectron volt |
| NASA | National Aeronautics and Space Administration |

| Acronym/Abbreviation | Definition |
|---|---|
| NDA | new drug application |
| NDC | national drug code |
| NLM | National Library of Medicine |
| NOAEL | no observed adverse effect level |
| NOEL | no observed effect level (any effect) |
| NSRL | NASA Space Radiation Laboratory |
| OECD | Organisation for Economic Co-operation and Development |
| OPQ | U.S. FDA Division of Product Quality |
| ORISE | Oak Ridge Institute for Science and Education |
| PD | pharmacodynamics |
| PEG | polyethylene glycol |
| PK | pharmacokinetics |
| QSAR | quantitative structure-activity relationship |
| RH | relative humidity |
| RxCUIs | unique drug identifiers |
| SLEP | Shelf-Life Extension Program |
| SME | subject matter expert |
| SODF | solid oral dosage forms |
| SOW | statement of work |
| Sv | Sievert |
| TTC | threshold of toxicological concern |
| USP | United States Pharmacopeia |
| UV | ultraviolet |
| WHO | World Health Organization |

## II. *INTRODUCTION*

The National Aeronautics and Space Administration (NASA) has performed multiple studies to evaluate the stability of drugs during spaceflight (Reichard, 2023). Most of these studies have been qualitative opportunistic studies without the appropriate controls needed to demonstrate whether spaceflight has a differential effect on drug stability. One well-designed pilot study showed increased degradation of some drugs during spaceflight relative to the degradation of terrestrial controls from the same manufacturing lot (Du, et al., 2011). Subsequent studies have been opportunistic in nature, lacking a controlled experimental design and are therefore not capable of quantifying the relative effect of spaceflight exposure on drug products (Cory, et al., 2016; Cory and Mangiaracina, 2017; Wotring, 2016; Wu and Chow, 2016). Furthermore, the observational design of these studies cannot test how individual environmental factors influence drug degradation. No NASA-supported pharmaceutical spaceflight study has clearly stated the hypothesis to be tested or used statistical methods to evaluate study results. For these reasons, and even though multiple studies have been performed, the risk(s) associated with drug deterioration during spaceflight remains speculative and poorly characterized.

This document describes the Exploration Medical Capability's (ExMC) research strategy to characterize the risk that medications will degrade during a prolonged spaceflight, resulting in a loss of active pharmaceutical ingredient (API) or accumulation of impurities. The scope of the ExMC pharmaceutical strategy is the chemical and physical stability of medications with respect to spaceflight. Risks associated with altered pharmacokinetics (PK), pharmacodynamics (PD), and efficacy are addressed elsewhere. The ExMC pharmaceutical stability strategy is applicable to space missions of any duration; however, the primary focus is for Mars preparatory and planetary design reference missions (DRMs). The *long-term goal* of this strategy is to characterize and reduce the collective risk[1] of ineffective or toxic medications during long-duration exploration spaceflight. The overall objective is to identify and characterize the key mechanisms that contribute to drug degradation during spaceflight. Successfully completing this objective will enable methods to be developed and validated to prolong drug stability under spaceflight conditions and ensure that the medications constituting the exploration candidate formulary (ECF) are safe and effective for the duration of the proposed mission. The strategy is formulated based on the working hypothesis that *environmental factors* (i.e., moisture, $O_2$, ionizing radiation, and $CO_2$) increase rates of *degradation* (relative to terrestrial conditions) of *susceptible* pharmaceuticals. This hypothesis is supported, in part, by a quantitative reanalysis of 6 previous

[1] Each medication has its own time-dependent risk of that it will degrade over time and not meet quality standards. The collective risk applies to the formulary, which is different than the risks of degradation for individual drugs.

NASA spaceflight drug stability studies (Reichard, et al., 2023), as well as U.S. Food and Drug Administration (U.S. FDA) guidance, U.S. Pharmacopeia (USP) standards, and close communications with the U.S. FDA Division of Product Quality Research (OPQ).

This strategic plan will investigate mechanisms through which spaceflight environmental factors affect pharmaceutical stability over time and will develop mechanism-based countermeasures to mitigate the risk of drug deterioration. This will mitigate the NASA Human System Risk Board risk, which is summarized as:

"…there is a possibility that provision of a safe and effective drug treatment will be significantly limited, impacting crew health and performance."

The ExMC pharmaceutical stability strategy will produce evidence to characterize stability risks for most pharmaceuticals applicable to human spaceflight, not just those products that are tested. This evidence can be used to identify the environmental factors that are the most significant contributors to the degradation of medications and to identify and implement countermeasures to reduce the effects of these factors. Fully implemented, this strategy will close the Human Research Program (HRP) knowledge gaps relevant to medication stability during exploration space missions, which are listed below:

- *Pharm-101: We need to determine the optimal packaging/storage strategy for medications in space that balances the needs of mitigating toxicity, preserving effectiveness, and minimizing resource "costs" (mass, volume, power, etc.).*
- *Pharm-201: We need to establish an exploration formulary that identifies medications with maximal clinical benefit and minimal resource "costs" (mass, volume, etc.).*
- *Pharm-301: We need to categorize all medications that are included in the iterative ECF based on the current state of knowledge of their effectiveness and safety in the spaceflight environment.*
- *Pharm-401: We need to perform further research to understand and characterize the API and degradation profiles of medications for which we have low to moderate confidence in their safety and effectiveness for exploration missions.*

The *rationale* for the pharmaceutical stability strategy is that evidence-based countermeasures that prolong drug shelf life under spaceflight environmental conditions will reduce uncertainty ("gaps") for ineffective *and* toxic medications during long-duration exploration missions and reduce the time-dependent risk of drug failure. This strategy will complete the following *specific aims* to test the central hypothesis and achieve the expected outcomes:

Aim 1. *Characterize the Expected Shelf Life of ECF Pharmaceuticals and Estimate Time-Dependent Failure Rates.* NASA does not have access to shelf-life data for most exploration formulary medications. A collaborative interagency agreement (IAA) with the U.S. FDA is proposed to collect proprietary data submitted to the FDA by pharmaceutical manufacturers. Through this collaboration, NASA will gain information on drug shelf life, drug degradation rates, and formulations that contain excipients that influence drug shelf life.

Aim 2. *Develop a Dynamic Drug Data Architecture for "Stoplight" Classification of Drugs.* Each pharmaceutical product's susceptibility to degradation is a function of the drug's ingredients and the environmental factors acting on the drug product. NASA is collecting data pertinent to each formulary medication's chemistry, safety, and stability. To accomplish this aim, ExMC will develop a data architecture that will collect, organize, structure, and store curated pharmaceutical data. These data will be used to computationally classify the suitability of each drug product for exploration space missions using a "stoplight chart" (i.e., red, yellow, or green).

Aim 3. *Identify Protective Drug packaging and Repackaging and Select Optimal Formulation for Solid Oral Dosage Forms (SODF) that will Extend their Spaceflight Shelf Life.* SODF are commonly repackaged into zip-lock bags to reduce their mass and volume for spaceflight. Nonprotective drug repackaging exposes drugs to environmental factors that accelerate degradation of susceptible drugs. To achieve this aim, terrestrial stability studies will determine how current and alternative repackaging procedures impact the degradation rates and the failure probability of representative drugs. These studies will provide a basis for testing spaceflight stability of drugs.

Aim 4. *Assess How Ionizing Space Radiation Affects Drug Degradation.* The susceptibility of drugs to ionizing radiation is influenced by several factors, including absorbed dose, drug formulation, and exposure to environmental factors. To achieve this aim, the effects of ionizing space radiation on susceptible liquid and solid drugs will be evaluated, and the effectiveness of protective repackaging to prolong shelf life of repackaged drugs will be tested.

A. EXPECTED OUTCOMES AND IMPACT

The expected outcomes of successfully *completing* the proposed research aims include the following:

- *A stoplight chart that classifies each exploration formulary drug based on the current state of knowledge of their effectiveness and safety in the spaceflight environment*

- *Identified critical environmental factors that facilitate degradation of medications*
- *Confirmed mechanism-based pathways through which spaceflight environmental factors mediate drug degradation*
- *A proposed ECF that comprises the most stable formulations of each evaluated drug (expected FY2027)*
- *Characterized effects of spaceflight ionizing radiation on drug failure risk*
- *A comprehensive database of drug stability data for research and operational use/reuse*
- *Guidelines for selecting the most stable brands of drug products*
- *Generalized prediction of time-dependent risk of drug failure based on a random sample of drugs in the ECF*
- *Risk-based limits for exposures to hazardous degradation impurities*
- *Validated countermeasures to preserve or to extend the shelf life of repackaged medications relative to the shelf life of medications repackaged using current practices*

The *positive impact* of this work will be a formulary of pharmaceuticals with a defined risk of failure, as informed by USP quality specifications, and specific countermeasures that mission planners can implement to help ensure the therapeutic efficacy and safety of the pharmaceuticals.

B. SIGNIFICANCE

*1. IMPORTANCE OF THE PROBLEM TO BE ADDRESSED*

NASA and its international partners are developing capabilities to conduct exploration space missions beyond Earth orbit. A roundtrip mission to Mars will exceed 2 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. Future exploration class spaceflight missions will therefore need to be increasingly Earth-independent. Long-duration space missions will expose crews to new and increased hazards that could increase the potential for adverse medical conditions. Pharmaceuticals are a critical resource to help maintain crew health and performance and manage highly probable or potentially severe medical conditions during deep-space missions. Concurrent with the increased risks of medical conditions, the necessary pharmaceutical resources will be constrained by mass, volume, and power requirements (Patel, et al., 2020). Therefore, pharmaceuticals must be carefully selected and

packaged for long-duration missions to ensure they remain stable and retain efficacy throughout the entire timeframe of exploration missions (Hanson, et al., 2019).

To date, NASA has supported 6 spaceflight drug stability studies. All of these studies focused on repackaged solid dosage forms (tablets or capsules). Only the study by Du et al. (2014) included a small subset of non-solid formulations. It is well established that, in the absence of protective packaging, atmospheric factors, particularly humidity and $O_2$, can facilitate chemical and physical degradation of most pharmaceuticals (e.g., (Asafu-Adjaye, et al., 2011; Berendt, et al., 2012; Khan, 2009; Waterman, et al., 2002; Yang, et al., 2010). This is the basis for U.S. FDA guidance on drug packaging (U.S. Food and Drug Administration (FDA), 2017; U.S. Food and Drug Administration (FDA), 2020a), the USP requirements for container quality (United States Pharmacopeia, 2020a; United States Pharmacopeia, 2020b), and the U.S. FDA guidance on shelf-life testing (U.S. Food and Drug Administration (FDA), 1999; U.S. Food and Drug Administration (FDA), 2003). A quantitative reanalysis of data from all 6 studies indicated that repackaging may have contributed to the premature failure of several medications in the control arm of a prospective spaceflight drug stability study (Du, et al., 2011). Of the 34 drugs in the terrestrial control group, 11 failed, based on API content, prior to the label expiration date. Of the 11 failed medications, 9 were repackaged oral drugs, whereas the remaining 2 were non-solid topical medications (suppository and cream). The fact that 41% of control solid oral drug products failed prematurely (i.e., failed to meet USP drug content prior to their labeled shelf life) is incredibly consequential because manufacturers guarantee that their products meet quality specifications throughout the entire shelf life of their product (Reichard, et al., 2023).

For the few drugs with publicly available data on shelf life, these drugs substantially underperformed in NASA studies, both in terrestrial and spaceflight conditions, compared to the shelf life reported by the U.S. FDA (Lyon, et al., 2006). The baseline probability of drug failure, independent of spaceflight, accounts for the largest portion of the overall failure risk. Because most spaceflight medications are repackaged, it is critical to determine how drug repackaging affects the susceptibility of a drug to degradation, and the extent to which environmental factors (e.g., ionizing radiation, relative humidity (RH), $O_2$, $CO_2$) impact time-dependent failure. However, no NASA-sponsored study has identified which factor(s) contributes the most to the increased rate of deterioration, or whether current repackaging practices contribute to reduced shelf life. Mechanistic investigations are necessary to identify effective countermeasures that prolong medication shelf life, ensure therapeutic efficacy, and minimize potential health risks of degradation impurities. In the absence of this information, it is impossible to fully

determine the likelihood of drug failure (as defined under USP standards) or to adequately assess the therapeutic and toxicological consequences therein. Furthermore, mechanistic information supports risk-based clinical decisions (i.e., risk-benefit analysis) on the use of medications that will expire prior to the completion of a mission.

An understanding of drug stability is essential for characterizing risks attributable to PK and PD. Chemical degradation decreases therapeutic efficacy of a drug because concentrations of the API in the blood and tissue are reduced (PK) and PD activity is therefore decreased. Physical degradation can impact a drug's behavior, such as its dissolution rate, which governs the rate a drug is released from solid dosage forms. If the dissolution rate is increased, the active ingredient may be released too quickly, resulting in elevated blood concentrations and an increased risk of side effects. If the API is released too slowly, then blood concentrations are reduced, increasing the risk of therapeutic failure. Both chemical and physical deterioration occur due to the interaction of drug ingredients with environmental factors. Thus, the ExMC pharmaceutical strategy will evaluate both chemical and physical characteristics of drug stability.

## *2. REVIEW OF THE RIGOR OF PRIOR SPACEFLIGHT PHARMACEUTICAL STABILITY RESEARCH*

Six separate studies have evaluated the spaceflight stability of 42 individual APIs from 44 different drug products (inclusive of different formulations containing the same API or combinations of APIs). All these studies focused on repackaged SODF. None of the studies included pair-matched samples in manufacturer packaging as a control for repackaged drugs. For this reason, no data exist to evaluate the effect of drug repackaging practices on drug stability, and therefore it cannot be determined if the primary factor(s) contributing to accelerated degradation or altered impurity profiles associated with spaceflight are simply related to the differences in atmospheric conditions of the different storage conditions, or due to intrinsic conditions associated with spaceflight, such as ionizing radiation.

A comprehensive analysis of all available spaceflight drug stability studies is provided in the ExMC Drug Stability Evidence Report (Reichard, 2023). Fundamental conclusions from this body of evidence includes the following:

- *None of the previous studies included a zero timepoint to set a baseline against which changes in drug quality can be compared over time. Baseline controls are especially important for longitudinal experiments when testing the hypothesis that a treatment condition affects the time-dependent rate of change for a measured parameter (e.g., drug potency).*

- *Most (5 of 6) NASA-supported drug stability studies examined single timepoints. Cross sectional studies cannot evaluate time-dependent changes, such as the change in drug potency during a period of drug storage. At least 3 timepoints are required to test the hypothesis that spaceflight alters the rate of drug degradation, whereas multiple timepoints are required to characterize the shape of the degradation curve.*

- *Most (5 of 6) NASA-supported spaceflight drug stability studies did not include matched terrestrial controls. In the absence of control samples, no conclusion can be made about the relative effects of any treatment condition.*

- *Some NASA-supported drug stability studies that describe increased drug degradation during spaceflight do not describe the analytical methods used or precisely which pharmaceutical products were tested[2]. The ExMC stability strategy described in the current document will strive for complete transparency and all data that are not deemed to be restricted by the Agency will be made publicly available for reuse and reanalysis.*

- *This ExMC stability strategy will overcome experimental design challenges by performing longitudinal stability studies with lot-matched controls, baseline measurements of drug content (impurities and potency), multiple time points, and independent sample replicates.*

## *3. SIGNIFICANCE OF THE PROPOSED RESEARCH*

The research proposed in this strategy includes studies with high methodological, scientific, and statistical consistency. Rigor is vital because risk-based decision-making requires data that minimizes uncertainty attributable to both the absence of knowledge, and the technical or experimental variability. A common limitation of previous spaceflight drug stability studies is that they all used a descriptive observational study design. Such studies can identify only that an association exists between a condition and an outcome; they cannot give insight into causation or test hypotheses (Aggarwal and Ranganathan, 2019). Therefore, prior studies do not elucidate *why* exposure to spaceflight affects stability of some drugs; instead, they only establish that there *may* be an association. In addition, understanding the

[2] Different manufacturers producing equivalent drug products may use very different ingredients in their formulations (i.e., binders, disintegrates, granulating agents, glidants) and different manufacturing techniques (i.e., wet vs. dry granulation, tablet compression force, applied coating and films etc.). These differences can substantially affect the efficiency of the extraction of drug products for analytical analysis. If extraction of the API is inefficient, drug potency (API content) is underestimated. Therefore, USP methods should be optimized for each brand and NOT assumed to be equally efficient across different brands of equivalent products (U.S. Food and Drug Administration (FDA), 2015; United States Pharmacopeia, 2019a; United States Pharmacopeia, 2022).

chemistry underpinning “why” some drugs appear to degrade during spaceflight is essential because this mechanism dictates which countermeasures will be effective for slowing degradation and prolonging the shelf life of drugs.

## III. *APPROACH*

### A. AIM 1. CHARACTERIZE THE EXPECTED SHELF LIFE OF EXPLORATION CANDIDATE FORMULARY (ECF) PHARMACEUTICALS AND ESTIMATE TIME-DEPENDENT FAILURE RATES

#### *1. INTRODUCTION*

The U.S. FDA maintains databases containing proprietary information on the stability and formulation of all drug products marketed in the US. These data would significantly assist NASA HRP’s efforts to close knowledge gaps related to the risk of ineffective or unsafe pharmaceuticals. These data could inform selection of drug products with the longest manufacturer’s shelf life, products with validated shelf-life extensions, and products that do not form hazardous impurities as they degrade, and could identify products containing excipients that increase stability, among other uses. The *objective* of Aim 1 is to identify drug features that predict degradation rate. To attain this objective, the *working hypothesis* that specific pharmaceutical excipients mechanistically facilitate the degradation of finished drug products will be tested. The *rationale* is that successful completion of Aim 1 will enable the selection of medications best suited for exploration-class space missions *before* they are removed from manufacturers' primary packaging. As detailed in the Research Design, this objective will be attained by performing qualitative and quantitative analyses of brand-specific drug stability data collected from the U.S. FDA. After Aim 1 is complete, it is *expected* that NASA will have: (i) manufacturer shelf-life data for each drug product evaluated; (ii) statistical information to identify problematic excipients that facilitate drug degradation, and which should be avoided for pharmaceuticals included on the ECF; (iii) data on expected stability that will be used to generate the stoplight decision framework (Aim 2) to classify suitability of drugs for all DRMs; (iv) information on potentially hazardous degradation products and their formation pathways; and (v) information to prioritize tests of pharmaceutical stability in terrestrial and spaceflight settings (Aim 3).

#### *2. REVIEW OF RELEVANT INFORMATION AND LITERATURE THAT JUSTIFY RESEARCH STUDIES*

In the US, all drugs must be labeled with an expiration date, which is the final day the manufacturer guarantees full potency and safety of a medication. Because the expiration date is based on the day the drug was manufactured, it changes with production batch (lot). Expiration dates are calculated based on a product

shelf life, which is determined experimentally by the drug labeler[3] (i.e., manufacturer, repackager) using both long-term and accelerated stability studies. Because shelf life is experimentally determined for each finished drug product, unlike the expiration date, the shelf life is the same for all batches produced and does not change. It is common for manufacturers to produce multiple batches of product during a single manufacturing campaign, and then slowly release that product from long-term storage until the next campaign (Shah, 2004). The distinction between shelf life and expiration date is important because in the US no requirement exists for manufacturers to disclose shelf life of a medication, and expiration dates cannot reveal shelf life without knowledge of the manufacturing date. The situation is different in the European Union (EU) and United Kingdom (UK) because labelers are required to disclose shelf life in the summary of product characteristics, which is similar to the manufacturer's package insert in the US.

ExMC has no reliable information regarding the shelf life of most drugs in the candidate exploration formulary, and only a few drugs have shelf-life extension information. Most of the drugs with shelf-life information are European brands and the shelf-life data were collected from the Electronic Medicines Compendium (emc®) website. A "functional" shelf-life estimate is available for several drugs, which is determined as the duration from the date the drug was repackaged for spaceflight to the drug's expiration date. Functional shelf life is substantially shorter than the manufacturer's shelf life. For a handful of other drugs, shelf-life estimates were obtained from nonauthoritative sources, such as research publications. Consequently, a clear ***need*** exists for the manufacturer's shelf-life information and stability data for the drugs on the ECF.

Before a drug can be sold in the US, the drug labeler must submit stability testing data to the U.S. FDA supporting their claim of the product's shelf life. These data include results from both accelerated and long-term stability studies. Stability studies are the gold-standard for characterizing degradation rates, and the manufacturer's shelf life is the benchmark for the expected shelf life of any drug during spaceflight. The manufacturer's shelf life typically underestimates the actual shelf life of a drug (see below). However, the drug content data (API potency and impurities), obtained from stability studies submitted to the FDA as part of a market application or drug master file can be used to estimate the probability of time-dependent failure and degradation rate. Such information can inform models that estimate the probability of expiration and failure over the course of a spaceflight mission, assuming medications are properly packaged and stored.

[3] A drug labeler is any company that manufactures, repackages relabels or distributes (under its own name) a drug product.

Interactions between drug and ingredients can directly affect API stability. These interactions can be due to direct interactions between the API and excipients (incompatibilities) or reaction of the API with excipient contaminants (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, *they are not chemically inert* (Narang, Desai, and Badawy, 2012; Waterman, Adami, and Hong, 2004). Several commonly used excipients often contain trace levels of reactive aldehydes, peroxides, or nitrites (U.S. Food and Drug Administration (FDA), 2020b; Waterman, Adam,i and Hong, 2004). For example, polymeric ethers (i.e., polyethylene glycols (PEGs), polyethylene oxides, polysorbates, etc.) and polyvinyl pyrrolidone (e.g., Povidone and Crospovidone) (Waterman, Adami, and Hong, 2004) are commonly associated with peroxides, which can be formed through oxidative degradation of the excipient (i.e., aging). Peroxides 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 established properties of the excipients. Significantly, environmental factors, most importantly temperature, can directly influence the rate and extent of degradation reactions.

Brands must be considered when selecting a pharmaceutical formulary for long-duration exploration missions because manufacturers use different excipients when formulating equivalent drug products[4]. Excipient selection can significantly affect the stability of finished drug products. The Shelf-Life Extension Program (SLEP)[5] showed large variations in shelf-life extension times for some drugs, such as ciprofloxacin tablets (242 lots tested with a range of 12 to 142 months) and 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 that excipients can have a dramatic effect on the stability of an API. Ibuprofen brands containing polymeric excipients (i.e., PEG polysorbate 80) degraded 5–30% within 3 weeks under accelerated testing conditions; brands without these ingredients showed a negligible change from baseline (Cory, Harris, and Martinez, 2010).

[4] A generic drug manufacturer may produce multiple equivalent products containing different ingredients and sold under different trade names.

[5] SLEP, a joint effort of the U.S. FDA and the Department of Defense (DoD), 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).

The U.S. FDA requires all drug manufacturers to demonstrate drug stability before marketing a drug product, and equivalent drug products from different manufactures contain different excipients and have different types of packaging. FDA Guidance for Industry defines the contents of the "stability data package", which the drug labeler must submit to the U.S. FDA as part of either a new drug application (NDA) (U.S. Food and Drug Administration (FDA), 2003; U.S. Food and Drug Administration (FDA), 2004) or an abbreviated NDA (ANDA) (US FDA,2013). Stability studies must be 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). The labeler derives a shelf-life period from these studies. However, many drugs have been shown to have shelf lives that are much longer than the shelf life approved by the FDA (Khan, et al., 2014; Lyon, et al., 2006; Stark, Fawcett, and Tucker, 1997). The reason is because a drug's shelf life is the minimum period that the labeler guarantees that the marketed drug will meet quality specifications. However, shelf lives are conservative and account for practical business considerations, including added development cost associated with longer stability studies, increased production costs involving more protective packaging containers, manufacturing supply chain factors, market strategy and corporate profits.

Recognizing that labelers have little incentive to seek shelf-life extensions, the FDA administers the SLEP for the U.S. Department of Defense (DoD). A 2006 study evaluated a subset of drugs tested under SLEP and showed 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 SLEP have increased and now exceeds the 122 drugs reported by Lyons et al. (2006). Furthermore, the FDA has now accumulated over 35 years of data since the start of the program, which is nearly double the period reported by Lyons et al. 2006. This is the reason NASA is pursuing a collaboration with the U.S. FDA to obtain and analyze stability data for drugs in the ECF.

## *3. RESEARCH DESIGN*

### a. *Unique dataset*

Shelf life and formulation data from the FDA are confidential proprietary industry data that are only accessible within the FDA. The information that the FDA can make available would be unprecedented and would help NASA immeasurably.

### b. *Data Access*

Under the proposed NASA-FDA statement of work (SOW), a dedicated FDA-based researcher will be funded by ExMC to collect required data from available FDA databases. Access to FDA databases is restricted

to FDA personnel. For this reason, the FDA will hire or otherwise allocate staff to perform the tasks proposed under Aim 1 (Appendices 1 and 2).

SLEP operates under the US Department of Health and Human Services Center for Disease Control and Prevention and has custody of the SLEP data. The FDA maintains the database of collected stability results. Access to SLEP data will be obtained from the US Department of Health and Human Services Center for Disease Control and Prevention and provided through partnership with FDA.

c. *Data Types to be Acquired*

The information will be collected from 2 different FDA sources, as listed in the SOW (Appendix 1). The 2 sources are the FDA/DoD SLEP and the manufacturer's drug information database. The SLEP contains data regarding drug shelf life *after* the manufacturer's expiration date, and results from mathematical models that predict drug quality during a set extension period. The SLEP data are maintained in a relational database that is expected to facilitate ease of data access, and data can be acquired through an application programming interface (also known as an API but designated here as "API software" to avoid confusion with active pharmaceutical ingredient, which is also abbreviated as "API", as noted above). The manufacturer's drug information database(s) consists of any "drug master file" they submitted to the FDA in support of NDA or ANDA. These documents, which are typically PDF files, contain shelf-life information that were determined from long-term and accelerated stability testing studies, as well as formulation ingredients and impurity data. Stability testing results contained in NDAs and ANDAs also include results of mathematical models that are used to support the FDA-approved shelf life (U.S. Food and Drug Administration (FDA), 2004). In all cases (both SLEP and the manufacturer's data), predictions of shelf life are obtained from stability testing studies on finished drug products in *sealed manufacturer's containers*.

d. *Exploration Candidate Formulary (ECF)*

Successful completion of Aim 1 will require NASA consensus on a formulary of candidate drugs for exploration space missions. Currently, no consensus on the candidate formulary exists. At least 6 separate, overlapping lists of pharmaceutical resources exists for exploration missions that have been compiled as a basis for a drug data repository:

- *ExMC Level of Care IV/V drug list. This list of drug products was compiled by the NASA Space Medicine Operations pharmacists as a resource to support the ExMC Clinical Science team. It is based largely on the drugs currently available in the ISS medical kits.*

- ***Approved Orion formulary.*** *This is a list of medication resources that will be implemented for the first crewed Orion missions. Access to this list of medications is restricted and is currently unavailable for evaluation or analysis due to data sharing concerns.*
- ***Human landing system medication formulary.*** *The human landing system formulary was compiled by Space Medicine Operations to support upcoming lunar missions. Access to this list of medications is restricted and is currently unavailable for evaluation or analysis due to data sharing concerns.*
- ***ISS Medical Accessory Kit (IMAK).*** *This kit consists of medications personalized for individual crew members of the ISS. The available list of IMAK medications is anonymized and was obtained through the NASA Life Sciences Data Archive in 2021. No information is provided on how many crewmembers this list of medications was intended for, or the demographic of crewmembers (e.g., sex, age, experience, mission duration, mission dates covered). For these, it is uncertain if the available IMAK drug list can be considered representative of current or future crewmembers.*
- ***ISS Formulary.*** *This list of medication was made available to ExMC through a 2022 Freedom of Information Act (FOIA) request submitted by a group outside of NASA. This is the second FOIA request for this information that the ExMC Element is aware of. The first FOIA request was filed in 2015 and the information was released in 2016.*
- ***Condition Resource Trace (CRT) list****. This list was compiled by the ExMC Clinical Science Team from Clinical finding forms (CliFFs) and represents the medication resources required to treat anticipated medical conditions during exploration space missions.* ***This list is regarded as the current ExMC ECF.***

Key details needed to evaluate stability include the API, dosage form ( e.g., solid, aqueous, semi-solid, etc.), formulation (i.e., ingredients and concentrations), manufacturer, and packaging (Bokser and O'Donnell, 2013). In support of Aim 1, the various formulary lists have been consolidated to generate a master list consisting of all formulary medications and previously tested drugs that ExMC Element is aware of. Each drug is associated with supporting information and stability data (See Aim 2 for details). This master list comprises the ExMC Drug Data Repository (DDR), which is discussed in detail in **Aim 2.**

The current[6] DDR consists of more than 466 drug formulations and more than 244 APIs from 9 formulary or research lists, including the ExMC ECF. The ECF consists of 279 drug products and 184 unique APIs. Of the drug products in the ECF, 98 are tablets, 22 are capsules, 82 are solutions or suspensions, 3 are

[6] As of December 2023

aerosols, and various ointments (~5), creams (9), gels (4), patches, strips, suppositories, and others are included. Of these drugs, ~50% are solids dosage forms (capsules, tablets, lyophilized powders), 45% are SODF, 36% are liquid formulations (injectable solutions, otic solutions, etc.), 24% are nonsolid formulations (creams, ointments, suppositories, etc.) and 16% are miscellaneous (topical patch, aerosol inhaler, etc.). Because NASA is in the early stages of planning for long-duration exploration missions, it is expected that the exploration formulary will grow and change as new drugs are added to keep pace with changes in clinical standards of care and as factors affecting drug stability are characterized and mitigated.

e. *Selection of Drugs for Evaluation and Testing (a.k.a. "prioritized" subset)*

Due to time and resource constraints, it is unlikely that the full set of required attributes for the entire list of exploration formulary drugs can be obtained from the U.S. FDA databases. Therefore, ExMC researchers will acquire data from a subset of drugs (50–60 drugs total). To meet the objective of Aim 1, researchers will prepare 2 lists of drugs for data collection. The first list will consist of specific drug products and dosage forms in the ExMC formulary that are also in the SLEP database. Because this list will not be a random subset of the full range of drugs on the formulary, statistical interpretation of these data may be limited.

The second list will consist of drugs randomly selected from the formulary. Random selection is expected to provide a representative sample of formulary drugs enabling broad statistical interpretation. Stability-related data will be collected for this list of drugs from manufacturer's NDA and ANDA submissions. Randomized selection allows valid statistical inferences about the larger group from which a subset is drawn. Selecting drugs based on arbitrary or heuristic criteria, such as "clinical importance" or "commonly used spaceflight medications" will be incompatible with statistical inference because all statistical methods fundamentally assume that any selected subset is representative of the population from which they are selected. Although it may seem prudent to rely on experience or some preferential criteria when selecting the drugs, this will limit analysis of the results; however, such criteria can be applied post hoc for analysis and evaluation if there are concerns that information on specific drugs has been missed. Random selection helps ensure that the subset is an unbiased representation of the larger group. For each API selected, data will be gathered on all dosage forms (capsules, injectable ointment, etc.) in the formulary that contain that API. Potency/concentration will be ignored in the selection process because these attributes do not affect the kinetics of degradation or excipient-API interactions (Almalik, Nijhuis, and van den Heuvel, Edwin 2014; Altan

and Raghavarao, 2003; van den Heuvel, et al., 2011).[7] Data will be retrieved for as many drugs in the formulary as time and resources permit.

f. *Data Retrieval and Evaluation*

During this project's data mining pilot phase, ExMC will seek to "discover" the availability and quality of data for 6 –10 formulary drug products and will assess the suitability of this data for subsequent analysis. The focus of the pilot phase is not to complete the acquisition of data. Rather, the focus is to develop a protocol for acquiring data that will be applied consistently throughout the subsequent data retrieval phase to limit bias and ensure consistent data capture. During the pilot phase, the data retrieval processes will be iteratively refined, and methods will be developed to enable structured data to be stored for analysis. API software or similar approaches are preferred to retrieve the data, with data saved as JSON, XML, or other suitable or convenient formats.

A prioritized approach is proposed to retrieve data from the SLEP database and U.S. FDA NDA, ANDA, and drug master files. The SLEP database will be mined for information first because the data are in a format that is easily accessible. The highest priority is retrieval of brand-related shelf life, shelf-life extension information, and stability testing results will be assigned. The next priority is obtaining information on the inactive ingredients of each drug product based on National Drug Code (NDC) or RxNorm Concept Unique Identifier (RxCUI; see *Drug identifiers* section III. B. 2. d. 4) a). The third priority is to acquire the remaining information listed in Appendix Table 1 (e.g., ionizing radiation including gamma-ray and X-ray and electron beam stability, if available).

After completing the pilot phase of data collection, information will be sought on as many drugs from the NASA ECF as possible; the total number of drugs assessed will depend on the complexity of the information retrieval process. In addition, a prioritized subset of manually retrieved data (about 50–60 drugs mutually agreed upon by NASA and FDA) will be obtained. Information that requires manual retrieval should be obtained for at least 8 medications per month from the prioritized medication list. Data and information that support predictive stability modeling are of particular interest.

g. *Statistical and Descriptive Analysis of FDA Shelf-Life Data*

*1) Descriptive Analysis*

[7] This assumption does not apply to degradation mediated by ionizing radiation where API concentration does influence degradation rate.

Researchers will collect data from different manufacturer brands (for each drug dosage form, e.g., doxycycline lyophilized injectable powder or oral capsule) to establish the brands with the longest manufacturer's shelf life and the shelf life that extends the most beyond expiration date.

*2) Statistical Methods*

Statistical inference on the NASA formulary will be performed using a randomly selected subset of formulary drugs including those not in the SLEP study. Statistical tests may include the following:

- *Ingredient analysis. Unsupervised machine learning will be used to evaluate ingredients associated with reduced drug stability. Least Absolute Shrinkage and Selection Operator regression allows shrinking parameter space (ingredients) to be the most impactful for building linear models to predict degradation rate. Principal component analysis can likewise be used for dimensional reduction and control parameter collinearity to identify the most impactful ingredients on stability.*
- *Failure-time analysis. Parametric Bayesian accelerated failure time model (Reichard, et al., 2023). This will provide the cumulative risk of drug failure, across all formulary drugs, as a function of time.*
- *Rate of degradation. For individual brand/lots, linear regression of the natural log (ln) of concentration or potency will be used to estimate degradation rate. Time-dependent drug failure based on API potency will be calculated by comparing the regression curve's lower 95% confidence interval to the USP threshold limit (U.S. Food and Drug Administration (FDA), 2015). Percent API remaining at any point in time will also be estimated based on the lower 95th percent confidence interval.*

*4. POTENTIAL PROBLEMS, RISKS, AND ALTERNATIVES*

a. *FDA Data Collection*

FDA researchers agreed in 2021 to make the information listed in Appendix 1 available to ExMC; however, due to the COVID pandemic and other public health priorities, the IAA has not been finalized by the FDA as of December 2023. The FDA and individual drug manufacturers are the only sources of drug shelf-life data and stability data for medications marketed in the US. Alternative source of non-U.S. shelf-life information exist. The UK Medicines and Healthcare Products Regulatory Agency together with the European Medicines Agency (EMC: the UK and EU equivalents of the FDA, respectively) maintain the emc®, a database of public drug information that includes information on drug shelf-life of European drug products. Although emc®-listed drug products are not manufactured by the same manufacturers that produce equivalent drugs for the US, these data have been collected in the DDR to support shelf-life approximations for NASA formulary

medications. Likewise, Medthority, MedSafe (New Zealand (NZ) and the Australian Register of Therapeutic Goods are possible sources of shelf-life information. One limitation of relying on non-U.S. drug data is that most drug products on the exploration formulary do not have European Medicines Agency (EMA) information shelf-life. Additionally, one-to-one equivalence of drug products is not always possible because manufacturers, formulations and packaging of European products often differ from comparable US products.

If shelf-life data cannot be obtained from the U.S. FDA, it may be worth contacting other national regulatory agencies, including Canada, Australia, or the UK to explore collaboration. Health Canada could be especially useful because Canada and the US share many of the same pharmaceutical manufacturers. Because these agencies, like the U.S. FDA, have also adopted the International Counsel on Harmonisation (ICH) guidance directly, the drug stability data should be comparable for similar products. A major limitation of relying on regulatory agencies outside the US for stability data is that drug products sold elsewhere may not be produced by the same manufacturers as the products sold in the US. Therefore, these products may differ in formulation and packaging. For this reason, these data may be more appropriate for qualitative analysis than for identifying specific products most suitable for exploration space missions. In addition, the FDA is the only source of shelf-life extension data, which is distinct from shelf-life information because extension reflects actual degradation rate, not an arbitrary period of time during which a manufacturer guarantees stability of its marketed product, which is generally much shorter than the actual stability of the product (Lyon, et al., 2006).

b. *Prioritization List for Data Collection*

ExMC researchers will select a list of drugs from a comprehensive ECF; however, at this time, no consensus exists on the candidate formulary and the pharmacopeia continues to evolve as the ExMC Clinical Science Team determines medical conditions that may arise during exploration missions and recommends adding resources. As a result, it is expected that the ECF will grow and evolve throughout this project. The candidate formulary used for data collection will include all drugs on the CRT resource list at the time the project starts.

c. *Statistical analysis of degradation rate and failure time*

It is difficult to estimate the number of drugs required to test the null hypothesis that an excipient will impact the stability of a drug because the baseline time-dependent failure rate for drugs in manufacturer containers (events per time) is unknown. In addition, the extent of censoring in the manufacturer's stability study data or the SLEP data is unknown. It is reasonable to expect that the data the manufacturer submits to

U.S. FDA in support of their marketing application will be highly right censored (i.e., no observed failures within the timeframe of the stability test) because the U.S. FDA only requires long-term stability testing lasting a minimum of 12 months. Drugs on the NASA ECF are not expected to fail in less than a year; manufacturers can perform lengthier stability studies; however, they typically have little incentive to do so (Khan, et al., 2014).

d. *Relevance of Manufacturer Stability and Shelf-Life Data to Spaceflight Conditions*

It is possible but unlikely that the manufacturer's shelf life will be irrelevant for drugs stored in the spaceflight environment, which differs from terrestrial conditions such as elevated levels of ionizing radiation and $CO_2$, and possibly other factors. Radiation will be addressed in Aim 4. Any effects of $CO_2$ on repackaged drugs would likely be attributable to ingress of atmospheric conditions into packaging, which is addressed in Aim 3. Aside from these concerns, elevated temperature and humidity are the major factors that affect drug stability. The FDA requires drug labelers to perform stress testing of medication under conditions of elevated temperature and humidity that exceed spacecraft environmental tolerances; therefore, manufacturer's stability data are likely highly relevant to spaceflight, and can be used to identify degradation-prone APIs. Consequently, FDA stability data will be useful to prioritize APIs for further testing in Aim 3.

## *5. NOTIONAL TIMELINE AND BENCHMARKS FOR SUCCESS*

The timeline of the project begins after the FDA approves the IAA and the contract is fully executed.

Table 1. Aim 1 Notional timeline.

| Proj. month / Task | FY 1 | | | | | | | | | | | | FY 2 | | | | | | | | | | | | FY 3 | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 1 | 2 | 3 | 4 | 5 | 6 |
| Hire FDA Fellow | X | X | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Pilot Drugs to FDA | X | X | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Orise Fellow | | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | | | | | | | | | | |
| Pilot Data Collection- FDA | | | | X | X | | | | | | | | | | | | | | | | | | | | | | | | | |
| Prelim. NASA Data Review | | | | | | X | | | | | | | | | | | | | | | | | | | | | | | | |
| Final Drug List to FDA | | | | | | X | | | | | | | | | | | | | | | | | | | | | | | | |
| Data collection - SLEP | | | | | | X | X | X | X | X | X | | | | | | | | | | | | | | | | | | | |
| Data collection - FDA | | | | | | | | | | | | X | X | X | X | X | X | X | X | | | | | | | | | | | |
| Data Analysis | | | | | | | | | | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | | | | | |
| FDA Manuscript 1 Draft | | | | | | | | | | | | | | | | | | | | | X | X | X | X | X | X | X | X | X | |
| Strategy Update | | | | | | | | | | | | | | | | | | | | | | | | | | | | X | X | X |
| FDA Manuscript 1 Submission | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | X |

*Data Mining of U.S. FDA databases for drug shelf life and stability data. Timeline starts from project kickoff (months). Abbreviations: Orise = Oak Ridge Institute for Science and Education (ORISE), FDA = U.S. Food and Drug administration.*

## *6. EXPECTED OUTCOME*

Aim 1 will provide detailed insight into the length of time medications are stable within sealed manufacturer's packaging (expected shelf life), environmental factors that facilitate drug degradation (i.e., heat, humidity), dosage form-dependent stability, and the effect of excipients on long-term drug stability. These data will enable basic rules to be established for selecting spaceflight drug products and repackaging. Such data should provide concrete shelf-life benchmarks that can be used to evaluate protective drug repackaging methods in terrestrial and spaceflight stability studies.

## B. AIM 2. DEVELOP A DYNAMIC DRUG DATA ARCHITECTURE FOR "STOPLIGHT" CLASSIFICATION OF DRUGS

### *1. INTRODUCTION*

The data architecture is a blueprint for transforming collected data into the information needed to achieve a strategic plan. Presently, no NASA or HRP data architecture exists to assess the safety and effectiveness of spaceflight medications. A comprehensive data architecture is essential to guide the collection, processing, utilization, and preservation of pharmaceutical data that will support efficient, evidence-based decision making. The objective of Aim 2 is to implement a data architecture that can automatically classify each formulary drug according to the state of knowledge of the drug's suitability for exploration space missions. The approach used to attain this objective will integrate the evolving exploration formulary with the information in drug knowledge databases and generate an electronic decision framework that can rapidly classify any set of drug products for any DRM. The rationale is that successful completion of Aim 2 will produce a curated drug information database that will enable rapid, accurate, and unsupervised classification of each candidate exploration formulary drug product based on cumulative evidence pertaining to the physical and chemical stability of the drug.

After Aim 2 is completed, ExMC should have (1) the tools required to collect, process, analyze, and retain data pertaining to pharmaceutical stability, and (2) a "stoplight chart" that classifies formulary drugs as red, yellow, or green based on the state of knowledge regarding their stability and safety during exploration spaceflight. The architecture will be an important resource for NASA because it can be used to identify pharmaceutical resources that have a high risk of failure for exploration space missions. The results of Aim 2 will guide ExMC research activities and target resources to address specific risks affecting medications.

*No aspect of Aim 2 will be static or final*. The exploration formulary will be a living product that requires periodic updates to incorporate new medications as market availability changes over time, as standards of

medical practice evolve, as pharmaceutical countermeasures to protect astronaut health are developed and adopted, and as study results and data become available. The stoplight chart will evolve as spaceflight factors impacting drug stability become better understood through research activities. As these changes are implemented, drugs on the exploration formulary will be reclassified through the decision framework to remain current. For these reasons, the proposed data architecture should be adaptive and dynamic and should minimize the need for manual data processing.

## *2. RESEARCH DESIGN*

The proposed data architecture integrates a single centralized repository of curated data, a list of required drug products (i.e., "Exploration Candidate Formulary"), and an automated decision tree[8] (i.e., the stoplight decision framework) for classifying the risk of drug failure over the duration of a mission. The proposed architecture will improve data quality, the efficiency of data collection, organization, and data use/reuse. The architecture differs from previous efforts in that the stoplight decision framework is implemented programmatically using a structured drug information database to evaluate any set of formulary drugs. This approach differs from the previous efforts to produce a "drug information database" because subject matter expert (SME) effort is required only once at the time data are gathered and entered into the database, rather than for both collecting information and for subjectively weighing information for each drug and each DRM scenario every time the framework is used. Previous efforts to construct a drug information database simply collected unstructured narrative information and unlinked references pertaining to various factors that might affect the stability of each drug. As a result, SMEs had to spend a significant amount of time looking up references and interpreting unstructured narrative information each time the decision framework was used, and each time it was revised or updated. Instead, under the proposed approach the SME focuses on curating actionable data when it is entered into the database using predetermined criteria required for decision making. Basically, before data are collected, the SME must answer the question, *what specific information is required for classifying drug stability with regards to a particular factor?* Answering this question focuses the data collection effort.

A curated approach to pharmaceutical data collection has several advantages, including defining the key parameters that will be used for decision making prior to data collection, establishing data collection standards for each type of data, transparently defining assumptions for categorical data collection, and consistently using the collected data over time. The proposed approach enables the drug classification process

[8] The decision tree is a series of dichotomous outcomes based on binary "True/False" outcomes at each step.

for any DRM to be implemented systematically and consistently. A structured database will increase confidence in stoplight classifications because data will be transparent, subjective ad hoc interpretations of information will be reduced, and consistent results will be produced for different users and over time. In the absence of these capabilities, classifying each drug will remain a slow, subjective, and a largely manual error-prone process.

a. *Exploration Candidate Formulary (ECF)*

The ExMC ECF is an evolving list of medications derived from several different sources, including the current operational formulary on board the ISS, CRT medications derived from CliFFs, the Informing Mission Planning via Analysis of Complex Tradespaces (IMPACT) tool, a historical list of drugs from flown ISS IMAKs, the formulary for Artemis missions, medications previously evaluated in spaceflight studies, and other sources. The current combined formulary list consists of approximately 450 drug products, inclusive of different strengths, formulation, and dosage forms of over 270 active ingredients. This entire list, or any subset of this list (i.e., the CRT list), can serve as input for the stoplight decision tree framework.

The ECF is not static; it must evolve to remain relevant for expected exploration medical operations. The ECF includes many drugs that are considered medically important for Earth-independent medical operations—drugs that are not currently considered pertinent for ISS medical operations. It is expected that the ExMC ECF will never be "finalized" because medications will continue to be added for the foreseeable future. The selected medications must reflect not only clinical considerations but also the physical and chemical suitability of each medication for long-duration space mission. Factors expected to contribute to the evolution of the formulary include the following:

- *Drug stability data*
- *The FDA shelf-life data*
- *Drug formulation information*
- *Spaceflight medication use and efficacy information*
- *Changes in medical practice and standard of care*
- *Newly proposed medical or other health-protective countermeasures*
- *Antibiotic alternatives suitable for treatment of emerging antibiotic-resistant infections*

- *Addition of alternative drugs to accommodate astronaut gene polymorphisms (e.g., the liver enzymes CYP2D6 and CYP4A4 together metabolize about 50% of all drugs. The metabolizing activity of these enzymes, as well as many others, are frequently affected by gene polymorphisms).*

The ECF will need to adapt to the evolving medical operations environment. Although versions of the ECF will be locked down, it is likely that medical experience and research data acquired from increasingly longer missions will drive ECF updates.

b. *Stoplight Decision Framework*

The stoplight decision framework (herein referred to simply as "the framework") is an acyclic decision tree for classifying the risk that each medication on the ECF will fail during a specified DRM. The decision tree is based on available "knowledge of [each drug's] potency and safety for exploration spaceflight"[9]. It is expected that the decision framework will consider key mission parameters and will classify drugs for any mission DRM. The framework consists of a sequence of evaluation criteria that result in binary (true/false) outcomes at each node based on available information regarding drug stability and the selected DRM ("unknown" may also be included as a third outcome). The framework classifies each drug into one of 3 categories: "green", which indicates that the drug requires no further research (i.e., mission ready); "yellow", which indicates important data gaps or uncertainties exist that required further research; and "red", which indicates that known risks must be mitigated with further research, or an alternative drug should be selected. Framework classifications[10] are not absolute; instead, they are contextually linked to the space environment, clinical considerations, and information quality.

*1) Programmatic implementation*

The framework is simply a sequence of if-else statements that test whether a logical condition is true or false. The outcome of each test determines subsequent actions that classify each formulary drug. This means that the decision framework is easily automated, assuming the necessary input data are machine readable. The critical element for automating the decision framework is a database with a reliable and consistent structure, as discussed in the DDR section below. The framework has been implemented in R software.

[9] Pharm risk reformation 02/19/20, Aim 3.1.

[10] In the current paradigm, drug failure equates to changes in the chemical and physical characteristic of a drug product beyond the threshold set by USP standards. USP thresholds are not based on any measure of clinical efficacy; rather they are defaults based on reasonable limits for manufacturing variability (product quality) and analytical variability in testing (analytical variance).

*2) Rationale for a programmatic framework*

Stoplight classification of all formulary drugs are needed for all DRMs. Classifications must be reevaluated as new drug stability information becomes available and as drugs are added to or removed from the ECF. In short, stoplight classification is not a onetime event yielding a final classification for each drug; it is an ongoing process. Drugs must be classified for each DRM scenario and must be reclassified when new data become available that affect framework decision outcomes, or for any new drugs that are added to the formulary. Because parameters for exploration space missions are still evolving and because ExMC is actively performing pharmaceutical research, stoplight chart drug classifications remain iterative. Implementing the stoplight decision framework shifts the SMEs' efforts away from repeatedly re-evaluating each drug every time the framework is used, to curating up-front information when data are initially entered into the database. In FY21, SMEs evaluated 20 drugs over a one-month period. At this rate, it would take 10 –12 months for the SMEs to evaluate all drugs on the exploration formulary. Implementing the stoplight framework will save significant SME time, while also producing a more versatile and reliable database. However, if ExMC prefers to manually implement the framework, a well-curated and systematic DDR will still significantly improve the quality, reproducibility, and efficiency of preparing stoplight charts for mission scenarios. The first complete iterations of this integrated decision-making framework (v.2.0) have been implemented programmatically in R software. The results of this effort are presented in Appendix 3.

*3) Framework inputs*

- *DRM length in months*
- *Drug data repository (described below)*
- *Exploration candidate formulary or other list of drugs*

c. *Approach for Developing the Framework*

The framework development is staged to coincide with execution of pharmaceutical strategies, inclusive of the future PK and PD strategies, and the timeline for acquiring experimental data.

- *Phase 1—Stability. To classify drug stability, the stoplight framework (Appendix 3) focuses on factors that may influence chemical and physical drug stability during spaceflight, which include intrinsic shelf life, sensitivity to ionizing radiation, and the effects of packaging. Data that ExMC needs to collect to address these 3 factors are listed in* Table *1; data sources are discussed in greater detail in DDR Content section III.B.2.d.4)*. Phase 1 is currently ongoing and will need to be updated to remain current with changes to the framework inputs listed above.

- *Phase 2—Effectiveness. Effectiveness of medications is determined by several factors that include: the amount of API released from the medication (i.e., API content, dissolution); PK disposition (i.e., bioavailability, distribution, clearance); PD activity (i.e., ligand binding affinity, signaling pathway activity); and appropriate drug selection for the clinical indication. In support of the PK strategy, API physicochemical data will be collected to assign each drug to an appropriate Biopharmaceutics Drug Disposition Classification System (BDDCS) (Benet, Broccatelli, and Oprea, 2011; Lindenberg, Kopp, and Dressman, 2004; Wu and Benet, 2005). This classification scheme is a key parameter that is expected to be implemented in the PK strategy.*

- *Phase 3—Drug safety. Determining drug safety depends, in part, on the chemical and physical integrity of the drug (phase 1) and the PK disposition (phase 2). Assessing drug safety also requires health-based risk assessment of impurities, which depends on drug stability (Phase 1). Assessing the risk from pharmaceutical impurities is a well-established practice that is formalized in several regulatory guidance documents and health-protective procedures. The expansion of the stoplight decision framework should include health risks associated with hazardous impurities. Impurities and ingredients in medications with known or predicted (DNA-reactive, immunologic sensitizers) health hazards are rare, but when they do occur, a standard chemical risk assessment analysis will be performed, as summarized in the Impurity hazards and chemical risks section III. B. 2. d. 4) i).*

| Table 2. Framework Data Requirements for Drug Stability Classification | | | | |
|---|---|---|---|---|
| Factor | Data | Source | Data types | Status as of May 2024 |
| Intrinsic shelf life | Manufacture shelf life | Electronic Medicines Compendium (emc®) | Shelf life | Completed |
| | | Food and Drug Administration (FDA) (see Aim 1) | Approved shelf life<br>Degradation rate<br>Timepoint potency from stability studies | On Hold—Waiting for NASA agreement with FDA. See Aim 1 timeline |
| | Shelf-Life Extension Program (SLEP) | FDA (Aim 1)/literature | Mean extension (range or ± variance)<br>Number of lots tested,<br>Number of lots failed,<br>Failure reason | On Hold— Waiting for NASA agreement with FDA. See Aim 1 timeline |
| | Operational shelf life | NASA JSC Pharmacy | Delivery date in pharmacy<br>Expiration date | Completed |
| Radiolytic sensitivity (ionizing radiation) | Radiosterilization studies | Literature | No Observed Effect level (NOEL) in units of kilogray (kGy)<br>Lowest Observed Effect Level (LOEL) in units of kGy<br>Percent change in active pharmaceutical ingredient at LOEL<br>Form tested (solid, solution)<br>Concentration (solutions)<br>Identification of degradation products | In progress |
| | NASA testing results | NASA Space Radiation Laboratory (NSRL) or contractor, New ground analog studies | | NSRL study: in progress; Analog studies: not started |
| | Redox susceptibility | Lhasa Zeneth® | Probability<br>Degradation products | In progress |
| Packaging | Testing studies | Aim 3 | Last passing potency time<br>First failure potency time<br>Degradation rate with lower 95$^{th}$ confidence interval | Not started – see timeline |
| | Spaceflight studies | Du et al., 2011, Dribble study (in press) | Last passing potency time<br>First failure potency time<br>Degradation rate | In progress |
| | Degradation pathways | Lhasa Zeneth® | Probability<br>Degradation products | In progress |

d. *Drug Data Repository (DDR)*

The stoplight decision framework will use the DDR drug information to classify drugs (III.B.2.b). This centralized DDR will enable drug stability during exploration spaceflight to be classified transparently and consistently, as discussed above.

*1) Data Management Plan*

No NASA data management plan or architecture for collected pharmaceutical information exists. Consequently, data from several NASA HRP-supported studies have been lost, including data from 2 identifiable radiation studies (see Aim 4 [Section III.D.2.a] and (Reichard, 2023) for discussion), experimental raw data from one study of spaceflight drug stability (Du, et al., 2011)[11], and data from one study that assessed spaceflight medication use (Wotring and Smith, 2020). A data management plan, including a coherent data architecture, is essential for preserving data from NASA-supported studies and is necessary for data reanalysis and for future reuse for unforeseen purposes. The data management plan should adhere to FAIR (**F**indable, **A**ccessible, **I**nteroperable, and **R**eusable) principles of data management and stewardship of all pharmaceutical data that is not privacy protected health information.

*2) The DDR is a crucial component of the data architecture*

The first step will be to develop a DDR with standardized and organized NASA pharmaceutical data. The DDR will be used jointly with the decision framework and the ECF to repeatably and precisely classify the failure risk for each medication during a specified DRM, regardless of the user or when the analysis is performed. Previously, pharmaceutical data related to several research tasks were collected in Microsoft Excel spreadsheets. One such file was the Drug Information Database, which contains a large amount of pharmaceutical information in an unstructured format that was collected from FY2019–FY2021. These data are not machine readable and therefore not interoperable. In contrast, the DDR includes data in a structured, machine-readable format. SMEs help to develop the rules on data collection, identify the metrics that need to be collected, and develop standards and curation rules for data collection. For the proposed joint framework/ECF/DDR infrastructure, the SMEs will focus on the structure and content of the information collected in the database rather than combing through documents to a make subjective, ad hoc decision. This approach enables each drug to be rapidly and consistently evaluated based on stable parameters that are transparently defined in a corresponding data dictionary, enabling future reuse. Versioning of the database and framework will allow changes to be tracked and analyzed over time.

*3) DDR organization*

All drug data, regardless of source, will be organized by API(s). Because each manufacturer's finished product containing a particular API is formulated differently from other manufactures' equivalent products, it

[11] Summary data remain available as a supplement to the original published study – see Appendices at the publisher's website.

makes sense to structure drug information in a hierarchical database with all associated information related to particular drug products organized by API(s) (although other database structures also exist). For example, when stability study data are collected for a specific manufacturer's product[12], these become descriptive attributes of the particular product, and the products are listed under their API. These data and relationships are captured in the DDR, along with experimental study results, treatment parameters, descriptors, and other attributes. Hence, all experimental data and metadata are captured in the DDR and updated according to the Data Maintenance Plan. The resulting repository will simplify data collection, will be scalable to allow new drug products and information to be added as they become available, and will be reusable for use by future researchers because data types and assumptions are defined. The proposed structure is illustrated and described in Figure 1.

[12] This system works for drugs in the U.S. market, which are assigned NDCs and RxCUI identifiers. To our knowledge, there is no analogous system in the EU or UK, which is a limitation for using the UK emc® database for assigning shelf-life data.

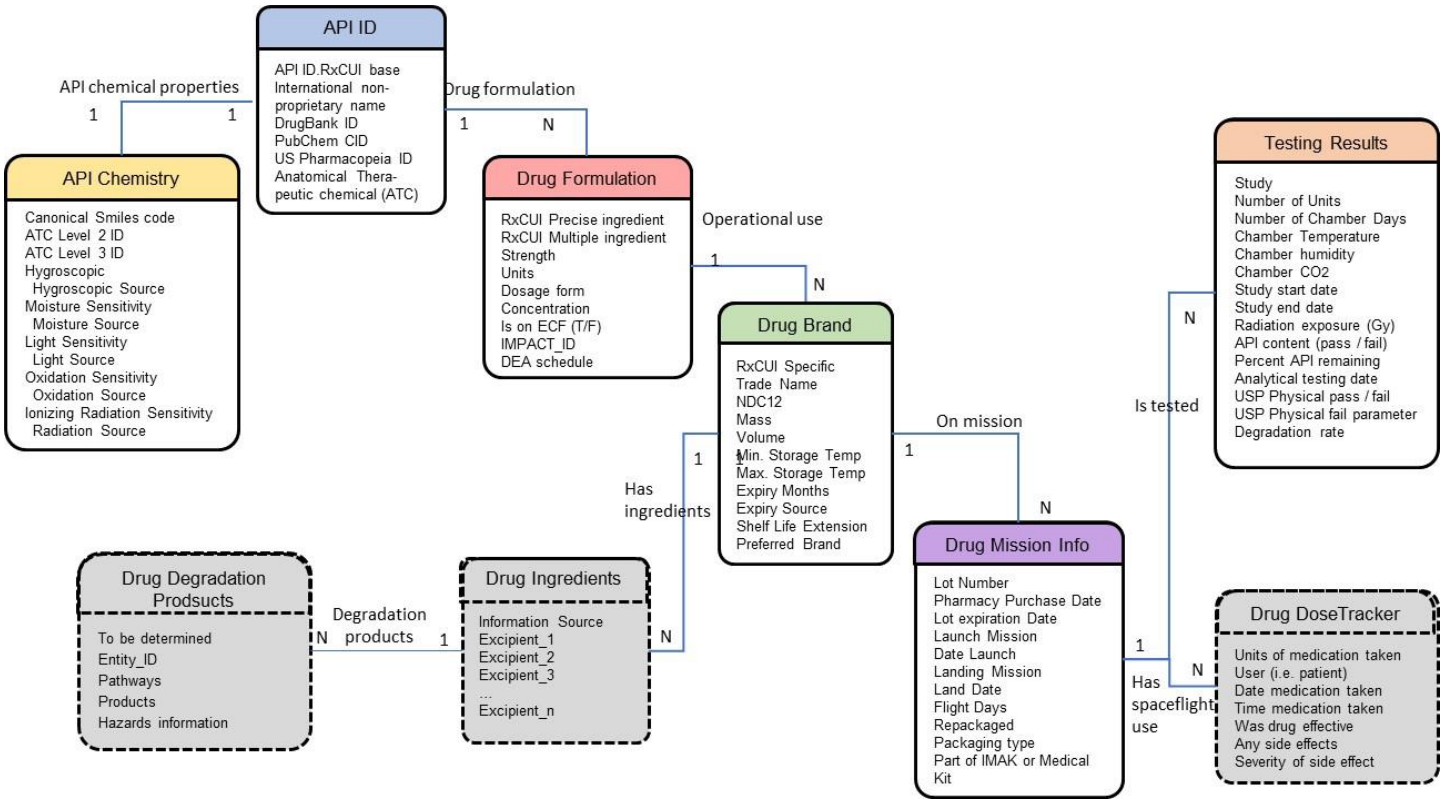


***Figure 1. Hierarchical structure of the relational DDR.*** *Lines represent relational connections. Notation adjacent to each line shows the nature of the relationship, with numbers or the letter "N" to indicate either 1:1 or 1:N (many) relationships. Grey-shaded hashed boxes are information that may be collected in future studies. The highest level of the data hierarchy is the drug API, which is identified in the Index table (box API ID [blue]). The index tableconsists of unique identifiers (ID) for each API, and unambiguously cross-references to other authoritative databases (i.e. International Nonproprietary Name (INN), US Pharmacopeia, National Library of Medicine (NLM) PubChem database, DrugBank database). Each API is described by a set of chemical and therapeutic properties (box API Chemistry [yellow])—these will be especially relevant in the pharmacokinetic strategy. Each API is also an ingredient in a dosage formulation (Drug Formulation [pink]). Each formulation is uniquely identified by an RxCUI as a primary ingredient (RxCUI_PIN) or one of multiple ingredients in a formulation (RxCUI_MIN). Each drug product is marketed by one or more labelers with a specific identifier for that formulation and strength, known as a National Drug Code (NDC) number. Experimental studies linked to each manufacturer's product, such as shelf life and expiration date are collected in drugBrand [green]. The drug Mission box [purple] includes data from studies that include drugs flown on space missions or tested in ground-based stability studies, including the dates over which the experiment was performed, packaging type and whether the drug was part of a medical kit or ISS Medical Accessory Kit (IMAK). Conditions under which stability studies are performed, inclusive of both spaceflight and ground-based studies, involve a range of environmental conditions. The drugTested box [orange] captures the specific exposure conditions, including radiation exposures, if relevant. The remaining grey boxes represent how the database can be expanded to collect and relate medication use tracking data (drugDoseTracker), inactive ingredients (drugIngredients) and degradation products observed in manufacture studies reported to FDA. Abbreviations: API = Active pharmaceutical ingredient; ATC = Anatomical Therapeutic Chemical classification; CID = Pubchem Compound Identifier; DEA = U.S. Drug Enforcement Agency; ECF = Exploration Candidate Formulary; ID = Identifier; IMAK = ISS (international space station) medical accessory kit; IMPACT = Informing Mission Planning via Analysis of Complex Tradespaces tool; NDC12 = U.S. National drug code, 12-digit; RxCUI = RxNorm Concept Unique Identifier, and it is a unique identifier for each concept in RxNorm. RxNorm is a system that provides normalized names and unique identifiers for drugs and medicines that enables computer systems to communicate drug-related information efficiently and unambiguously; T/F = binary classification of true or false; Temp = temperature.*

*4) DDR Content*

a) Drug identifiers

The hub of the DDR is the drug identifier "index table" (Figure 1, "apiID" box). Drug names and synonyms are often used inconsistently (e.g., fluoxetine, fluoxetine HCl, fluoxetine hydrochloride). To prevent errors and inconsistencies, the index table will use the National Library of Medicine (NLM) RxNorm unique drug identifiers (RxCUIs) [13] that unambiguously identify each drug substance (API) in finished drug products (Figure 1, "drugFormulation" box). RxCUIs for drugs that the FDA approve to be marketed in the US are accessible through the NLM RxNAV website[14], or programmatically via a web-based RESTful Application Programming Interface (webAPI)[15]. The DDR index table connects each drug's API, via its API ingredient (RxCUI_IN) to the precise drug ingredient (i.e., salt or hydration form, RxCUI_PIN) and each formulated drug product (Formul_RxCUI). The greatest advantage of RxCUI identifiers is that they link drug-specific information in the ECF to several authoritative information providers (Table 3). These external data repositories are needed to conduct PD, PK, toxicology, and pharmaceutical analyses.

b) Descriptive information on drug and formulation

The index table cross-references each formulary drug and dose form to key descriptive drug information sources applicable to stability testing, PK, and PD. None of these data need to be collected within a database; instead, these data can be accessed as required with a programmatic call to online compendial data sources listed in Table 3. Such databases include authoritative repositories of drug-specific pharmacologic, toxicologic, structural, and PK information, as illustrated in the Venn diagram shown in Figure 2.

c) Drug Shelf Life

Pharmaceutical manufacturers in the US are required by U.S. law to perform stability testing of each finished drug product and provide an expiration date (Code of Federal Regulations Title 21 —Expiration dating,

[13] RxCUI is a unique identifier assigned to a drug entity in the National Library of Medicine (NLM) RxNorm database. It is used to relate to all things associated with that drug. RxNorm is a system used by the NLM to name generic and branded drugs. Hospitals, pharmacies, and other organizations use computer systems to record and process drug information. RxNorm allows computer systems to communicate drug-related information efficiently and unambiguously. https://www.nlm.nih.gov/research/umls/rxnorm/overview.html

[14] https://mor.nlm.nih.gov/RxNav/.

[15] RxNorm API: See https://lhncbc.nlm.nih.gov/RxNav/APIs/RxNormAPIs.html . See https://lhncbc.nlm.nih.gov/RxNav/APIs/RxNormAPIs.html for descriptive tutorial.

and Code of Federal Regulations Title 21—Stability testing https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm). In the US, manufacturers are not required to disclose shelf life, which is typically regarded as manufacturer's proprietary information, unlike in the UK and EU where disclosure of shelf life is required. Approximate shelf-life periods for a large portion of the ECF can be obtained from the EU/UK EMC database[16].

d) The Shelf-Life Extension Program (SLEP)

Published drug data are also available in the SLEP (Lyon, et al., 2006). These data are retained in the "drugBrand" unit of the proposed DDR, in Figure 1.

Table 3. Content of The Pharmaceutical Database Relevant to Drug Stability

| Descriptor | Purpose | Source |
|---|---|---|
| Dose form/strength | Specific formulary drug ID | NLM RxNav (TTY = SCD) https://mor.nlm.nih.gov/RxNav/ |
| National Drug Code (NDC) number | Drug/brand/manufacturer | NLM RxNav https://rxnav.nlm.nih.gov/api-RxNorm.getAllProperties.html |
| SMILES code | Drug structure notation; for cheminformatics, pathway prediction and PK analysis | Drugbank https://go.drugbank.com/releases/5-1-8/downloads/approved-structure-links |
| Manufacturer storage conditions-EU | Recommended environmental conditions for shelf life | EMA Electronic Medicines Compendium (emc); https://www.medicines.org.uk/emc |
| Functional shelf life | Branded shelf-life estimates | NASA Ops pharmacy; Upon request availability permitting |
| Manufacturer shelf-life-EU | Branded shelf-life estimates | EMA Electronic Medicines Compendium (emc); https://www.medicines.org.uk/emc |
| Shelf-Life Extension (Published) | FDA/DOD shelf life beyond expiry | See manuscript (Specific to NDC) |
| Degradation Pathway | Grouping of drugs by susceptibility, Protective packaging studies | Lhasa Zeneth ® software (software subscription) |
| Radiosterilization | Effect of ionizing radiation | Literature |
| Susceptibility to oxidants (electrophiles) | Effect of ionizing radiation | Lhasa Zeneth ® software (software subscription) |
| Spaceflight drug stability study data | Observed stability under spaceflight conditions | Curated from NASA supported studies. |

[16] https://www.medicines.org.uk/emc. The emc® drug information portal of the European Medicines agency (EMA) and UK Medicines and Healthcare Products Regulatory Agency.

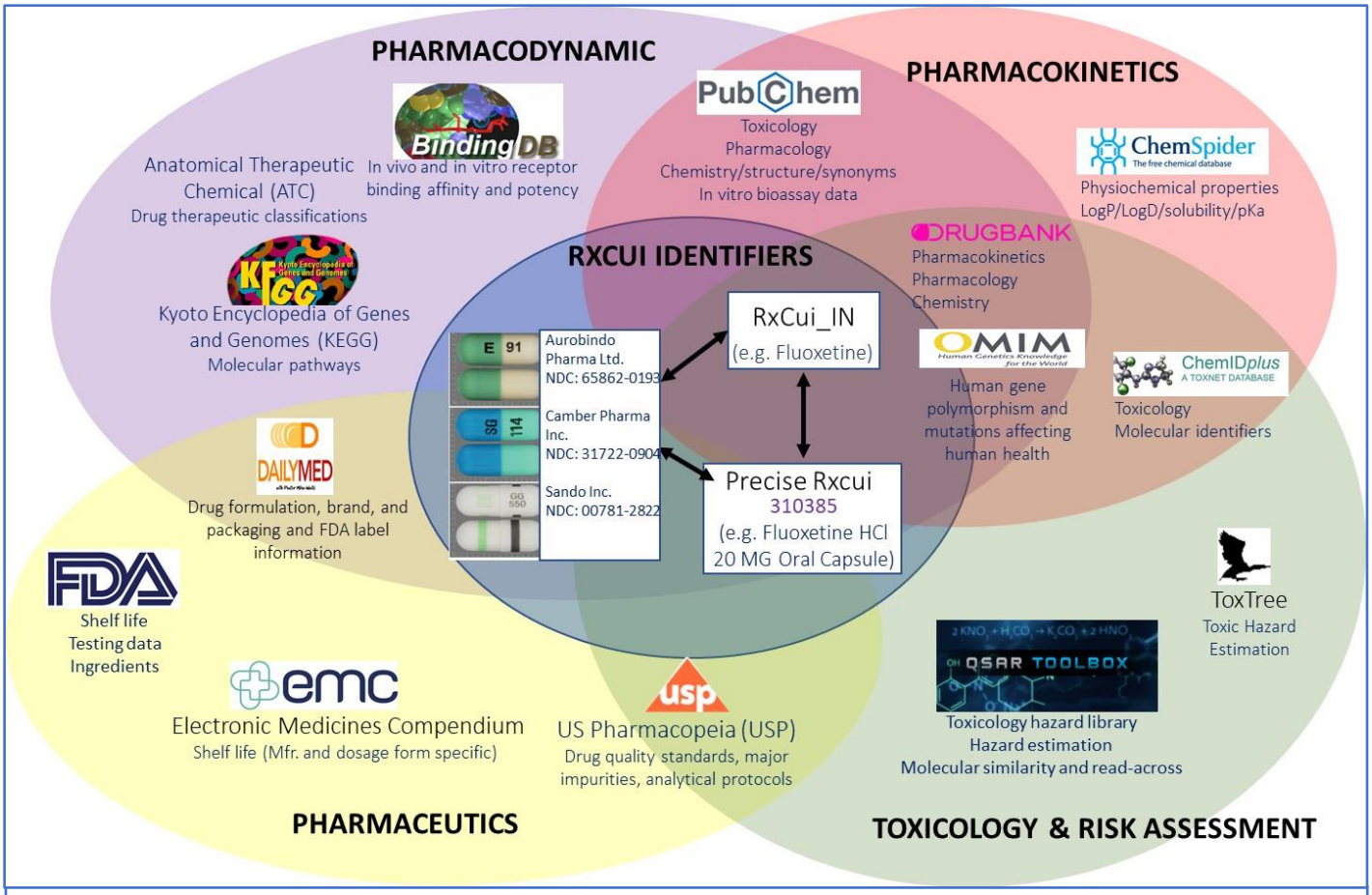


***Figure 2. Venn diagram illustrating some of the available data sources linked in the DDR.*** *RxCUI identifiers(RxCui_IN) in the Drug data repository (DDR) link each drug to publicly available information across a wide array of authoritative data sources. These sources include data from US agencies (e.g., U.S. EPA, U.S. FDA, National Library of Medicine (NLM)), international agencies (World Health Organization (U.N.WHO), U.N Organisation for Economic Co-operation and Development (OECD), European Medicines Agency (EMA)) and others. These data sources support the pharmaceutical strategy by providing necessary pharmaceutical, pharmacokinetic, pharmacodynamic and toxicological information and tools. Repositories with data that fit multiple purposes are shown in overlapping domains. Data from each repository are available via web API software or direct download, and such information can be pulled as needed for any exploration formulary drug, or can support manual search activities. Note that in addition to the relationship depicted above, PubChem also contains substantial toxicology information that was that previously provided through NLM ToxNet. Similarly, DrugBank also contains substantial drug product information*

e) Drug degradation information

Two types of drug stability information will be collected: Predictive degradation pathway (computational) and information from published studies[17].

[17] Information obtained through collaboration with U.S. FDA were previously considered for inclusion, however recent challenges in establishing a collaborative relationship between NASA ExMC and FDA means that, at present, no assurance of such data can be obtained.

- *Predictive degradation pathway. Information on drug degradation pathways and first degree [18] reaction products will be captured as probability scores for each API using the Lhasa chemoinformatic Zeneth® software. Probability scores can be used to group drugs by pathway susceptibility to support experimental studies discussed in Aims 3 and 4. Drug degradation pathways can be anticipated from knowledge of a molecule's functional groups (i.e., molecular structure)[19]. Zeneth® uses the established chemistry of functional groups to predict degradation pathways, most commonly hydrolysis, oxidation, and photolysis (Guillory and Poust, 2002). Thus, through knowledge of functional groups and environmental conditions, it is possible to anticipate drug degradation susceptibilities (Guillory and Poust, 2002).*

- *Information from published studies. Reports of drug product stability under specified testing conditions have been previously collected. It requires substantial manual effort and expertise in organic chemistry to extract relevant data from such narrative documents and to record experimental conditions pertinent to NASA's needs. The focus for extraction of data will be high-quality published literature. The literature search will be performed using Google Scholar, Embase, and Web-of-Science to capture chemistry and pharmaceutics information, which is often not indexed by PubMed. The literature search should use a rapid review method (Garritty, et al., 2021). Abstracts for articles returned by a search will be filtered using a priori established inclusion/exclusion criteria and scored/ranked for relevance. Filtered search results will be electronically retained as supporting metadata for each API. Systematic weight of evidence analysis will be performed using line of evidence analysis to identify degradation products (Hardy, et al., 2017). Where possible, weight of evidence analysis will also include an article quality rating based on the Klimisch score (Klimisch, Andreae, and Tillmann, 1997).*

f) Radiosterilization

Radiosterilization is a common step in the drug manufacturing process that ensures the finished drug products are sterile before being released to the market. It is expected that the very high level of ionizing radiation, such as the doses to sterilize drugs during manufacturing, can be used to classify the susceptibility

[18] Reaction products can undergo further reactions to form daughter (second degree) reaction products, which can also react to form tertiary products. Second- and third-degree reaction products can result in over prediction of degradation products. Controlling first degree reactions also controls subsequent reactions, so an understanding of the initial reaction steps essential.

[19] A functional group is a group of atoms in a molecule that gives the molecule its characteristic chemical reactions. The same active group 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).

of drugs to ionizing space radiation (see in Aim 4 **Review of Relevant Information and Literature**). Because radiostability of drug substances is inversely proportional to absorbed radiation dose, it follows that if the drug is demonstrated to be stable at high radiation levels >1 kGy, it will be stable during spaceflight at *much* lower radiation levels that are permissible for human exposures. In addition, a rapid review of available radiolysis literature will be performed as described in the *high-quality published literature* section.

g) Inactive ingredients (excipients)

Excipients are therapeutically inactive ingredients used in the formulation of pharmaceuticals. Excipient ingredients for each drug product in the DDR will be collected to attempt to correlate excipients with shelf life. In some instances, excipients are added to formulations to stabilize susceptible APIs from environmental factors like oxidation (e.g., the antioxidant butylated hydroxytoluene). The excipients a manufacturer chooses to include in a product can have very significant effects on API stability (Asafu-Adjaye, et al., 2011; Chen, et al., 2012; Waterman, Adami, and Hong, 2004; Yang, et al., 2010).

h) Results of spaceflight studies

Data from previous experimental studies has already been compiled and are included in the DDR to the extent they are available. More importantly, the DDR will formalize the types of empirical information collected for every drug and experimental method going forward (See Aim 3).

i) Impurity hazard assessment

Information required to assess the safety of drug degradation impurities will be collected. Pharmaceutical impurities are evaluated using a chemical risk assessment. Standards and practices of risk assessment are established under national, international, and non-governmental guidance. Candidate spaceflight formulary drugs known to have hazardous degradation impurities will be identified. When health-based exposure limits for impurities are not available, risk assessment will be performed to set permissible daily exposure limits for these impurities. For drugs having structurally identified degradation products but unknown hazards (i.e., “data-poor” chemicals), a threshold of toxicological concern (TTC) approach will be used to set exposure limits. A margin of exposure approach will be used to distinguish the drugs that have health risks. Under this approach, a hazard is not considered a risk unless the expected exposure is within a margin of approximately 100-fold of the no observed adverse effect level (NOAEL), or if the expected daily dose exceeds the TTC for data-poor chemicals. Information requirements for human health chemical risk assessment include:

- *Chemical identifiers. Where possible, impurity Chemical Abstract Number and PubChem compound Identifier will be collected for impurities. These identifiers are commonly used to identify chemical compounds and distinguish racemates.*
- *Canonical simplified molecular-input line-entry system (SMILES) string. SMILES strings are the characterization of a chemical's 2D or 3D molecular structure as a 1D "string". SMILES strings are used in toxicology to identify hazards and to assess TTC. Convenient sources of information and dose-response evaluations are the U.N. Organisation for Economic Co-operation and Development OECD quantitative structure-activity relationship (OECD QSAR) Toolbox and the U.S. Environmental Protection Agency's EPI Suite ™ software.*
- *Authoritative human exposure limit(s). If human health risk assessment evaluations have been performed for chemical impurities, human exposure limits (in terms of estimated daily dose) and associated supporting information will be collected.*
- *Cramer classification. Budget, time, and data limitations preclude full risk assessment for all the highest priority degradation impurities.*
- *The TTC chemical classification approach is a pragmatic screening and prioritization tool to assess the risk from impurities (Kroes, et al., 2004; Kroes, Kleiner, and Renwick, 2005; Munro, Renwick, and Danielewska-Nikiel, 2008). Open-source hazard assessment software (e.g., ToxTree, OECD QSAR Toolbox)[20], and commercial software (e.g., Lhasa DEREK® and MulitCASE®) can be used to estimate toxic hazards through the application of structure-based TTC and other QSAR approaches. TTC assessment uses Cramer 'decision tree' rules to assign chemical entities to one of 2 classifications based on structure features. These classes have validated maximum daily doses of 30, 9, and 1.5 µg/kg [body weight]/day) (Cramer, Ford, and Hall, 1976; Kroes, et al., 2004; Kroes, Kleiner, and Renwick, 2005; Munro, Renwick and Danielewska-Nikiel, 2008). Only chemical structure is required for TTC classification.*
- *Most sensitive effect. When assessing human health risk, the default assumption (unless data shows otherwise) is that humans are 3–12 times more sensitive than animal species (depending on guidance followed and the animal species tested). For this reason, when toxicity data are available, the most sensitive effect in the most sensitive species is always used to derive the human exposure limit. The*

[20] ToxTree (http://toxtree.sourceforge.net/); OECD QSAR Toolbox (https://www.oecd.org/chemicalsafety/risk-assessment/oecd-qsar-toolbox.htm)

*apical adverse effect observed at the lowest doses in the most sensitive species will be collected, when available.*

- *NOAEL. The NOAEL is the highest dose of a chemical at which no adverse effect is observed. The NOAEL for the apical effect in the most sensitive animal species exposed to the impurity will be collected, when available.*
- *Lowest adverse effect level (LOAEL). The LOAEL is the lowest dose of a chemical at which an adverse effect is observed. When available, the LOAEL for the most sensitive effect in the most sensitive animal species exposed to the impurity will be collected.*
- *Benchmark dose (BMD) analysis. Benchmark dose is an accepted regression-based approach that is more precise than the NOAEL for identifying the dose at which no adverse effect is anticipated in animal models. The BMD will be collected, when available, or calculated using the U.S. EPA Benchmark Dose Software (available at no cost from the EPA), if dose-response data are available for the apical effect (Crump, 2002; Haber, et al., 2018).*

*5) Curation of DDR information*

Curating data is essential for a practical decision framework. Accurate classification requires error-free data collection based on transparent and consistent assumptions. Therefore, the DDR must not contain freeform annotations, except in designated columns; instead, data should be entered as a defined format into defined fields based on consistent definitions and structure. Each column of the DDR will contain only one type of data: logical, numeric, factor, character string, or date. Each field in the database will be defined in a data dictionary that provides a clear description of each term, stated assumptions or calculations (if a derived variable), data source(s), and other descriptors required for transparency. Associated information necessary to support each parameter in the database will be consistently collected and saved. For datatypes where SME judgment is needed, parameters affecting data selection will be established before collecting data. Accordingly, team members will implement a quality review process to ensure consistency.

*6) Data uncertainty*

Shelf lives of drugs are currently discrete values without variance or other uncertainty metrics; however, drug stability has associated uncertainty. Where possible, the stoplight decision framework should use the lower 95th confidence interval for drug stability, or the lower range of shelf-life extension results for classifying drugs. Accounting for uncertainty gives essential insight into the reliability of the data, which is a

critical step in risk-based decision-making. These approaches have been demonstrated in the literature (Reichard, et al., 2023).

## *3.* POTENTIAL PROBLEMS, LIMITATIONS, AND ALTERNATIVES

### a. *Structuring Complex Data*

It is expected that some data will be difficult to structure. For example, radiostability can be measured by several very different analytic techniques, each with different meanings and reported in different ways. It will be necessary to identify the metrics that are the most meaningful predictors (i.e., independent variable, modifying factors) of drug stability. The SMEs must determine what data are required to classify each feature of a drug and must define how these data are used. This process is designated as "SME data curation". A data dictionary will be prepared to define each feature in the database and how it is determined, or to provide the information source. The data dictionary will enable transparency and consistency of all data collected for future stakeholders and data users.

#### *1) Subject Matter Experts*

Individual SMEs in pharmaceutics are not expected to have the full range of expertise necessary to define essential criteria for classifying drugs or understanding analytical methods used in all areas of pharmaceutics. For this reason, SMEs in specialized fields should be consulted to ensure the correct information is collected and processed. These specialized fields may include radio pharmaceutics, formulation chemistry, pharmaceutical engineering, analytical chemistry, and impurity risk assessment.

## *4. NOTIONAL TIMELINE AND BENCHMARKS FOR SUCCESS*

Table 4. Notional timeline for Aim 2.

| Project | Task | FY2024 | | | | | | | | | | | | FY2025 | | | | | | | | | | | | FY2026 | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | 10 | 11 | 12 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| Systematic Search Tasks | Radiation Literature Analysis | X | X | X | X | X | X | X | X | X | X | | | | | | | | | | | | | | | | | | | | | | | | | | |
| | Hazardous API degradation products | | | | | | | | X | X | X | X | X | X | X | X | X | | | | | | | | | | | | | | | | | | | | | |
| | Collect high probability pathway data from Zeneth | | | | | | | | | | | | (X) | (X) | X | X | X | X | X | X | X | X | X | X | X | | | | | | | | | | | | | |
| Framework | Programmatic framework implementation | X | X | X | | | | | | | | | X | X | X | | | | | X | X | X | | | | | | | | | | | | | | | |
| | **Decision Framework v3.x** | | | | | | | | | | | | | | | X | X | X | X | X | X | | | | | | | | | | | | | | | | |
| ECF | **Lockdown Formulary (v3)** | | | | | | | | | | | | | X | X | X | X | X | X | X | X | X | | | | | | | | | | | | | | | |
| | **Stoplight chart v3.x** | | | | | | | | | | | | | X | X | X | | | | | | | | | | | | | | | | | | | | | |
| | **Stoplight chart final (v3)** | | | | | | | | | | | | | To be determined | | | | | | | | | | | | | | | | | | | | | | | |
| Data collection | Relational DDR (v.1.0) | | | | | | | | | | | | | To be determined | | | | | | | | | | | | | | | | | | | | | | | |
| | **FDA Shelf Life Data- Aim 1** | | | | | | | | | | | | | To be determined | | | | | | | | | | | | | | | | | | | | | | | |
| | **FDA Drug Stability Testing - Aim 3** | | | | | | | | | | | | | To be determined | | | | | | | | | | | | | | | | | | | | | | | |
| | **Gateway Testing - Aim 4** | | | | | | | | | | | | | To be determined | | | | | | | | | | | | | | | | | | | | | | | |

*Timeline for data collection, stoplight framework and formulary development. This timeline represents the initially period of data collection and framework development for drugs currently on the ECF. All aspects of Aim 2 will be ongoing as mission requirements and corresponding medical requirements evolve. "To be determined" indicates that the timeline is dependent on kickoff (See Aim 1 test and Table 1). Abbreviations: DDR = drug data repository; FDA = U.S. Food and drug administration; API = active pharmaceutical ingredient; **X** = established milestone, X = tentative effort on task; (X) = effort on task.*

## 5. EXPECTED OUTCOMES

- *Tangible outcomes produced by Aim 2 include a structured **DDR** and a computational algorithm (**decision framework**) for classifying each drug product in the ECF. The DDR is the central element of the data architecture containing all data needed to support the pharmaceutical strategy for classifying each drug in the ECF, as well as data required for the PK and PD strategies, which are under development.*

- *The proposed architecture includes developing a data management plan that will specify how data are collected, processed, quality reviewed, and archived. The data management plan will include a process for preserving data to prevent the loss of raw and processed data gathered in future studies and other research efforts.*

- *The machine-readable DDR will enable rapid classification and reclassification of pharmaceuticals. By automating the subjective, labor-intensive, and manual process of classifying drugs, the proposed architecture improves the efficiency and productivity of SMEs by focusing their efforts on up-front data entry (i.e., data curation), in place of subjective and time-consuming interpretation of inconsistent information for making inferences for each drug. The curation process will use clearly stated assumptions, definitions, and criteria to ensure reliability of analyses.*

## C. AIM 3. IDENTIFY PROTECTIVE DRUG PACKAGING, REPACKAGING, AND SELECT OPTIMAL FORMULATION OF SOLID ORAL DOSAGE FORMS (SODF) THAT WILL EXTEND THEIR SPACEFLIGHT SHELF LIFE

### *1. INTRODUCTION*

The *objective* of Aim 3 is to evaluate how repackaging influences the stability of SODF and to evaluate whether protective packaging and rational selection of drug products based on excipients will prolong shelf life. The hypothesis is that the interaction of atmospheric factors with active pharmaceutical ingredients or excipients is the primary mechanism that facilitates degradation of repackaged SODF. The approach for testing this hypothesis is to conduct terrestrial stability studies using different packaging conditions for a set of drugs known to be susceptible to physical or chemical degradation. Packaging conditions used in these studies will include the current NASA operational pharmacy repackaging process, sealed manufacturer's packaging, and candidate protective repackaging technologies. The *rationale* is that successful completion of Aim 3 will establish whether there is a causal relationship between current drug repackaging practices and pharmaceutical degradation and demonstrate the extent to which protective repackaging technologies prolong shelf life compared to shelf life of drugs repackaged during the current process. These experiments will also provide estimates of drug degradation rates and failure probability and will evaluate accumulation of degradation impurities. Without this evidence, the role of drug repackaging on medication failure will remain unresolved, which could increase the risk of time-dependent medication failure. It is important to begin these studies as soon as possible because a single long-term study requires 1–2 years to complete. The *expected outcomes* of successfully completing Aim 3 will be (1) evidence that non-protective packaging accelerates drug degradation; (2) measures of the size of the effect that current repackaging procedures have on the stability of susceptible drugs; (3) evidence that protective packaging extends shelf life and is at least as protective as the manufacturer's sealed packaging; and (4) evidence that brand selection is an important determinant of shelf life for medications that are exposed to atmospheric factors for prolonged periods.

### *2. REVIEW OF RELEVANT INFORMATION AND LITERATURE THAT JUSTIFY RESEARCH STUDIES*

It has been reported that some pharmaceuticals exposed to spaceflight fail[21] to meet USP standards for drug content before their specified expiration dates, or to degrade more quickly than matched control samples (Blue, Bayuse, et al., 2019; Du, et al., 2011; Wotring, 2016). However, no causal relationship has been demonstrated between spaceflight exposure and accelerated drug degradation. Nevertheless, there appears

[21] Based on the United States Pharmacopeial (USP) thresholds for API content or physical characteristics.

to be an association between spaceflight and reduced potency for some SODF. Presently, explanations of the mechanistic effects for this association are based entirely on supposition. Suitable countermeasures to preserve drug shelf life during a long-duration space mission cannot be developed without understanding the mechanisms by which spaceflight affects drug stability.

Explanations for the apparent degradation of some SODF during spaceflight have been proposed, including exposure to cosmic ionizing radiation, physical effects of vibration and microgravity, and elevated levels of atmospheric $CO_2$. It is well established that many medications are susceptible to atmospheric factors, particularly $O_2$ and moisture (Asafu-Adjaye, et al., 2011; Carstensen, 1988; Leeson and Mattocks, 1958). What is notable about all NASA studies is that, with the exception of promethazine suppositories, all drugs exhibiting extensive degradation were solid formulations repackaged into non-protective packaging (United States Pharmacopeia, 2020c; United States Pharmacopeia, 2021) before storage (Reichard, et al., 2023). This is an unexpected observation because liquid formulations are typically less stable than corresponding solid formulations and are much more sensitive to radiation (see in Aim 4, Review of Relevant Information and Literature). Thus, one factor common across studies is repackaging of medications into non-protective packaging, which permits permeation by atmospheric constituents (e.g., $O_2$, $CO_2$, humidity) that definitively mediate chemical and/or physical degradation of medications.

The role that RH and $O_2$ play in facilitating chemical degradation and physical deterioration of pharmaceuticals is well established. The science surrounding moisture and gas permeation into (and out of) pharmaceutical packaging is known, and rigorous models are available to predict the performance of packaging configurations (Nelson and Huang, 2011). Pharmaceutical manufacturers can mitigate the effects of environmental factors on medications using several strategies, including selecting primary packaging materials with desirable barrier properties. However, in most cases, the atmospheric content within most manufacturer drug packaging changes slowly over time at a rate determined by the characteristics of the package and its contents until it equilibrates with the external storage environment.

Repackaging pharmaceuticals into non-protective containers significantly increases exposure to atmospheric factors, including moisture, $O_2$, $CO_2$, and other gases or vapors. Consequently, repackaging facilitates degradation, increasing the risk of drug therapeutic failure and the accumulation of degradation impurities. All NASA spaceflight drug stability studies have focused on testing the stability of SODF repackaged at the Johnson Space Center (JSC) under ambient room air into either polypropylene containers or low-density polyethylene plastic bags with zipper-seal closures (i.e., zip-lock bags). Such non-protective repackaging is suitable for ISS space missions that are regularly resupplied but are not suitable for Earth-independent

exploration missions because exposure of the pharmaceuticals to ambient atmospheric factors can facilitate the degradation of many drugs.

At present, the NASA Space Medicine Operations Pharmacy repackages SODF using polymeric plastic bags with zip-lock closures purchased from Healthcare Logistics or Consolidated Plastic. These packages are readily permeable to gases and vapors, and do not meet the USP standards for 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*" (United States Pharmacopeia, 2020b). Likewise, current repackaging containers do not meet USP performance testing standards, which apply to pharmacists and institutional repackages of medications (United States Pharmacopeia, 2020c). NASA's current repackaging practices expose medications to atmospheric factors at concentrations that are equivalent to the ambient atmosphere because polymeric zip-lock bags are highly permeable to $O_2$ and moisture (Putcha, et al., 2016; Waterman, et al., 2002). Because atmospheric moisture and are detrimental to drug shelf life (Roy, et al., 2018; Waterman, et al., 2002; Waterman, Adami, and Hong, 2004), repackaging into low barrier packages likely compromise the long-term quality of susceptible pharmaceuticals (Putcha, Taylor, and Boyd, 2011). This would likely become a substantial problem during long-duration exploration missions because most SODF may need to be repackaged due to mass and volume limitations.

Drugs stored for a prolonged period in low Earth orbit degrade at a rate that is approximately 1.5-fold greater than the rate of degradation in terrestrial storage (Reichard, et al., 2023). That is, spaceflight increases the degradation rate by approximately 50%. However, as noted earlier, *both* the spaceflight samples and the matching terrestrial controls exhibited a substantial rate of premature failure. No previous NASA-supported study has tested samples in manufacturer's packaging, which is the gold standard for such comparisons (U.S. Food and Drug Administration (FDA), 1985; United States Pharmacopeia, 2020b). For this reason, a critical need exists to evaluate how current drug repackaging practices affect drug stability, compared to drug stability in protective packaging. Repackaging processes that protect the drugs most susceptible to degradation from atmospheric factors must be proven effective in high-quality stability studies.

### *3. RESEARCH DESIGN*

#### a. *Testing facility*

A partnership with the OPQ (separate from the work discussed in Aim 1) would be beneficial for accomplishing Aim 3. A formal SOW with the U.S. FDA would enable NASA ExMC to access necessary climate chambers, expertise, equipment, and personnel, and would cost much less than using a contract research

organization to perform this work because NASA would only pay for time and materials. The cost of employing contract testing laboratories or universities would be unfeasible due to significant overhead charges ("indirect costs") and the cost of materials, and the work would require more time to complete. Material costs primarily pertain to the purchase of reagents, standards, laboratory supplies, pharmaceuticals, and dedicated equipment (Appendix 4). Assuming a SOW with the FDA is established, accelerated (6 months) and long-term (12 months) repackaging studies would be performed on at least 10 drugs per year. An alternative approach to FDA testing is briefly discussed in the Potential Problems, Risks, and Alternatives section of Aim 3.

b. *Drug selection*

Initially, the ECF drug products that have the greatest susceptible to oxidative or hydrolytic reactions will be assessed for Aim3. The susceptibility of APIs to these reactions will be determined based on information obtained from U.S. FDA (Aim 1), predictive chemistry from Zeneth® software (Aim 2), and high-quality[22] published literature. ECF drugs containing APIs known to have low susceptibility to oxidation or hydrolysis, based on high-quality publications, will serve as negative controls. Any API that is predicted or reported to have DNA-reactive, mutagenic, or clastogenic hazards (i.e., nitrosamines) will be considered for stability testing.

It is well established that some excipients can facilitate degradation of a drug's API or contribute to the physical deterioration of a drug product. API susceptibilities (see Aim 2) will be considered in combination with known excipient effects to identify combinations of APIs and excipients that should be avoided (or favored) for long-duration space missions. Such interactions may be candidates for stability testing. Additionally, the APIs that are vulnerability to acid-facilitated hydrolysis will be identified. These medications could be susceptible to atmospheric $CO_2$ exposure when combined with atmospheric humidity and therefore these medications should be considered candidates for stability testing.

c. *Mechanism of degradation*

USP general chapter <1178> Good Repackaging Practices states that medications with stability problems, including those known to be sensitive to oxidation and moisture, should not be repackaged (United States Pharmacopeia, 2020b). A representative subset of sensitive medications from the ECF and from outside the formulary will be tested to evaluate the effects of repackaging on drug stability. The rationale for using a select set of drugs that are sensitive to atmospheric exposures is that medications known to be stable in the

[22] Study quality will be determined using Klimisch scores (Klimisch, Andreae and Tillmann, 1997), compliance with stability testing guidance (U.S. Food and Drug Administration (FDA), 2003; U.S. Food and Drug Administration (FDA), 2004) and standard analytical methods (Harrington, B., et al., 2014).

presence of humidity and $O_2$ are not expected to undergo chemical or physical degradation. It is assumed that packaging that improves the stability of sensitive drugs will also protect drugs that are less sensitive. Therefore, empirical testing of all drugs is unnecessary.

d. *Zeneth® degradation prediction*

Zeneth Software will provide a systematic, unbiased, and probabilistic tool for grouping and prioritizing drugs for stability testing. As described in Aim 2, this tool provides an efficient process for identifying mechanism-based drug sensitivities, especially for data-poor chemicals.

e. *Repackaging*

The shelf life of SODF will be tested with and without protective packaging. The same protocol and packaging products currently used by NASA will be assessed as the non-protective packaging. Selected drugs repackaged per current NASA repackaging methods will be compared to the same drugs, from the same manufacturing lots, in sealed manufacturer packaging and in at least one commercially available protective repackaging product.

Drug repackaging options have been reviewed previously in a comprehensive NASA preliminary market survey (Ronzano, 2014). Although this report is several years old, the candidate repackaging products listed appear to be commercially available at the current time (Dec 2023). Because the market survey report was preliminary, it did not evaluate relative product costs, product availability, current FDA approval status for use with foods and drugs, equipment required to review products, or physical considerations including mass. For these reasons, the report will be updated to capture new information and developments in the field that have occurred since 2014 and will follow up on items in the report listed as TBD or “future work”. The detailed information contained in the report does provide a reasonable basis for selecting packaging products for the proposed stability testing studies.

Temperature and humidity data loggers will be incorporated into the packaging of a subset of samples to track atmospheric permeation of the packaging, as previously described (Bowen, et al., 2007; Nelson and Huang, 2011). The U.S. FDA has lab-scale and commercial-scale manufacturing facilities that may be used to support packaging studies. Alternatives to collaborating with the FDA are the multiple FDA-compliant contract repackaging companies that advertise protective packaging capabilities. Such contract repackaging companies will be contacted for further information.

f. *Chemical stability testing approach*

*1) Drug stability studies*

Under Aim 1, stability testing will be used to quantify degradation kinetics and pathway susceptibility, and to identify major degradation impurities for each tested drug product and packaging condition. Two types of FDA guidance-compliant stability studies will be conducted: accelerated stability studies and long-term stability studies. First, accelerated stability studies will be performed at elevated temperatures and relative humidity (40°C and 75% RH) for 6 months. The FDA requires accelerated testing studies (a.k.a. stress testing) of all drugs marketed in the US.[23] Such studies determine how elevated temperatures and RH affect degradation pathways and impurity formation, and to set shelf-life periods. Conditions typically used for accelerated stability testing studies are considered off-nominal conditions for a NASA crewed mission. Therefore, drugs determined to be stable under these testing conditions would likely be suitable for exploration space missions. Next, long-term drug stability studies will be performed at 30°C and 65% RH for a minimum of 12 months (U.S. Food and Drug Administration (FDA), 2003; U.S. Food and Drug Administration (FDA), 2004) to confirm the accelerated test results. Long-term studies calculate degradation rates and shelf-life extension times for the tested drug products.

*2) Accelerated and long-term stability tests*

If possible, both accelerated and long-term stability tests will be employed. Accelerated stability studies are preferred for identifying drugs that are most susceptible to degradation or that develop major impurities, and for testing countermeasures to inhibit degradation. Long-term studies, which are much slower, are preferred to confirm the results of the short-term analyses. If a contract laboratory is used rather than the U.S. FDA, then accelerated studies will be the primary focus to reduce experimental costs while still obtaining the multiple timepoints required to accomplish the objective of Aim 3. According to FDA guidance, "[t]he use of accelerated testing data to establish a tentative expiration dating period of greater than 3 years is discouraged when it is based solely on accelerated data." (U.S. Food and Drug Administration (FDA), 1985). For this reason, accelerated testing studies may *not* be adequate for estimating shelf-life with a high degree of confidence for some medications; long-term stability studies may be needed in these cases. It is possible that cost could be reduced by using the drug repository chamber currently available at JSC for long-term studies, which will provide cost savings relative to a contract testing facility; however, it is imperative that timepoint samples undergo immediate analytical analysis.

[23] https://www.fda.gov/files/drugs/published/ANDAs--Stability-Testing-of-Drug-Substances-and-Products--Questions-and-Answers.pdf, https://www.federalregister.gov/documents/2013/06/20/2013-14674/guidance-for-industry-guidance-on-abbreviated-new-drug-applications-stability-testing-of-drug.

*3) Analyses of Results*

Degradation rates will be calculated directly from analytic potency results of long-term studies. Linear statistical methods (The International Council for Harmonisation (ICH) of Technical Requirements for Pharmaceuticals for Human Use, 2003; U.S. Food and Drug Administration (FDA), 2004) and non-linear mixed models (Chen, Hwang, and Tsong, 1995; van den Heuvel, et al., 2011) will be used, as previously described, to calculate degradation rates and shelf life extension times. The Arrhenius relationship to describe the relationship between temperature and degradation rate obtained from the accelerated studies will be used if the chemistry follows zero- or first-order kinetics. When necessary, degradation models will incorporate pH and RH parameters (Some, et al., 2001). Methods to infer drug shelf life from accelerated tests are well documented (Tsong, et al., 2003), although it is recommended that testing protocols, analyses, and statistical models be developed in close partnership with the U.S. FDA Office of Product Quality, if feasible.

*4) Replicates*

Drug potency tests (termed "assay" in USP guidance) typically involve reporting only the *average value* of replicate composite preparations. Composite samples are prepared by combining multiple dosing units (i.e., tablet, capsules) in a homogenized sample. Pharmaceutical manufacturers use composite samples to reduce the variability attributed to individual dose units. Composite samples yield a pseudo-average of drug potency. This "average" is the reported value. No replicates are required under typical USP specifications for drug potency, which has several important limitations (Nickerson, et al., 2017). Independent replicates are required for statistical hypothesis testing. Hence, independent replicates are essential for any study that aims to test whether (or not) environmental factors influence medication quality. Therefore, the approach described by the USP is inadequate for statistical testing and should *not* be relied on. The number of replicates depends on the variability of the method and the required degree of confidence for the results (i.e., 95%, 80%). The ExMC stability strategy defines experimental replicates as independent samples from similar treatments and not repeated analyses of the same processed sample, which are often referred to as technical or analytical replicates. The strategy for testing stability shall account for variability due to the dosage form (e.g., tablets) and due to the analytical method (inclusive of sample preparation, standard preparation, analytical analysis). The basis for this rationale, in the context of performing potency assays, is well recognized (Harrington, et al., 2014; Nickerson, et al., 2017).

To achieve the desired outcomes, stability testing shall include multiple independent analytical replicates to characterize methodological variability, multiple timepoints to estimate degradation rate, and pair-matched samples from the same manufacturing lot starting at day zero across all time points.

*5) Metadata*

Metadata for each drug will always include the manufacturer, the dosage form, the packaging lot number (12-digit NDC number), the expiration date, the storage dates, the flight/landing dates, and the repackaging methods. In addition, storage metadata should also include summary data on RH, temperature, $O_2$, and $CO_2$ levels, and the cumulative radiation exposure, rate, and type. Conditions inside the packaging will be collected and retained using atmospheric data loggers as discussed above.

g. *Physical stability testing approach*

Tests of the physical stability of SODF will include measurements of hardness, weight, color, and API release (i.e., dissolution) that are consistent with USP specifications at each time point. Absorption of atmospheric moisture commonly affects tablet hardness and weight, which are used to assess softening of the dosage form because softening can significantly increase the rate of API release from the drug. Dissolution tests measure the rate at which the dosage form dissolves and releases API. Drug aging can slow dissolution of drugs that include polymeric coatings or polymer excipients (i.e., cellulose, PEG) because crosslinking of polymer chains increases with time (Waterman and Adami, 2005), and ionizing radiation can increase polymer crosslinking (Sarcan and Ozer, 2020; Sintzel, et al., 1997). Quotes for the cost of physical stability testing from 3 contract testing labs have been obtained to support this testing strategy. The U.S. FDA has offered to provide these same physical tests for the cost of the time and materials.

*1) Timepoints*

Real-time testing for the entire duration of an exploration mission, which is 2–3 years (Smith, 2020), will be challenging and expensive. Instead of testing stability for the full duration, tests will include an adequate number of sampling timepoints in the same packaging used for flight, and degradation kinetics over a much shorter period will be extrapolated to estimate content for the duration of the mission. During the accelerated studies (6 months), drugs will be analyzed at the initial and final time point and at least 2 additional time points for a total of at least 4 timepoints (0, 2, 4, and 6 months). More timepoints will improve the estimate of degradation rate and will help identify nonlinearities in rates. Similarly, long-term testing (1–2 years) will analyze product quality at similar intervals through the first 6 months, after which samples may be drawn approximately every 3 or 4 months through the end of the study.

*4.* EXPECTED OUTCOMES

- *Completion of Aim 3 will produce estimates of drug potency at the time of use for drugs that exhibit susceptibility to environmental factors (e.g., humidity, $O_2$, temperature), and time-dependent drug*

*potency levels, estimated from degradation rates calculated using linear statistical methods. It is expected Aim 3 will demonstrate that drugs repackaged using current methods undergo significantly greater deterioration than controls, which will justify the development of best practice protocols for drug repackaging.*

- *Completing Aim 3 will update and complete the2014 drug packaging market survey that reviewed commercially available options for drug packaging. This will enable objective section of the most appropriate packaging strategy for each drug product, which in turn will inform the design and best practices for provisioning the medical kits for exploration space missions.*
- *To the extent possible, under time and budget constraints, Aim 3 will demonstrate the effects of atmospheric exposure on the accumulation of degradation impurities. Because impurities can form through the interaction of the drug API or excipients and atmospheric factors, and protective packaging prevents this interaction, it is expected that Aim 3 will confirm that protective packaging reduces the risk of hazardous impurity formation.*
- *The API content of medications at the time of use, which were estimated from brand dependent degradation rates, will provide input for the stoplight framework discussed in Aim 2. Testing several brands of the same drug product containing different excipients ingredients will determine how formulation affects the products' susceptibility to environmental exposure under the described testing conditions.*

## *5.* POTENTIAL PROBLEMS, LIMITATIONS, AND ALTERNATIVES

### a. *Hypothesis Testing*

Although unlikely, it may be determined that the drugs selected under Aim 3 are as stable as controls under the different treatment conditions tested (i.e., packaging). This result would support the continuation of the current repackaging process for exploration missions. Failure to reject the null hypothesis in terrestrial studies (i.e., there is no difference in stability between repackaged drugs and matched samples in manufacture packaging) would suggest that low dose-rate ionizing radiation or other environmental latent variables (those not measured in previous spaceflight studies) contribute to increase drug degradation during spaceflight (i.e., $CO_2$, non-ionizing UV radiation, elevated temperature exposures). These concerns, particularly ionizing radiation, will be addressed under Aim 4.

### b. *Nonsolid Drug formulations*

Aim 3 does not address the stability concerns associated with non-solid drug formulations. A focus of Aim 1 is to acquire information on manufacturer's shelf-life from FDA databases, which includes aqueous solutions. Many aqueous drug formulations (i.e. ophthalmic, otic, oral, and injectable solutions) likely have shelf lives much shorter than the duration needed for exploration missions. Overpackaging of liquid medications may provide some level of protection from ambient atmospheric conditions. However, some drugs may require alternative approaches such as replacing these drugs with more stable formulations, reformulating drugs such as lyophilization or adding preservatives, or storing them at low temperature, which substantially slows chemical reactions and is acceptable under USP standards (United States Pharmacopeia, 2021). Required approvals should be carefully considered before a reformulated drug product is administered to humans, including attaining approval from the Institutional Review Board and submitting an Investigational New Drug application to the U.S. FDA.

c. *Repackaging*

Aim 3 will not compare different types of protective drug packaging. Determining the most effective, efficient, and acceptable type(s) of packaging will require input from operational stakeholders to ensure that concerns such as off-gassing, waste disposal, convenience, mass and volume, and other relevant operational concerns are addressed. The focus of Aim 3 is to determine the limitations of current repackaging methods and the extent to which a representative repackaging technology may prolong shelf life of susceptible drug products. The results of the tests discussed in this aim should provide justification for using established methods for future studies to compare alternative repackaging strategies, as warranted.

d. *Testing Laboratory Selection*

Collaboration between ExMC and the OPQ is expected to include the purchase of a dedicated instrument to significantly increase testing efficiency, increase the number of tests performed, and lower per test costs over time. This instrument would be located at the FDA in the laboratory facilities of OPQ Research but would belong to ExMC and will be returned to NASA when the project ends. In addition, the FDA Office of Pharmaceutical Testing has informally offered, as of September 2023, to provide access to climate chambers, labor, and testing at cost. The alternative to an FDA partnership is to perform testing through a contract lab, which will still achieve the overall aim, but the information obtained will be substantially more limited due to much higher per-drug costs, as based on quotes obtained from 4 contract testing labs (market survey performed by KBR, 2021). If a contract laboratory is used, much fewer drugs will be tested, which will increase uncertainty due to the smaller number of drugs tested. Additionally, quotes from candidate contract testing

labs do not include accelerated and long-term climate chamber storage costs; only the cost of analytical testing is covered by the price quotes.

e. *Impurity Analysis*

Aim 3 does not explicitly propose identifying and quantifying degradation impurities. The objective of Aim 3 is to elucidate the role of repackaging and environmental exposure on drug stability. Drugs that exhibit accelerated degradation under study conditions can be prioritized for subsequent impurity analysis. If a partnership with the FDA is established, as described in Aim 1, common impurities for each formulary medication can be collected from the FDA databases. When impurities are identified, analysis should focus on impurities that exceed the minimum qualification thresholds for daily intake of drug products per ICH Q3A and Q3B guidance. However, lower qualification thresholds may apply if the identified impurities are unusually toxic (i.e., DNA-reactive). In the absence of FDA data, a contract laboratory can characterize impurity profiles and analyze impurities as part of the contract.

*6.* NOTIONAL TIMELINE AND BENCHMARKS FOR SUCCESS

The timeline for completing this project is relative to when the project begins (kickoff). The timeline will start after the IAA between the FDA and NASA is approved, and the contract is fully executed. As presented in the FY2023 Pharmaceutical Risk budget, Year 1 of Aim 3 is tentatively anticipated to begin in FY2026.

## D. AIM 4. QUANTIFY THE EFFECTS OF IONIZING SPACE RADIATION ON DRUG DEGRADATION

*1. INTRODUCTION*

Table 5. Notional timeline for Aim3.

| Task | Y1 (ca 2025) | | | Year 2 | | | | | | | | | | | Year 3 | | | | | | | | | | | | Year 4 | | | | | | | | | | | | Year 5 | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 7 | 8 | 9 | 10 | 11 | 12 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| Assuming collaboration with FDA, Purchase Analytical Equipment | X | X | X | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Order drugs for testing | | | | X | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Drug Repackaging | | | | | X | | | | | | | X | | | | | | X | | | | | | X | | | | | X | | | | | | X | | | | | | | | | | | | | |
| Technician/Fellow/contractor | | | | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | | | | | | | | | |
| Accelerated Testing (chamber) | | | | | | X | – | – | – | – | > | X | – | – | | – | – | > | X | – | – | – | – | > | X | – | – | – | – | > | X | – | – | – | – | > | X | – | – | – | – | > | | | | | | | | | |
| Accelerated testing Analysis (Weeks 0, 1, 2, 4, 8, 12, 16, 24) | | | | | | X | X | X | X | | X | X | X | X | | X | | X | X | X | X | X | | X | X | X | X | X | | X | X | X | X | X | | X | X | X | X | X | | X | | | | | | | | |
| Long-term testing (Chamber) | | | | | | X | – | – | – | – | – | – | – | – | | – | – | > | X | – | – | – | – | – | – | – | – | – | – | > | X | – | – | – | – | – | – | – | – | – | – | > | | | | | | | | | |
| Long-term Stability Analysis , (months 0, 1, 3, 5, 7, 9, 12) | | | | | | X | | X | | X | | X | | X | | | | X | X | | X | | X | | X | | | | | X | X | | X | | X | | X | | | | X | | | | | | | | |
| Result analysis | | | | | | | | | | | | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Prepare summary report | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | X | X | X | X | X | X | X | X | X | X | X | X |
| Submit publication | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | X | X | X | X | X | X |

This timeline represents the initially period of data drug stability testing, data collection and interpretation for drugs currently in the exploration candidate formulary. Abbreviations: X = tentative

It has been suggested that ionizing radiation exposure during spaceflight facilitates the degradation of drugs, thereby increasing the risk of therapeutic failure or adverse toxicological effects (Blue, Chancellor, et al., 2019; Mehta and Bhayani, 2017). However, no controlled spaceflight studies have been performed to directly test if space radiation affects drug stability. Currently, it is unknown whether cumulative doses of ionizing space radiation, at levels at or below human exposure limits (National Academies of Sciences, Engineering, and Medicine, 2021) are damaging to even the most sensitive medications.

Radiosterilization literature supports a relationship between exposure to high dose ionizing radiation and drug degradation. This information has been qualitatively interpreted as an indication that prolonged exposure of medications to ionizing radiation can decrease drug potency and results in accumulation of hazardous degradation products. However, this interpretation fails to account for the dose-effect relationship between ionizing radiation and drug quality. Furthermore, the perceived risk fails to establish the critical contributions of drug formulation, environmental conditions, and reaction rate, among other factors. For these reasons, a need exists to systematically measure the effect of space ionizing radiation on the stability of *susceptible* drugs. The *overall objectives* of this aim are to measure the effect of ionizing space radiation on drug degradation and evaluate the interactions between atmospheric factors and ionizing radiation exposure. The *hypothesis* to be tested *is* that drugs that are prone to oxidation are more susceptible to spaceflight ionizing radiation than drugs that are not susceptible to oxidation. The approach to test this working hypothesis is to conduct terrestrial stability testing, mine data from radiostability literature and computational analysis of drug stability, in conjunction with performing controlled, long-term longitudinal spaceflight validation studies to compare degradation rates of representative radiation-sensitive and non-sensitive drugs. The *rationale* is that successful completion of Aim 4 will estimate the worst-case effects of space ionizing radiation on drug stability and provide insight into the effectiveness of packaging methods to inhibit degradation. In decreasing order of priority, the expected outcomes are (1) demonstrate the magnitude of the effect of charged particle radiation on drug degradation; (2) demonstrate the role of formulation (solid or liquid) on drug radiostability; (3) evaluate whether radiation dose-rate influences drug stability; (4) characterize the mechanistic contribution of atmospheric factors to radiation-mediated drug degradation.

### *2. RELEVANT INFORMATION AND LITERATURE THAT JUSTIFY RESEARCH STUDIES*

Ionizing radiation interacts with materials composing pharmaceuticals in one of 2 ways: (1) stochastic atomic displacement collisions with drug molecules, or (2) radiochemistry (i.e., ionization, radical production) (Shulman and Ginell, 1970). Of these 2 mechanisms, radiochemistry is the most applicable to spaceflight stability of drugs (Reichard, 2023). Through these 2 types of interactions, ionizing radiation can facilitate

degradation of drug ingredients, resulting in a potential loss of drug potency or formation of degradation products, some of which may be hazardous to humans.

a. *NASA-Supported Drug Stability Studies*

Ionizing radiation effects on drug stability during long-duration spaceflight remain unsubstantiated. Only a few NASA-supported studies have attempted to evaluate the effects of ionizing radiation on drug stability; however, for reasons related to either the study design or the loss of experimental results, previous studies have not adequately characterized this risk. These studies and their associated limitations are discussed in more detail in the ExMC Pharmaceutical Stability Evidence Report (see *The Effects of Ionizing Space Radiation on Drug Stability section)*. In the absence of scientific evidence, a research plan is proposed to close the gap related to the effects of spaceflight radiation on drug quality. This work will help characterize the risk that drugs may not be sufficiently stable during exploration space missions.

It has been proposed that ionizing radiation exposure during long-duration spaceflight could facilitate drug degradation (Blue, Chancellor, et al., 2019; Du, et al., 2011; Mehta and Bhayani, 2017; Putcha, et al., 2016; Wotring, 2012). This hypothesis is based primarily on a reported decrease in the potency of multiple drugs stored on board the ISS for up to 880 days (Du, et al., 2011). However, this hypothesis is not well supported by the Du et al. 2011 study because it is contingent on the assumption that potential confounding factors, both analytical and environmental, were the same for both arms of this pilot study. The evidence report for drug stability discusses the important methodological and statistical uncertainties of the Du et al. 2011 study (Reichard, 2023). Additionally, no NASA-supported spaceflight drug stability study has included controls needed to distinguish the effects of spaceflight radiation from other environmental factors that are known to mediate drug degradation (i.e., $O_2$, humidity) (see drug stability evidence report, section titled "Opportunistic Spaceflight Studies of Drug Content"). The evidence that is available does not appear to support a generalized effect for ionizing radiation on drug stability (drug stability Evidence report, Appendix 9)(Reichard, 2023). If it is true that galactic cosmic radiation significantly accelerates drug degradation, because aqueous drug solutions are generally much more susceptible to ionizing radiation than solid dosage forms (see *Drug Degradation in aqueous solutions* section III.D.2.d), then the aqueous solutions tested by Du et al. 2011 (lidocaine, epinephrine, promethazine solutions and ciprofloxacin suspension) should have shown a prominent and progressive change in drug content as a function of increasing radiation dose over the 880-day time course, relative to terrestrial controls. However, this was not observed. Instead, the aqueous

formulations tested by Du et al. 2011 show that spaceflight and control samples exhibit very similar degradation trends over time (Figure 3).

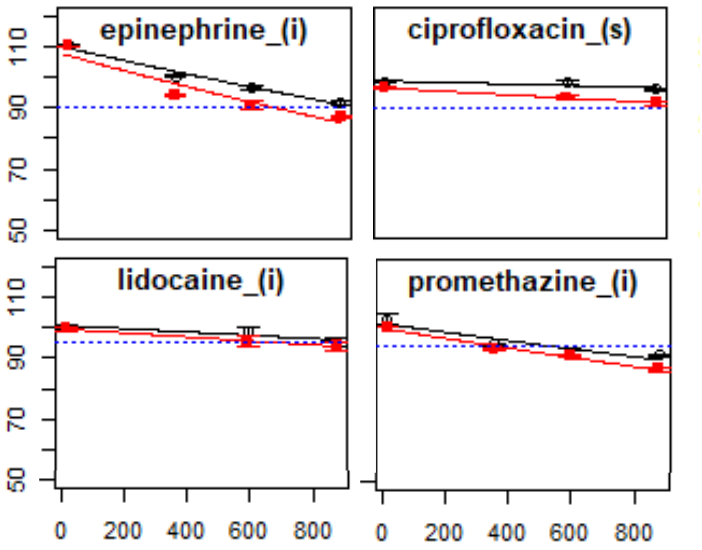


***Figure 3. Degradation of aqueous dispersion formulations in terrestrial and spaceflight conditions.*** *Symbols are the drug content reported by Du et al. 2011, lines are best fit first-order regression models of the available datapoints. Black lines and symbols correspond to terrestrial controls, red corresponds to spaceflight samples.*

Along similar lines, a NASA technical paper concluded that nanomolar concentrations of radiation byproducts could be produced in spaceflight-exposed liquid pharmaceuticals; however, the model predicts that the radiolytic yield of reactive species is low and would not have a substantive effect on drug content at the molar concentrations of the drug products, even for the most sensitive formulations (Kim and Plante, 2015). For further discussion, see the drug stability evidence report (see *In Silico Modeling of The Effect of Spaceflight Radiation on Drug Stability section* in Reichard, 2023). Together, these results suggest ionizing radiation exposure during prolonged spaceflight should not impact stability of drugs in a solid state; and effects on aqueous drug solutions are doubtful but should be confirmed.

b. *Previous studies of drug stability in ionizing space radiation environments*

Several important characteristics distinguish the radiation exposures used in radiostability studies from spaceflight ionizing radiation. These differences include radiation types, dose-rate, cumulative dose, and exposure time. These differences must be considered when evaluating radiation stability of pharmaceuticals.

Drugs are usually sterilized using very high dose and dose-rate gamma-ray irradiation, usually from a $^{60}$Co emission source. Less commonly, drugs are sterilized using accelerator-generated electron beam (e-

beam) irradiation (Marciniec and Dettlaff, 2008). Space radiation, however, is a complex mix of high-energy particles that are mostly protons as well as heavier charged nuclei (higher Z) and, to a much lesser extent, electromagnetic radiation (Chancellor, et al., 2018; Kim and Plante, 2015). Spaceflight drugs will be exposed to a shielded radiation environment in the spacecraft, which shifts the radiation spectrum towards lower Z and lower energy particles (Kodaira, et al., 2021; Naito and Kodaira, 2022; Simonsen, et al., 2020). Because protons constitute, by far, the largest component of accelerated particles within a spacecraft, it is not necessary to recapitulate the full spectrum of ionized particles constituting galactic cosmic radiation for analog studies; rather, drug radiostability can be reliably evaluated using simpler proton irradiations. Proton irradiation will adequately simulate the effects of space radiation on drug products. The NASA Space Radiation Laboratory (NSRL) will be considered for drug irradiation studies, although other irradiation contract facilities can be considered as well.

Dose-rates and cumulative doses used in radiostability studies of pharmaceuticals are *much* greater than those associated with long-duration spaceflight. Pharmaceutical products are sterilized using several manufacturing processes including heat, ethylene oxide, and ionizing radiation. The standard dose of gamma and beta radiation used to sterilize drugs is 25–50 kGy. For gamma radiation, this dose is administered at a rate of 0.1–1 Gy/s[24], depending on the radiation source (Marciniec and Dettlaff, 2008). By comparison, the cumulative ionizing radiation exposure for deep space mission is around 218.9 mGy/y ($6.0 \times 10^{-4}$ Gy/d) with a cumulative dose of approximately 1 Gy for a roundtrip Mars transit mission (National Academies of Sciences, Engineering, and Medicine, 2021). Hence, both total dose and dose-rate of space radiation is approximately 7–8-orders of magnitude lower than that used for drug radiosterilization. Although it could be argued that the very high absorbed dose and dose-rates commonly used for drug radiostability studies have little direct relevance to radiation levels expected during a space mission, the radiosterlization data have several important advantages:

1) *Drug radiostability studies performed over a range of doses have established that the dose-effect relationship between radiation and drug degradation is positively correlated over a wide range of doses under consistent environmental conditions. The relationship between radiation dose and degradation effect can be summarized by a linear rate constant. Because the dose-effect relationship is linear, radiation doses less than the threshold dose that elicits measurable degradation will not have a greater effect on stability than the higher doses.*

[24] 10–100 rad/s in the cited reference.

2) *Since drug radiosterilization exposures are many orders of magnitude greater than the acceptable occupational exposure for a Mars mission, the resulting margins of exposure greatly increase confidence that medications that are stable after exposure to high doses of radiation will be just as stable after exposure to much lower levels of radiation.*

3) *Radiation exposure during a planetary mission will accrue at a low rate over months to years, whereas radiosterilization involves very high rates delivered in minutes. This is important for solid state drugs because drug degradation initiates at imperfection sites in drug crystals. Ionizing radiation insults are always in the form of highly structured tracks of ionization and excitation events, and the ionization density in the track center increases with the linear energy transfer (LET) of the charged particle. High dose-rate radiation exposures induce large numbers of tracks in a short time period that nucleate regions of degradation, whereas low-dose rate radiation induces fewer tracks spread over longer time periods and the diffuse production of reactive species is much less likely to nucleate degradation reactions. Because drugs in aqueous solutions behave differently that drugs in solid forms, they appear to be MORE susceptible to degradation from low-dose rate radiation at kGy dose levels.*

Although ionizing radiation associated with spaceflight is quantitatively and qualitatively different from the types of radiation used for radiosterilization, radiosterilization study results may be useful for identifying drugs in the ECF that are the most sensitive to ionizing radiation. For the reasons discussed in the following sections, some drugs are exceptionally sensitive to ionizing radiation. These drugs, especially those formulated in aqueous suspensions, have been shown to undergo significant degradation after short-term exposures to relatively low doses of radiation. 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.

c. *Degradation Products are not Unique*

Studies have shown that radiolysis induced degradation products in food and pharmaceutical are generally not unique to irradiation (Jacobs, 1985; Jacobs, 1995; Jacobs, 2022). Multiple studies have reported that radiolysis induced drug degradation products are the same as those found in the same drug after they are sterilized using different procedures. Furthermore, the Food and Agriculture Organization(FAO)-International Atomic Energy Agency (IAEA)- World Health Organization (WHO) Expert Committee (WHO, 1981) on irradiated foods reported that the same toxicological effects occurred regardless of whether (or not) the food had been irradiated, and the same radiolytic products are identified regardless of the sterilization treatment process. Furthermore, radiation doses of up to 10 kGy pose no danger to consumers (WHO Joint FAO and IAEA Expert Committee, 1981). In the context of available evidence, there is no indication that

inferences from irradiated food studies would not also apply to pharmaceuticals (Jacobs, 2022). Taken together, evidence supports the conclusion that although prolonged exposure to a spaceflight environment may facilitate degradation of susceptible drugs, the degradation pathways and reaction products do not differ from those observed in FDA-compliant stability studies.

d. *Drug Degradation in Aqueous Solutions*

It is very well established that irradiating pure liquid water leads to the formation of reactive species, of which the most important are $^{\circ}OH$, $H_2O_2$, $H^{\circ}$, $H_2$ and $e_{aq}^-$ (hydrated electrons) (Kim and Plante, 2015; Marciniec and Dettlaff, 2008; Sintzel, et al., 1997). Of these reactive intermediates, $^{\circ}OH$, and $H_2O_2$ are potent oxidative moieties impacting drug substances (Illés, et al., 2013; Nisar, et al., 2016; Slegers and Tilquin, 2005; Slegers and Tilquin, 2006). If atmospheric $O_2$ is present, the formation of $^{\circ}OH$ and $O_2^{-\square}$ is favored, which can contribute to oxidation or reduction of drug substances, depending on the pH. Drug stability can be improved by purging the drug products with argon (Sintzel, et al., 1997) or other methods that remove $O_2$ (Jacobs, 2022). The production and diffusion of reactive intermediates in aqueous drug formulations makes solutions significantly more susceptible to degradation than solid formulations (Gopal, 1978; Marciniec and Dettlaff, 2008). As shown in Figure 4, after solid-state drugs are irradiated with 60 kGy of gamma radiation, they had only a few percent decrease in their API content, whereas the same drugs dissolved in water undergo significantly greater decomposition after radiation, with some degrading 40–50% after less than half the absorbed radiation dose (25 kGy) (Marciniec and Dettlaff, 2008). Aqueous formulations are more susceptible to radiation, in part, because water is a more likely target for radiolytic interaction than drug molecules; the result is a cascade of reactive species which, unlike solid-state medications, diffuse from the site of formation to interact with drug ingredients. By comparison, in the solid state, radicals and other reactive species are constrained by the “cage effect” and are less capable of reacting with drug contents. Freezing a susceptible solution at -80$^{o}$C significantly increases 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; Silindir Gunay and Ozer, 2009). Because a large portion of the medications on the ECF are aqueous dispersions (e.g., solutions, suspensions, creams), it is important to determine the radiostability of aqueous formulations.

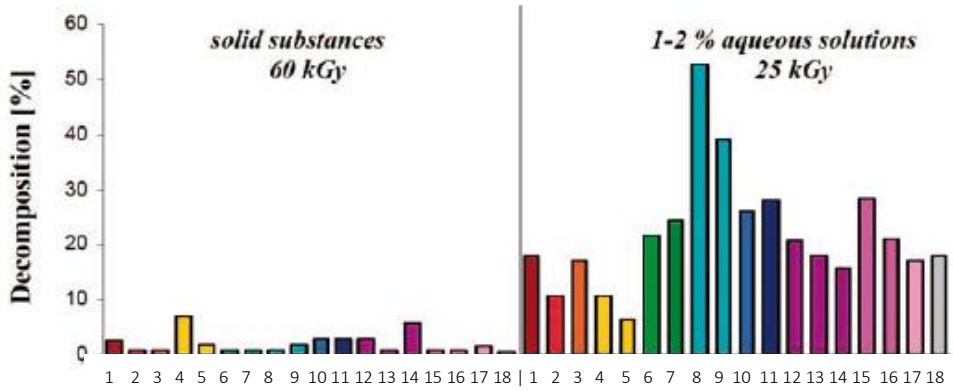


***Figure 4. Comparison of the decomposition of solid substances and aqueous solutions*** *subjected to 60 kG and 25 kGy of gamma radiation, respectively. Repeated colors are results from independent studies. From left to right: 1) atropine sulphate, 2) cocaine hydrochloride, 3) codeine phosphate, 4 and 5) ephedrine hydrochloride (x2), 6) hydrocodone hydrochloride, 7) hydrocodone hydrogentartrate, 8 and 9) hydromorphone hydrogentartrate (x2), 10) levomethadone, 11) methadone hydrochloride, 12–14) morphine hydrochloride (x3), 15 and 16) oxycodone hydrochloride (x2), 17) pilocarpine hydrochloride, and 18) scopolamine hydrobromide. (Boess and Bögl 1996)*

e. *Drug degradation is greater at low dose-rates of ionizing radiation*

An inverse relationship exists between the dose-rate of radiation exposure and drug stability. For low concentrations of a specific drug solution, a lower rate of irradiation causes greater decomposition (loss of the active substance) than the same radiation dose delivered at a higher rate. Experiments have shown that degradation increases monotonically with decreasing dose-rate in aqueous solutions of atropine (0.1%), benzalkonium chloride (0.3%), morphine (1%), or lidocaine (2%) irradiated with 10 kGy at rates of 0.01–10 Gy/s (Gopal, 1978). A 10 kGy dose of gamma-rays delivered at the rate of 2.5 kGy/h degraded 28% of atropine sulfate (1.0% solution), whereas, the same radiation dose administered at 0.1 kGy/h degraded 62% of the same drug (Boess and Bögl, 1996; Marciniec and Dettlaff, 2008). Thus, although the cumulative dose of ionizing radiation during spaceflight is many orders of magnitude less than the doses used for radiostability studies, it is plausible that the low dose-rates associated with spaceflight could result in greater degradation of medications than an equivalent radiation dose administered rapidly. For this reason, high-dose-rate studies such as nearly all terrestrial radiostability studies may underestimate the effect of low-dose-rate radiation exposure on medication stability. Studies of low-dose rate radiation exposures can be simulated terrestrially using a divided dose strategy that repeatedly exposes medications to a portion of a target cumulative radiation dose. Alternatively, a well controled spaceflight study can yield insight, especially if effects are compared to rapid radiation exposure of a similar cumulative dose and the drugs are stored for the same amoun of time. Before performing such long-duration studies, the radiostability of medications should be characterized.

## *3. RESEARCH DESIGN*

### a. *Literature-analysis of Drug Radiostability*

#### *1) Approach*

The literature on drug radiostability of pharmaceuticals is extensive. Quantitative analysis of data from these studies can provide insights into the stability of drugs exposed to spaceflight radiation, the shape of the dose-effect curve, and how dosage form affects radiostability. Quantitative radiostability data will be extracted from literature sources for cumulative stability analysis.

Drug degradation caused by radiation, regardless of dose, has been used to support the rationale that exposure to spaceflight radiation will degrade drugs (Blue, Chancellor, et al., 2019; Mehta and Bhayani, 2017). This rationale does not appear to be consistent with available evidence and the monotonic relationship between radiation dose and effect (Boess and Bögl, 1996; Gopal, 1978). The radiation dose used for radiosterilization is 25 kGy, which is ~25,000 times greater than the radiation dose limit for a Mars DRM, assuming approximately 1 Gy total radiation exposure (Naito and Kodaira, 2022), and more than 5,000 times greater than the acute lethal radiation dose for humans. Pharmaceuticals exhibit a non-linear radiation dose-effect relationship, and drugs have a threshold dose below which the effects of radiation on stability are negligible. This threshold dose is orders of magnitude higher than the dose that is lethal to 50% of exposed humans (~4.5 Gy) (National Academies of Sciences, Engineering, and Medicine, 2021). Because planetary DRMs are expected to have radiation levels well below the lethal dose (< 1 Gy), there should be a substantial margin between radiation doses that cause drug degradation and those that are permissible for human space missions. Therefore, the key to characterizing the risk of drug degradation due to ionizing radiation exposure is characterizing the distribution of the NOEL of drugs. From this information, the radiation dose at the lower $95^{th}$ or $99^{th}$ percentile can be estimated, below which the risk of drug degradation is minimal. The effects of different drug-related factors on the NOEL can be further investigated, as needed. The first task to be accomplished under Aim 4 is to collect and model NOEL data for all ECF drugs that have this data available.

#### *2) Data collection*

Radiation stability information will be collected from published literature and other sources. Data will be collected for drug substances in any form, including liquid, solid, or powder. The information collected will pertain to the drugs listed on the ECF, however, radiostability data for other drugs will be collected, when available.

Data will be collected from tables, text, or figures. Figures containing data will be digitized using available web-based tools for data extraction (e.g., https://automeris.io/WebPlotDigitizer/).

The tools used to search the literature will include Google Scholar, indexing services (e.g., Embase, Web of Science), and tree searching. Although NLM's PubMed is a convenient source for many original articles, pharmaceutical chemistry articles are often not available through PubMed, which focuses on life science articles written in English. Because several comprehensive reviews on drug radiostability have been published, the most recent in 2022, tree searching has proved to be very productive for identifying drug radiostability data so far. However, the review articles provide only summary information and therefore original articles are often required to obtain complete datasets.

Web of Science and PubMed should be used for systematic Boolean searches. An advantage of Web of Science is the broader range of topics and inclusion of multiple indexing services, including Medline. An advantage of PubMed is the controlled vocabulary (medical subject heading terms) that can improve the specificity of a search. A variety range of search terms have been evaluated including radiosterilization, radiostability, radiochemistry, and radiodegradation. These terms can be combined with other terms to narrow results including the United States Adopted Name or international nonproprietary name of the drug substance.

*3) Rule-in / Rule-out criteria*

Only drug content (API) data is adequate for assessing drug stability. Only drug content data collected using chromatography systems with photo diode array, infrared, mass detectors or other analytical methods that directly measure API content are suitable (i.e. stability indicating methods). Other methods that indirect infer stability from drug activity of effect quantitation such as spin resonance spectroscopy, efficacy (such as minimum inhibitory concentration) are not acceptable for quantifying threshold, but should be noted for other purposes.

Numerous studies exist on the ecological application of ionizing radiation to remove drugs from water systems, such as for purifying drinking water and treating sewage effluence. These studies are generally excluded from the proposed analysis because the high content of organic, non-organic, and biological materials in the water interact with the drug substance, and this does not reflect pharmaceutical products.

*4) Study factors to be collected*

The drug and radiation-related parameters to be collected from each study reviewed are listed in Table 6. Additional information may be added to the list as required to accurately capture parameters to compare studies and analyze groups of drugs.

| Table 6. Data to be Collected from Drug Radiation Stability Literature | |
|---|---|
| Dose rate | Units = Gy/Hour. The rate at which the absorbed radiation dose is administered in the study. |
| Irradiation power | Usually specified for electron beam in units of MeV. Gamma is usually given as isotope |
| Tested drug form | Form of the drug that was tested; usually powder, solution, solid, cream or tablet |
| Drug Concentration | Drug Concentration in the non-solid formulation tested. Units = mg/mL |
| Treatment Temperature | Units = Degrees Celsius. Temperature at which the drug was irradiated. |
| Degradation rate (K) | Units = Percent change per kGy. Calculated exponential degradation rate as a function of absorbed dose. Based on dose-effect relationship data. |
| No observed Effect Levels (NOEL) | Units = kGy. Highest radiation dose at which there is not significant changes in API content. No significant change can be either based on statistical change (if available) or a benchmark effect of ≤ 5% decrease from baseline. If a NOEL is not observed, then "NA" is entered. |
| Lowest observed effect levels (LOEL): | Units = kGy. Lowest radiation dose at which there is a significant change in API content. If statistical significance is not available, a benchmark chance of ≥ 5% from baseline is used. If a LOEL is not observed, then NA. |
| Percent change at the NOEL | The percent loss of API relative to baseline at the NOEL. This will always be 5% change from baseline. If a NOEL is not observed, then NA. |
| Percent change at the LOEL | The percent loss of API relative to baseline at the LOEL. This will always be greater than 5% change. If a NOEL is not observed, then NA. |
| Radiation type | Type of ionizing radiation used in the study. Usually Gamma, electron beam (e-beam) or Neutron radiation. |
| Information source | Includes lead author and date of publication. |
| DOI or Publisher link | unambiguous DOI for article, citation or link to the article at the publisher's website. |
| Abbreviations: Gy = Gray, kGy = kilo Gray, MeV = megavolt, mg = milligram, mL = milliliter, API = active pharmaceutical ingredient, DOI = Digital Object Identifier | |

*5) Radiation stability modeling*

The objective of the modeling is to identify the lower 95$^{th}$ confidence interval for a 5% change in API content for solid and liquid drug formulations as a function of radiation dose. An arbitrary 5% change from baseline is selected because this amount of change can be accurately detected with good precision for most drugs, and it is also less than the 10% departure from label strength that is commonly used by USP as the threshold for classifying drug failure. At the lower 95% confidence interval, there is only a 5 in 100 probability that a drug will degrade at a lower dose. This characterizes the risk of drug failure due to ionizing radiation exposure.

Linear methods will likely be used to model the data. Because some drugs will have only a single point (either a NOEL or LOEL) and others will have multiple points at a range of radiation exposures, the data are clustered. For this reason, simple linear regression and multivariate regression are not suitable because some drugs will have greater weight in the analysis than others. A generalize estimating equation (GEE) or mixed effect model will be considered for analysis; however, the precise method will depend on the data acquired. Experimental variables can be incorporated into the models to evaluate their contributions to drug stability.

b. *Terrestrial Studies*

*1) Approach*

Drug stability will be tested using terrestrial analogs of spaceflight radiation to evaluate uncertainties related to spaceflight radiation exposures. The goal of this task is to characterize the relative effect of ionizing radiation (gamma or particles to be determined) on radiation-sensitive drug products identified in the literature analysis phase of Aim 4. Uncertainties regarding drug stability that need experimental investigation include the following:

- *Relative sensitivity of liquid and solid drug formulations to low dose ionizing radiation. To date, NASA studies of drug radiostability have focused primarily on drugs in the solid states. Drug substances in aqueous solution are known to be much more sensitive to ionizing radiation than in solid state (Boess and Bögl, 1996; Marciniec and Dettlaff, 2008; Slegers and Tilquin, 2005). It is unknown if aqueous drugs are sensitive to radiation doses less than 1 kGy, which is about 1000-times the dose expected for planetary DRMs (~1 Gy).*
- *Effect of low dose-rate. Drug solutions exposed to radiation over seconds or nanoseconds show significantly less degradation than drugs exposed to the same radiation dose over minutes to hours (Slegers and Tilquin, 2005). This has been shown for radiation doses as low as 5 kGy. Although unlikely, it is possible that exposure of drug solutions to low kGy levels of particle radiation administered slowly over a prolonged period (e.g., 2 years) could maximize the interaction between nominal drug degradation chemistry (e.g., oxidation) and radiation, resulting in accelerated degradation.*
- *It is unclear if charged particle radiation (e.g., protons) and gamma rays induce similar levels of damage to drug solutions. Low-LET radiation (e.g., gamma) produces more hydroxyl radicals than the same dose of higher LET radiation (e.g., alpha)(Le Caër, 2011); hydroxyl radicals are considered*

*to be the primary mediators of drug degradation in solution (Illés, et al., 2013; Nisar, et al., 2016; Slegers and Tilquin, 2006; Tegze, et al., 2019)*

- *It is unclear if equivalent drug products with different ingredients are similarly susceptible to ionizing radiation. Many manufacturers include preservatives, such as antioxidants, in drug solutions to stabilize the drug product and extend shelf life, however, inclusion of such ingredients varies by manufacturer. Examples of antioxidants include bisulfate, ascorbate or non-polar solvents, etc. (Jacobs, 2022; Sarcan and Ozer, 2020; Slegers and Tilquin, 2006). The effect of antioxidant excipients on radiostability of the product should be compared and evaluated.*

*2) Irradiation and analytical testing*

Radiation stability testing requires 2 steps: first, drug irradiation by an appropriate facility; second analysis of drug content by an analytical facility.

Irradiation facility. The irradiation facility should be capable of administering proton irradiation to drug substances at doses as high as 25 kGy, if possible. Although this dose is far greater than the dose incurred during a Mars transit mission, a wide range of doses enables the shape of the dose-effect curve to be characterized (the NOEL/LOEL transition dose), which increases confidence in the experimental data and enables the exposure margin to be estimated. The irradiation facility does not need to be the NSRL, however, NSRL is preferred.

Analytical drug analysis. The chemical content and the physical properties of irradiated drugs will be analyzed, and the formation of radicals will be measured. API and impurities will be extracted from each treated or control medication based on optimized USP protocols for each drug substance. API potency and degradation impurities will be quantified using accepted stability-indicating methods capable of distinguishing the parent API from their degradation products (Harrington, et al., 2014; Nickerson, et al., 2017).

Physical analysis will include tablet breaking force (United States Pharmacopeia, 2019b), moisture content using the Karl Fischer Titration Test (United States Pharmacopeia, 2013), and dissolution rate assessed following USP standards. For non-solid formulations, qualitative changes in consistency and color, turbidity, and particulates will also be noted and classified on an ordinal scale.

Electron spin resonance (ESR) will be used to characterize the formation of radicals in solid-state drugs after exposure to low doses of radiation. This information is important because degradation of solid-state drugs is predicated on the assumption that radiation ionizes drug ingredients, leading to degradation

reactions. The radiation dose-related formation of radical species should be experimentally characterized for radiation-sensitive drugs (as determined in the literature analysis of Aim 4).

Although many contract laboratories are capable of performing chemical and physical analysis of irradiated drugs, a collaboration with the U.S. FDA under an IAA would be ideal, as discussed in Aim 3. Because ESR analysis is not a USP test and is not normally performed for drug content analysis, it is likely that a separate testing facility may be required for ESR Testing.

*3) Select drugs to be tested*

The radiostability of drugs in water solutions will be determined. This focus does not exclude testing solid formulations of drug substances, however, at least 3 NASA-supported studies have evaluated the radiostability of solid drug formulations, all of which reported minimal to no change, as reviewed in the HRP evidence report (see Effects of Ionizing Radiation on Drug Stability section in Reichard, 2023).

c. *Spaceflight studies using ISS or Gateway*

*1) Rationale for performing spaceflight studies of drug stability*

The primary purpose of using the spaceflight platforms (i.e., Lunar Gateway or ISS) for evaluating drug stability is to validate results observed in studies of terrestrial packaging and radiation stability. It is expected that spaceflight studies will confirm terrestrial testing results. Gateway, in particular, is the most precise analog available for the deep space environment of a Mars exploration mission and presents the only planned opportunity to validate terrestrial studies in preparation for exploration missions. It is important that countermeasures be developed based on results from terrestrial analog studies before committing to using pharmaceuticals for Earth-independent medical operations.

*2) Treatment Arms*

This task has 2 treatment arms: a low-dose radiation arm with samples stored in a terrestrial climate-controlled chamber (control), and a radiation arm with samples stored on board either the Lunar Gateway or the ISS. The terrestrial samples will serve as the reference group for statistical analysis. The Lunar Gateway is preferred over the ISS for irradiation testing because the Lunar Gateway can deliver prolonged exposures to higher dose-rate ionizing radiation, analogous to that is expected during a Mars mission. However, the ISS is a feasible alternative despite the lower dose-rate because it may be feasible to assess a greater number of drugs at more frequent testing timepoints on the ISS than the Lunar Gateway. Relative advantages of these options will be considered in more detail when payload and operational parameters for the Lunar Gateway are better defined. The experimental design is depicted in Figure 5

*3) Formulations*

As discussed above, solid dosage forms are more stable than liquid formulations during prolonged exposure to ionizing radiation. Therefore, determining the relative stability of solid and aqueous drug formulations when exposed to space radiation will be important. Under Aim 4, solid and liquid (i.e., aqueous) drug formulations will be tested. When a medication is available in both solid and liquid forms, representative samples of both should be tested to enable stability comparisons. Literature suggests that drugs formulated as SODF and as oil dispersions (i.e., ointments) have similar susceptibility to ionizing radiation, whereas the stability of semi-solid aqueous dispersions (i.e., creams) are comparable to the stability of solutions (Gopal, 1978; Jacobs, 1985). For this reason, aqueous solutions and semi-solid aqueous formulations should be the focus of experimental testing.

*4) Packaging conditions*

Ionizing radiation induced drug degradation is facilitated by $O_2$ and water (Jacobs, 1985; Marciniec and Dettlaff, 2008; Sintzel, et al., 1997). Previous spaceflight drug stability studies have all focused on repackaged SODF in unprotective packaging. Therefore, these studies did not control for the potential confounding effects of atmospheric factors (i.e., $O_2$, humidity, and possibly $CO_2$,) interacting with the drug substances. To measure the effect of ionizing space radiation on drugs, it is necessary to distinguish the effect of radiation from the effects of atmospheric factors. SODF in their sealed manufacturers' containers (i.e., not repackaged) will be used as reference controls for Aim 4. Repackaged SODF will be tested in plastic zip-lock bags consistent with the current NASA repackaging protocol[25], and in protective repackaging, as discussed in Aim 3 and illustrated in Figure 5, non-solid formulations, which are not repackaged by the NASA Ops pharmacy, will be tested in their sealed manufacturers' packaging.

[25] This packaging is considered moisture- and oxygen-permeable and according to the manufacturer does not meet USP requirements for protective packaging, as discussed under Aim 3.

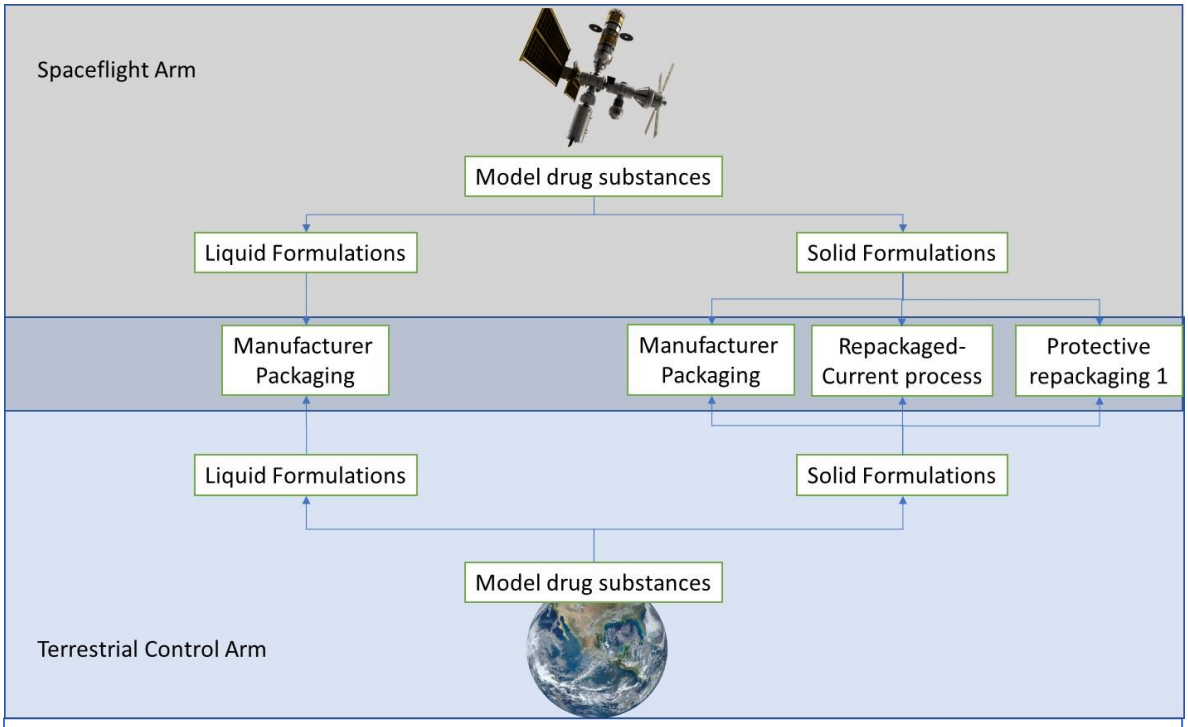


***Figure 5. Study design for spaceflight drug stability testing.*** *All drugs in the spaceflight arm and the terrestrial control arm will be matched by identical lot numbers. The spaceflight arm may use either the Lunar Gateway or the ISS, depending on availability and other operational considerations. "Protective repackaging 1" is the first-choice repackaging solution based on terrestrial stability testing experiments, or other performance metrics.*

*5) Shielding*

Although it may appear prudent to include a treatment arm to evaluate radiation shielding as a countermeasure to inhibit radiation-mediated drug degradation, such studies are premature. To date, no study has shown that ionizing radiation, at levels acceptable for human exposures, has any effect on drug stability. Experiments to investigate the effectiveness of shielding materials can be considered after it is established that acceptable human exposure levels of ionizing radiation facilitate drug degradation. Prior to conducting such experiments, SMEs should be consulted to determine feasible approaches for these experiments.

d. *Time Points*

A minimum of 4 different time points (one baseline and 3 spaceflight time points) are required to calculate a linear degradation rate over time; however, this minimum is not adequate for a high-quality study. A larger number of points are required if the dose-effect relationship departs from linearity. A greater number of time points also increases statistical power of the regression analyses, which is very important considering the variability reported across previous experiments. Unlike earlier studies, a zero timepoint *will* be included

as an initial baseline for rate analysis. The number of timepoints collected should be maximized to the extent possible.

e. *Environmental monitoring*

The same equipment will be used to monitor the local drug storage environment of both the spaceflight and terrestrial samples. Measured factors will include fluctuations in temperature, $CO_2$, RH, and ionizing radiation. Each group of samples, at each time point, will be monitored separately. Atmospheric conditions will be measured using appropriate real-time monitoring devices. HOBO® real-time monitors[26] were used to monitor temperature and humidity in previous studies and are considered appropriate for the proposed experiment. Cumulative exposures, maximum and minimum levels, and other summary statistics (mean, median, standard deviation) will be calculated from these atmospheric data. These metrics will be included in multiple regression models, as described in Aim 3. Excursions above and below recommended temperature and RH levels will be evaluated during data analysis. Thermoluminescence dosimeters (TLD-100 LiF:Mg, Ti) have been used in past drug radiation stability studies to measure the cumulative radiation exposure, as corroborated by the NASA, JSC, Space Radiation Analysis Group. A similar approach will be considered for this study; however, the Space Radiation Analysis Group will be consulted for their recommendations on real-time and cumulative dose monitoring.

To the extent possible, the environmental conditions for the control samples will be matched to the environmental conditions on the spacecraft, based on environmental telemetry. For example, if the temperature on the spacecraft is lower to 10°C when unoccupied, then the temperature of the control samples' environment will also be lowered. Temperature is the single most important factor affecting degradation reaction kinetics and large fluctuations in temperature of the flight samples need to be matched for the control samples.

f. *Statistical power and sample number estimation*

Statistical power is the probability that the statistical test will detect an effect if one truly exists; that is, the probability of correctly rejecting the null hypothesis when the alternative hypothesis is correct. We would like to achieve an a priori power of 0.8.

Previous NASA spaceflight drug stability studies did not use linear statistical methods to test the effect of any spaceflight condition on drug stability or to estimate the impact of spaceflight on degradation rate.

[26] https://www.onsetcomp.com/search/products/hobo

Rather, most have been qualitative evaluations (Du, et al., 2011) or single-point descriptive observational studies (Cory, et al., 2016; Cory, James, and Mangiaracina, 2017; Khan and Wotring, 2014; Wotring, 2016; Wu, and Chow, 2016). Such studies do not estimate model variance or needed effect size or include the number of samples required for adequate statistical power. For example, based on the Du et al. 2011 raw data, the effect size for the 353-day spaceflight storage samples assessed for API content (aggregate average) is estimated to be 5.3 using the Cohen's *d* for two-sample test (assuming equal variance and normality). However, variance is likely much greater than that reported by Du et al. 2011, which reduces the statistical power of the experiment. Assuming a large effect size, only 5 samples per drug are required for a power of 0.91. Because 0.91 > 0.8, it is concluded that, based on the results of Du et al. 2011, 5 samples will provide adequate statistical power for these studies. A statistician will be consulted on sample size estimates when detailed planning of these experiments commences. The number of replicates and samples should be maximized contingent on mass and volume restrictions of the launch mission(s).

g. *Mechanism-based selection of susceptible drugs*

Drug substances predicted to have a high probability of undergoing oxidative degradation reactions (according to Zeneth® software) will be among those considered to be susceptible to ionizing radiation. These predictions are evaluated jointly with high-confidence empirical literature reports[27]. From the joint (empirical studies and predictions) list of susceptible medication, validation of degradation pathways and reaction products will be attempted in collaboration with the U.S. FDA, as discussed for data collection under Aim 1 or in conjunction with a contract lab. Literature search efforts are also expected to identify drugs that should be prioritized for testing. Because Aim 4 is focused on testing mechanistic hypotheses regarding how spaceflight influences drug degradation kinetics, drug selection will be based on drug stability criteria, not experiential operational criteria or expert opinion.

h. *Analytical analysis*

*1) Laboratory facilities for chemical and physical analysis of drug products*

API content, impurities, and physical properties will be assessed by a contract laboratory, or if possible, through collaboration with the U.S. FDA, as discussed in Aim 3 and as discussed in terrestrial analogs of spaceflight radiation above under Aim 4.

[27] Early studies of drug stability that are cited in several review articles used methods that are not widely accepted as stability-indicating methods (i.e., thin layer chromatography), so evaluation of empirical reports of drug stability should consider the methods used.

i. *Data analysis*

For API potency, linear statistical methods will be used to characterize degradation rate constants for each drug formulation and to evaluate how storage factors affect degradation rate. Because these studies involve repeated measures on the same samples (i.e., a single manufacturing lot over multiple time points), a GEE model will be used for hierarchical analysis (Reichard, et al., 2023). This type of linear model is ideal for repeat measure experiments with 2 or more explanatory variables, and the assumption of homogeneity of variance does not need to be satisfied, which simplifies analysis.

*4. EXPECTED OUTCOMES*

- *Mission, time, and budget constraints mean it is not feasible to perform spaceflight stability testing of all drugs in the ECF. Aim 4 will enables identification and characterization of worst-case susceptibilities of drugs to low-dose-rate ionizing radiation exposures.*
- *The proposed experimental design allows the effects of radiation to be isolated from the confounding effects of atmospheric factors, thereby yielding an estimate of degradation attributable to the ionizing radiation and the interaction of atmospheric factors with radiation.*
- *In general, Aim 4 will provide data to address the gap Pharm-101 by validating the packaging strategy for medications reduce the risk of adverse toxicological effects and preserving potency. The results of Aim 4 will also address gap Pharm-401 by completing a body of research to fully determine and characterize the active pharmaceutical ingredients and degradation profiles of medications for drugs exposed and susceptible to ionizing radiation.*

*5. POTENTIAL PROBLEMS, LIMITATIONS, AND ALTERNATIVES*

a. *Lunar Gateway*

- *Using the Lunar Gateway platform to test drug stability involves several risks. The most significant risk is whether authorization will be granted to use the Lunar Gateway platform to perform Aim 4. If a drug stability experiment is authorized, it is unknown what the mass and volume restrictions will be, and whether enough samples can be evaluated to test the hypothesis with the desired statistical rigor. It is also uncertain how samples will be returned, or how frequently returns will occur. If the Lunar Gateway is not an option for pharmaceutical stability testing, the alternative is to use the ISS as the testing platform. The ISS is expected to have a lower dose-rate for ionizing radiation than the*

*Lunar Gateway, which is roughly 103–153 mGy/y[28] on the ISS (Chancellor, et al., 2018). However, the cumulative upper bound exposure limit for a Mars mission is estimated in the range of 1 Gy, and ideally below the proposed career limit of 600 mGy (National Academies of Sciences, Engineering, and Medicine, 2021). Hence, 3 years on the ISS will yield a cumulative radiation exposure of roughly one-third (~0.31 Gy) to one-half (~0.46 Gy) of the cumulative dose of a 3-year Mars transit. Although not ideal, this should be an adequate exposure to test the hypothesis that ionizing space radiation increases drug degradation, assuming the effect size is large enough to detect with sensitive analytical methods. If the effect size is not large enough to detect, then it is unlikely that doubling or tripling the exposure will have functional consequences for drug stability.*

- *When the Lunar Gateway platform is unoccupied, environmental conditions, in particular temperature and humidity, may be inconsistent with the drug's labeled storage conditions. If the environmental conditions on board the Lunar Gateway are known, then it should be possible to match terrestrial controls to the onboard temperature and humidity conditions by using a refrigeration chamber during these periods. The relationship between temperature and the rate of chemical reactions is well established, as described and predicted by the Arrhenius equation. This law demonstrates that at lower temperatures, chemical reaction rates are reduced, and stability of most drugs would be prolonged, with the possible exception of the physical stability of drug products containing amorphous substances (Szakonyi and Zelkó, 2012).*

[28] Based on dosimetry data provided in Figure 1-1 of NAS, 2021 (National Academies of Sciences, Engineering, and Medicine, 2021).

- *The freezing temperatures on the Lunar Gateway could affect some drug products. This concern does not apply to all drugs equally. "freezing" is defined as the temperature at which liquid water undergoes phase transition between liquid and solid states via ice nucleation, which at sea level is ~0°C. Freezing is not directly applicable to drug substances because drug substances do not undergo a phase transition at this temperature. Rather, freezing affects the water present in the drug. For this reason, the effect of freezing depends on the nature of the water in the drug product as well as the physical and chemical susceptibility of the drug product (Szakonyi and Zelkó, 2012). In the case of drugs susceptible to ionizing radiation, freezing of free water, particularly at temperatures below - 20°C will generally increase the stability of the drug (Sarcan, et al., 2020). Drug products that contain free water or freezable bound water, and which are susceptible to degradation by water crystallization, are expected to exhibit decreased stability at freezing temperatures or because of freeze-thaw cycling. Drug products containing non-freezable bound water would likely be unaffected by freezing. Drug products containing amorphous substances that are stored below the glass transition temperature are expected to be considerably stabilized due to reduced devitrification (Craig, et al., 1999).*

## *6. TIMELINE AND BENCHMARKS FOR SUCCESS*

The timeline for literature analysis of drug radiation stability and radiation drug stability testing tasks are as specified in the FY2023 Pharmaceutical Risk budget. Tasks will be delayed if task funding is delayed.

Spaceflight-based stability testing is generic toward either the ISS or the Lunar Gateway as the experimental platform. For this reason, the timeline is relative to available launch date for sending medications to the ISS or the Lunar Gateway, rather than as an explicit start date/end date.

Table 7. Notional Timeline for Aim 4

**Terrestial Study Timeline Based on FY24 Budget (Months)**

| | Fiscal Year | Year 1 (ca. 2024) | | | | | | | | | | | | Year 2 (ca. 2025) | | | | | | | | | | | | Year 3 (ca. 2026) | | | | | | | | | | | | Year 4 (ca. 2027) | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Task | 10 | 11 | 12 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | # | # | # | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | # | # | # | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | # | # | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| Radiation Literature Analysis | Literature search | X | X | X | X | X | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| | Data management | | | X | X | X | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| | Modeling | | | | | | X | X | X | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| | Draft Manuscript | | | | | | | | X | X | X | X | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| | Publication | | | | | | | | | | | X | X | X | X | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Radiation Stability Testing | Prioritized drugs for testing | | | | | | | | | | | | | | | | | | X | X | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| | Set up irradiation contract | | | | | | | | | | | | | | | | | | X | X | X | X | | | | | | | | | | | | | | | | | | | | | | | | |
| | Set up analysis lab contract | | | | | | | | | | | | | | | | | | X | X | X | X | | | | | | | | | | | | | | | | | | | | | | | | |
| | Drug irradiation | | | | | | | | | | | | | | | | | | | | | | X | | | | | | | | | | | | | | | | | | | | | | | |
| | Analytical sample analysis | | | | | | | | | | | | | | | | | | | | | | | X | X | X | (X) | (X) | | | | | | | | | | | | | | | | | |
| | result analysis | | | | | | | | | | | | | | | | | | | | | | | | | X | X | X | X | X | X | | | | | | | | | | | | | | | |
| | report preperation | | | | | | | | | | | | | | | | | | | | | | | | | | | | X | X | X | X | X | X | X | X | X | X | | | | | | | | |

**Spaceflight Stability Testing Timeline Starting From Project Kickoff (Months)**

| | Time Period | Pre-flight | | | | | | Year 1 (ca. 2028?) | | | | | | | | | | | | Year 2 | | | | | | | | | | | | Year 3 | | | | | | | | | | | | Year 4 | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Task | -6 | -5 | -4 | -3 | -2 | -1 | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 |
| Gateway Drug Testing | Prioritized drugs for testing | X | X | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| | Set up analysis lab contract | X | X | X | X | X | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| | Purchase monitoring equip. | | | X | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| | Drug repackaging | | | | | X | X | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| | Gateway Launch | | | | | | | X | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| | Baseline sample analysis | | | | | | X | X | X | X | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| | Return sample set 1 | | | | | | | | | | | | | | | | | | | | X | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| | Analysis Sample set 1 | | | | | | | | | | | | | | | | | | | | | X | X | X | X | | | | | | | | | | | | | | | | | | | | | |
| | Return sample set 2 | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | X | | | | | | | | | | | | | | | |
| | Analysis Sample set 2 | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | X | X | X | X | | | | | | | | | | |
| | Return sample set 3 | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | X | | | | |
| | Analysis Sample set 3 | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | X | X | X | X | |
| | Experimental analysis | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | X | X | X | X | X | X | X |
| | Summarize and publish | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | X | X | X | X |

Abbreviations: DDR = drug data repository; FDA = U.S. Food and drug administration; API = active pharmaceutical ingredient; X = tentative effort on task; (X) = effort on task.

## IV. *CONCLUDING COMMENTS*

The strategy presented here is designed to address the pharmaceutical risk of "ineffective or toxic medications" resulting from *drug degradation*. A major challenge for assuring that a drug is suitably stable for long-duration exploration missions is that high quality stability data for most drugs are not available in the public domain. The U.S. FDA maintains databases that contain detailed stability data for all drugs marketed in the U.S.; however, these data are not publicly available. For these reasons, it will be important to develop a collaborative relationship with the FDA to enable analyses of proprietary drug products. However, NASA has been conducting collaboration discussions with FDA since 2018 and no collaboration has been implemented. Although discussions are currently ongoing, there is no timeline for implementing an agreement. Although there is no substitute for the information the U.S. FDA could provide, alternative tasks can be implemented to advance the pharmaceutical strategy. One option is to prioritize tasks specified in this strategy that do not involve the participation of FDA. These tasks include the following:

- *Drug degradation pathway analysis*

    - *Zeneth software has been evaluated as a tool for identifying drug degradation pathways. A software license has been purchased and this work began in 2022. (Aims 2, 3, 4).*
    - *ECF drugs known to form hazardous degradation products need to be identified (i.e., gabapentin), impurity exposure limits should be determined, and permissible daily exposures calculated.*
- *Classification of drug sensitivity to radiation stability*
    - *A large amount of primary, secondary, and tertiary information on radiolytic drug stability has been collected. These data need to be evaluated for ECF drugs and entered into the drug data repository (Aim 4).*
- *Evaluation of drug repackaging options*
    - *The ExMC market survey of drug repackaging products from 2014 needs to be updated and completed. Suitable products for experimental testing should be identified (Aim 3).*
- *Gateway/ISS studies*
    - *Investigations of what is required to initiate a carefully designed, controlled spaceflight drug study on board the ISS or Lunar Gateway need to be conducted, as discussed in Aim 4.*
- *Research paper with FDA*
    - *NASA has conducted several studies related to drug stability and degradation impurities that remain unpublished. These data should be presented in a manuscript that discusses the risk of toxic impurities and the challenges involved in analyzing drug potency.*

A second and complementary option is to pursue other components of the overall pharmaceutical strategy. Shifting focus towards the PK and PD effects of spaceflight would allow progress to be made while the FDA is unavailable to collaborate with NASA. Because this is currently the situation, it makes sense to commit effort to tasks that will support this strategy, including the following:

- *Physicochemical drug attributes need to be identified and data will need to be collected to enable drug prioritization for PK analysis (discussed briefly in Aim 2)*
- *A systematic literature search needs to be performed to identify NASA and terrestrial spaceflight analog studies that have evaluated physiological changes associated with spaceflight. Required parameters include changes in cardiac output, renal and liver blood flow,*

*fluid volume changes/shifts in plasma and tissues, and any effects on serum protein concentrations or pH. The NASA Life Science Data Archive (LSDA) may have some data that needs to be evaluated.*

- *A systematic literature search needs to be conducted for NASA studies that have investigated in vivo and in vitro changes in liver enzyme expression associated with drug metabolizing enzymes. There are several studies in the LSDA related to this topic that need review and analysis.*

The pharmaceutical risk is an interesting and challenging problem to investigate because it requires insight into multiple scientific fields. This is likely one reason this risk has been under investigation since the early 2000s. However, the complexity of the problem ensures that there is also substantial work to completed and questions to be investigated.

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# VI. *APPENDICES*

## A. APPENDIX 1: DATA MINING STATEMENT OF WORK WITH U.S. FDA

### Statement of Work (SOW)

Data mining the FDA databases to inform the NASA HRP Pharmaceutical Stability Risk

### Background

In recent years, the objectives of our nation's space program have grown increasingly sophisticated and ambitious. Future missions will focus on exploration at greater distances from Earth with extended stays in space. To ensure that these goals are achieved, NASA astronauts must be able to perform at peak productivity under even the most daunting conditions. The HRP is dedicated to discovering the best methods and technologies to support safe, productive human space travel and extend human presence beyond low Earth orbit. HRP scientists and engineers work to predict, assess, and solve the problems that humans encounter in space as planned future missions will dramatically increase the challenges and demands faced by NASA's astronauts.

One such challenge is the 'Risk of Ineffective or Toxic Medications During Long-Duration Exploration Spaceflight' which states that, 'Given that there is no current method to sufficiently characterize medication use, drug quality and performance, clinical outcomes, and the impact of a hostile space environment on pharmaceutical stability and potency during long-duration exploration missions, there is a possibility that provision of safe and effective drug treatment will be significantly limited, impacting crew health and performance'. The NASA HRP has identified a variety of factors that could contribute to ineffective or toxic medications, specifically, (1) drug stability, (2) shelf life, (3) packaging, (4), storage conditions, (5) drug compound formulation, (6) spaceflight environment (including radiation and vibration), and (7) microgravity-induced physiological alterations in humans. The NASA HRP performs research to better understand these contributing factors and develop countermeasures that decrease the risk of ineffective or toxic medications during long-duration exploration spaceflight.

### Justification

The U.S. FDA, the world's premier pharmaceutical regulator, has extensive drug product databases containing stability and formulation information for every drug marketed in the US. Some of these data could significantly assist NASA HRP's efforts to decrease identified Risks of ineffective pharmaceuticals due to loss of strength and accumulation of potentially toxic degradation products. It is recognized that the FDA data on the

shelf life, quality, and performance of medications on Earth could be extrapolated to performance beyond Earth and could be used to help guide selection of medications for long-term deep space missions.

### Objective

The NASA HRP and the FDA seek to better understand factors that impact the chemical and physical stability of medications exposed to the spaceflight environment and characterize impurities produced by degradation. To this end, the FDA maintains a large knowledgebase of stability and shelf-life data for approved drug products. This knowledgebase is pertinent to understanding factors that impact drug shelf life. *The objective of this SOW is to retrieve data from FDA databases that supports selection of drug products suitable for exploratory space missions*. These data are necessary *but not sufficient* to mitigate the risk of ineffective or toxic medications. The deliverables under this SOW will *complement* experimental testing studies on drug stability and in silico prediction analysis that together will inform the decision framework for selecting and prolonging the storage shelf life of medications to help ensure safety and effectiveness for long-duration exploration missions.

### Scope

To supply a safe and effective pharmaceutical formulary for long-term exploration space missions, NASA needs shelf-life and susceptibility data for formulary drugs. These data are maintained by the U.S. FDA in different databases and in different formats. To enable collection of these data, FDA will conduct an internal study to include NDAs, ANDA, the Department of Defense/FDA SLEP database, and other data archives pertinent to the collection of specified stability data (Table 1). The FDA will work locate, retrieve, collect, and organize medication stability and ingredient information from the FDA databases. After the required data are collected, organized, and transferred to NASA, the FDA may coordinate with NASA in the analysis of retrieved data to the extent feasible based on bandwidth of personnel.

### Tasks

The NASA HRP and the FDA shall conduct the following activities:

Task 1: Staffing. The FDA, in collaboration with NASA, will identify and select personnel committed to this SOW. The FDA will evaluate existing staff (including but not limited to federal employees, staff/research fellows, and contractors) in addition to hiring personnel for assignment and execution of this project. The FDA will appoint personnel with reasonable database, programming, and

computational skills to enable efficient access to the FDA databases for many medications and manufacturer brands, as well as the capability to organize the expected complex data structures.

Task 2: Identification of drugs and resources. NASA and the FDA will meet to prioritize drugs in the NASA spaceflight formulary for data retrieval. Prioritization will be based on factors including dosage form, chemical structure, API susceptibility to environmental factors, operational needs, and availability of information from the FDA data sources. This task will finalize the specific data to be retrieved, the sources from which data will be revived, and the logistics for data retrieval.

Task 3: Data mining pilot phase. Information will be retrieved for no more than 6 medications to assess data availability, quality, and suitability for subsequent analysis. The purpose of the pilot phase is to develop data retrieval methods, refine data retrieval processes, review the suitability of the retrieved data for the intended purpose, and demonstrate proof of concept prior to extending the effort to the full list of prioritized medications.

Desirable data and information for retrieval are listed in Table 1; however, the final list of data to be collected will be mutually agreed on by NASA and the FDA. Programmatic data retrieval using Application Programming Interface (API software) or similar approaches are preferred, with data saved as JSON, XML or other suitable files. At the completion of the pilot phase, outcomes of this task will be assessed in terms of the stated objective, scope, and overall success of obtaining requested data. Depending on the quality, structure, and content of the data, it is expected that some adjustments to method and scope may need to be implemented prior to initiating Task 4.

Task 4: After assessment of the outcomes described in Task 3, the list of medication for which information is sought will be expanded to include as many drugs from the NASA Exploration formulary as is reasonable, depending on the information retrieval process. The information assigned the highest priority is brand expiry periods (i.e., NDC numbers or RxCUIs and their corresponding shelf-life period and the SLEP drug lot failure data). The second priority is to obtain inactive ingredients for each formulary NDC/RxCUI. The third priority is to obtain the remaining information in Table 1 (e.g., gamma and UV radiation testing results). For data that must be retrieved manually, a prioritized subset of 50–60 drugs may be used that are mutually agreed on by NASA and FDA. For information that requires manual retrieval, information should be obtained for 6–8 drugs per month from the prioritized medication list. Data and information that will support predictive stability modeling are of interest.

Task 5. Data analysis. If programmatic approaches are used to retrieve data from electronic databases, the data retrieval tasks may be completed ahead of schedule, depending on efficiencies identified and used in executing this project. Therefore, once the data are retrieved, the FDA and NASA will identify if the analysis of data and/or preparation of the manuscript s feasible, as described below.

| Appendix 1 Table 1. Desirable data to be collected from the U.S. Food and Drug Administration (FDA) for prioritized drugs | |
|---|---|
| Criterion | **Purpose** |
| Current list of drug products and formulations tested in the Shelf-life Extension Program (SLEP) | Prioritization |
| Brand and lot failure times from the SLEP | Failure analysis |
| Brand/lot inactive ingredients for drug products tested in the SLEP | Expiry correlation |
| Percentage of active pharmaceutical ingredient (API) remaining at tested SLEP timepoints | Regression analysis; correlation |
| The stability attribute responsible for each SLEP lot failure determination | Identify mode of failure |
| Manufacturer shelf-life expiry from New Drug Applications and Abbreviated New Drug Applications (may be anonymized by FDA) | Used with other factors |
| Manufacture lot failure times from the stability studies | Failure analysis |
| Manufacturer drug product inactive ingredient list | Expiry correlation |
| Major API degradation products that are shelf-life limiting attributes from manufacturer long-term and accelerated stability studies | Toxicological risk assessment |
| Major API degradation products from manufacturer long-term and accelerated stability studies | Toxicological risk assessment |
| Ionizing radiation stability testing results. | Spaceflight-related failure susceptibility |
| UV radiation stability testing results | Spaceflight-related failure susceptibility |

### Meetings/Reporting

The NASA HRP and the FDA shall participate in monthly review meetings to discuss at a high level all ongoing activities and their progress. The date/recurrence of this meeting will be determined at project kick-off. At a minimum, the coordination meetings should review the following information:

- *Review of progress and assessment (including raw data) from the previous period*
- *Deviance from previous planned progress (either positive or negative)*
- *The future planned progress (including planned execution of optional task activities)*
- *Issues and recommendations*
- *Schedule performance (schedule variance)*
- *Estimated costs versus actual costs (cost variance)*
- *Program risks, risk mitigation plans, risk mitigation actions taken, and resolution of risks*

### Roles and Responsibilities

Requesting Agency (NASA)

- *Provide funds to the FDA, as outlined in this agreement, for materials and services described under the scope, inclusive of potential contractors/staff fellows*
- *Participate in technical meetings (in-person or web-based virtual conferences), informal discussions, email correspondence with FDA personnel to conduct project status discussions and provide technical direction as necessary (monthly status meetings are anticipated for this project)*
- *Ensure no more than a 10 business-day turn-around time for draft document reviews (including quarterly reports and final report drafts)*
- *Provide any requested changes to the methods of work in writing to the FDA*

*Performing agency (FDA)*

- *Provide necessary resources, including staffing, to perform the work identified in this Statement of Work.*

- *Conduct monthly project status meetings to review project progress and discuss outcomes, sample availability, and (as necessary) additional testing procedures*
- *Provide final technical reports and supporting analytical data in alignment with the statement of work*

### Information Assurance and Data Management

The parties to this agreement acknowledge the importance of maintaining the security of information and managing the data exchanged hereunder in compliance with all applicable legal authorities, affording the highest degree of protection practicable. The parties agree to the following:

1) *The data regarding stability and degradation of medications that NASA intends to use to support exploration missions will be collected, shared, used, or stored in support of this fee-for-service agreement.*
2) *All data generated under this agreement, as well as all rights in that data, will be transferred to the funding party at the end of the agreement. Once transferred, the funding party assumes responsibility for storing, protecting, and managing data in compliance with applicable legal authorities. The supplying party remains responsible for storage, retention, maintenance, and security of data in its possession until it is destroyed. Each party will notify the other party prior to the destruction of any data in their possession that is generated under this agreement.*
3) *Both parties will ensure that their personnel handling the data described above satisfy all necessary training requirements and obtain any requisite clearances to handle said data on any applicable information system. All personnel participating in data exchange must be under a duty to hold said data confidential. If there will be any individual lacking such a duty of confidentiality, that individual must sign a non-disclosure agreement before handling the data.*
4) *Both parties are responsible for ensuring that any data shared is both transmitted and stored in a secured information system network that is fully compliant with all applicable Federal legal authorities.*
5) *The data generated as a result of this interaction may be used to support the funding entities' regulatory filings, professional publications, and other purposes.*
6) *Any public release of data prior to final transfer to the funding agency requires review and approval by the public affairs and security offices of both signatories to this agreement.*
7) *Commercial proprietary information will be sent to NASA only with FDA approval and consent.*

### Research Publications

It is understood that this research project may result in new scientific knowledge that may be suitable for publication in peer-reviewed scientific journals and/or presented at scientific meetings. It is anticipated that the research results will be published jointly by the Parties, or as mutually agreed in writing by the principal investigators for the research project, presented independently by either Party. In all such oral or written publications concerning the research project, each Party's contribution will be expressly noted, by either acknowledgment or co-authorship, as appropriate, with authorship being determined in accordance with the policies and customs for authorship of scientific publications.

## B. APPENDIX 2: OAK RIDGE INSTITUTE FOR SCIENCE AND EDUCATION FELLOW POSITION ANNOUNCEMENT PREPARED BY THE U.S. FDA

A research opportunity is available in the Office of Pharmaceutical Quality/Office of Testing and Research, Center for Drug Evaluation and Research (CDER), FDA in Silver Spring, Maryland.

CDER performs an essential public health task by making sure that safe and effective drugs are available to improve the health of people in the United States. As part of the U.S. FDA, CDER regulates over the counter and prescription drugs, including biological therapeutics and generic drugs.

The project goal is to develop a mechanistic understanding of the stability and extended shelf life of innovator and generic drug products. The FDA maintains databases of stability and shelf-life data for approved drug products. The project will require the Oak Ridge Institute for Science and Education (ORISE) Fellow to identify and collect analytical and stability information from a relational database that contains testing, stability, and shelf-life extension information to determine factors that impact the shelf life of drug products that include solid oral dosage forms, parenterals, and combination drug-device products. Collection of similar data from a set of New Drug Applications or Abbreviated New Drug Application will also be required. A primary objective is to understand the chemical and physical factors that may impact the pharmaceutical quality of products extended beyond expiry during long-term spaceflight. A secondary objective is to understand how drug substance, formulation excipients, and the manufacturing process affect the stability and product quality of extended shelf-life of pharmaceuticals.

The candidate should possess a, MS or PhD in chemistry or pharmaceutics and should be familiar with relational databases, analytical procedures, and structure-activity relationships. Especially helpful is training and experience in organic reaction mechanisms, pharmaceutical, or medicinal chemistry. Experience in statistics including M/ANOVA, PLSA, principal component or accelerated failure time analysis would also be helpful.

Under the guidance of the mentor, the Fellow will have the opportunity to acquire training on relational databases and statistical analysis and to gain an understanding of the current regulatory requirements and the stability assessment of innovator and generic drug products. The mentor will also provide training opportunities to the participant about the FDA, The International Council for Harmonisation and USP regulatory guidance on stability, analytical method validation, and testing of drug products and drug product quality.

This program, administered by Oak Ridge Associated Universities through its contract with the U.S. Department of Energy to manage the ORISE, was established through an interagency agreement between DOE and the FDA. The initial appointment is for one year but may be renewed on recommendation of the FDA contingent on the availability of funds. The participant will receive a monthly stipend commensurate with educational level and experience. Proof of health insurance is required for participation in this program. The appointment is full-time at the FDA in the Silver Spring, Maryland area. Participants do not become employees of the FDA, the DOE or the program administrator, and there are no employment-related benefits.

Completion of a successful background investigation by the Office of Personnel Management is required for an applicant to be on-boarded at FDA. The Office of Personnel Management can complete a background investigation only for individuals, including non-US Citizens, who have resided in the U.S. for a total of 3 of the past 5 years.

The FDA requires ORISE participants to read and sign their FDA Education and Training Agreement within 30 days of his/her start date, setting forth the conditions and expectations for his/her educational appointment at the agency. This agreement covers such topics as the following:

- *Non-employee nature of the ORISE appointment*
- *Prohibition on ORISE Fellows performing inherently governmental functions*
- *Obligation of ORISE Fellows to convey all necessary rights to the FDA regarding intellectual property conceived or first practiced during their fellowship*
- *Research materials and laboratory notebooks are the property of the FDA.*
- *ORISE fellow's obligation to protect and not to further disclose or use non-public information*

## Qualifications

The qualified candidate should be currently pursuing or have received a master's or doctoral degree in one of the relevant fields. The degree must have been received within the last 5 years.

## Eligibility Requirements

- Degree: MS or PhD Degree received within the last 60 months or is currently pursuing the degree.
- Discipline(s):
  - Life Health and Medical Sciences (Pharmaceutical Science)
  - Physical Sciences (Chemistry)

## C. APPENDIX 3. THE STOPLIGHT FRAMEWORK FOR CLASSIFYING EXPECTED STABILITY OF EXPLORATION SPACEFLIGHT

### *1. Objective*

The 2022 version of the ExMC ECF stoplight chart summarizes available information for each drug product at this point in time. The stoplight chart summarizes objective stability data available for each drug product on the ECF. These data are summarized using a sequence of standardized decision steps applied to each drug product, together with data curated for each step of the decision tree.

The objective of the stoplight chart is to guide research activities by prioritizing drugs for further research. Stoplight classification is ***not*** intended to guide or influence drug selection for operational activities nor to indicate "readiness" of drug products for current or future space missions. The stoplight chart is a research classification tool only.

### *2. Results Synopsis*

Overall, the ECF consists of 183 unique drug substances (i.e., active pharmaceutical ingredients, [APIs]) constituting 243 finished drug products. Of these, 28 individual APIs constitute 15 combination products (Appendix 3 Table 1).

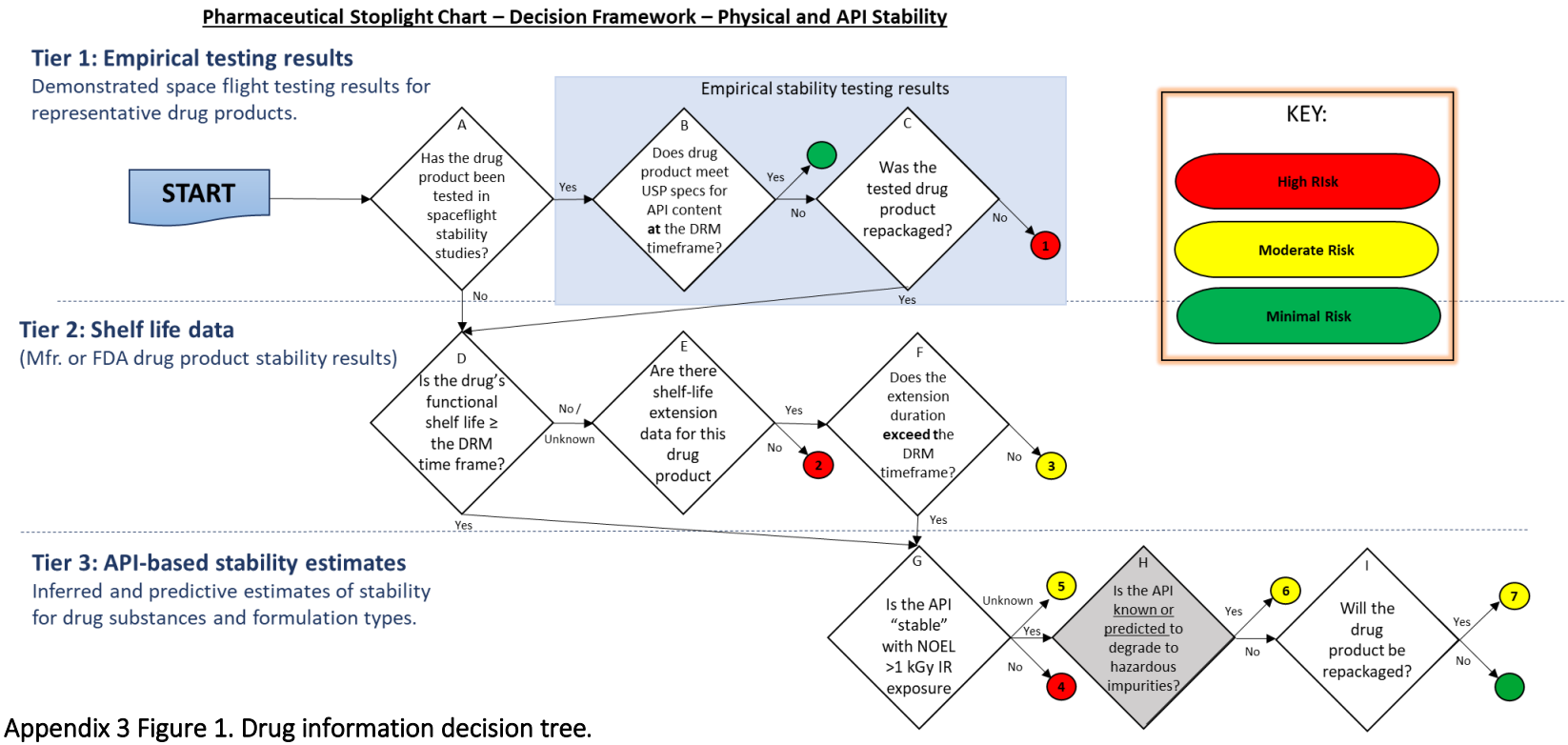
The decision tree (Appendix 3 Figure 1) is composed of 9 steps that evaluate various aspects of drug stability and quality to identify drug products that required additional research information to mitigate stability issues. Of the 9 decision steps, 6 produce clarification outcomes and 3 direct drugs to classification pathways.

Appendix 3 Table 1. ExMC Candidate Exploration Formulary Dosage Forms

| Formulation | Product type | | |
|---|---|---|---|
| | **Single active pharmaceutical ingredient** | **Combination** | **Total** |
| Aerosol | 3 | 0 | 3 |
| Capsule | 21 | 0 | 21 |
| Cream | 9 | 0 | 9 |
| Gel | 4 | 0 | 4 |
| Gel cap | 4 | 0 | 4 |
| Lozenge | 0 | 1 | 1 |
| Ointment | 5 | 0 | 5 |
| Pad | 0 | 1 | 1 |
| Paste | 1 | 0 | 1 |
| Patch | 4 | 0 | 4 |
| Powder | 13 | 1 | 14 |
| Solution | 81 | 5 | 86 |
| Strip | 1 | 0 | 1 |
| Suppository | 1 | 0 | 1 |
| Suspension | 1 | 1 | 2 |
| Tablet | 81 | 5 | 86 |
| Total | 229 | 14 | 243 |

The decision tree is used to assign each ECF drug to one of 3 categories—green, yellow, and red—according to collected data and pre-established criteria. Although the data and criteria used for drug classification are objective, the categorical classifications are subjective and generally correspond to level of uncertainty. The 3 levels of classification are described as the following:

- *Green classification is assigned to drugs that have data supporting stability that exceeds the timeline of the assigned DRM. Drugs classified as green are considered to be low priority for further research.*
- *Yellow classification indicates an absence of data or the need for further investigation. Drug products classified as yellow are prioritized for further investigation.*
- *Red classification is assigned to drugs with data that positively demonstrate the drug product is not sufficiently stable for the DRM; however, the basis of this classification should be evaluated to determine whether shelf-life stability can be prolonged. Red category drugs also have low priority for further research.*




Appendix 3 Figure 1. Drug information decision tree.

Outcome Footnotes (colored circles):

*1)* ***Risk****: Stability failure of a drug in protective mfr. packaging. Investigate alternative storage conditions (e.g. low temperature storage), other packaging methods, selection of different drug product or formulation, etc.*

*2)* ***Risk:*** *Manufacturer shelf-life data and extension data are required. Investigate obtaining stability information from drug mfrs., FDA or DoD SLEP. Consider substitution with a different drug product or formulation that has stability data.*

*3)* ***Risk****: Risk-benefit analysis recommended to determine whether the benefit of sending a drug with insufficient stability on a DRM exceeds the risk of therapeutic failure or toxic impurities (if these are reasonably anticipated).*

*4)* ***Risk****: Drug is highly sensitive to ionizing Radiation. Investigate factors affecting sensitivity to radiation including formulation (i.e., aqueous solution, antioxidant excipients), packaging, drug selection, storage temperature or shielding.*

*5)* ***Risk****: Evidence indicated that exposure of pharmaceuticals to 1 Gy of radiation is extremely unlikely to affect drug stability. Consider risk-benefit analysis or need for additional radiostability studies.*

*6)* ***Risk:*** *Evaluate the risk of hazardous degradation impurities. Use accepted risk assessment procedures (e.g., ICH, EPA, or Risk-MAPP) to determine if risk is acceptable based on expected daily dose of the hazardous impurity.*

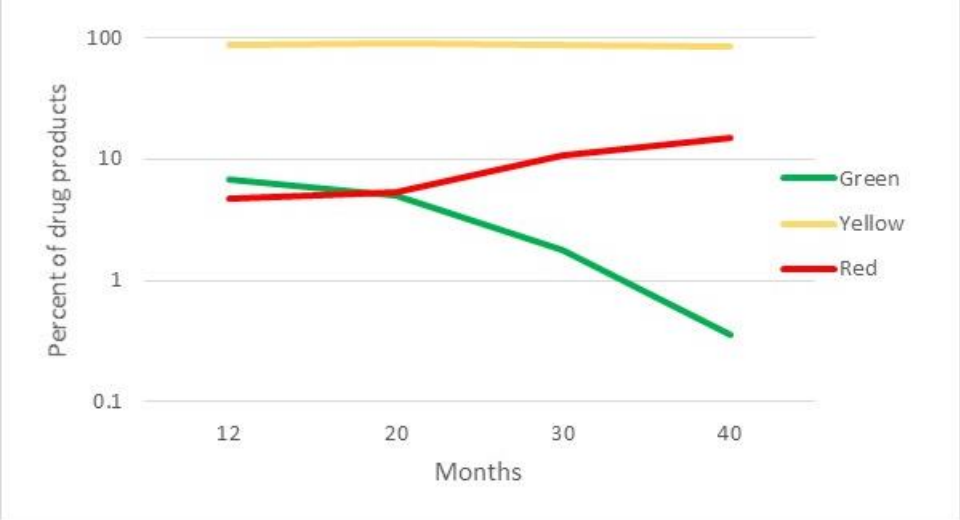
*7)* ***Risk****: For long-term storage, drug products must be in protective packaging. Validate protective repackaging methods.*

*Abbreviations: USP, United States Pharmacopeia; Mfr, manufacturer*

Most of the drugs by far are classified as yellow (Appendix Table 2, Appendix Figure 2). The large number of drugs classified as yellow at different steps of the decision tree are strongly related to missing information. Categorization of drugs as green or red require the presence of experimental data, and to some extent green classification decreases with DRM length, whereas red classification increases. This inverse relationship is expected to increase as more data are acquired. Missing data fall into 3 key areas: shelf life (Steps E and F), stability to ionizing radiation (Step G), and degradation pathways/hazardous degradation products (Step H). Missing data are primarily attributable to the following:

- *The absence of publicly available shelf-life data.* *Only manufacturers and the U.S. FDA have experimental shelf-life information. For this version of the stoplight chart, surrogate data are used, as discussed below.*
- *Incomplete evaluation of radiostability information.* *The literature includes radiostability data for many drugs, however, most of this information have yet to be extracted from collected sources. The key challenge has not been data access; the challenge has been performing the somewhat time-consuming activity of extracting the required information and the fact that this activity requires subject matter expertise. The procedure used for extracting radiostability data from literature sources is discussed below. In addition, the U.S. FDA has radiostability data for drug products that were radiosterilized during the manufacturing process.*
- *Acquisition of information regarding toxicity of chemical degradation impurities.* *The simplest and most straight forward first step for identifying toxic degradation impurities was expected to be a literature search. Successful collection of this information requires some familiarity with basic literature searching methods including use of key words, Boolean terms, and MESH headings. However, this effort was unsuccessful, and it was concluded that these efforts should not continue. It is possible that this process can be circumvented by partnership with the U.S. FDA or direct communications with pharmaceutical companies.*

| Appendix 3 Table 2. Number of Drugs Classified for Each Color Category in each Step of the Decision Framework | | | | | | |
|---|---|---|---|---|---|---|
| | 12-month DRM | | | 30-month DRM | | |
| | Red | Yellow | Green | Red | Yellow | Green |
| Step B | 0 | 0 | 4 | 0 | 0 | 0 |
| Step C | 3 | 0 | 0 | 4 | 0 | 0 |
| Step E | 0 | 57 | 0 | 0 | 133 | 0 |
| Step F | 0 | 0 | 0 | 21 | 0 | 0 |
| Step G | 10 | 160 | 0 | 5 | 90 | 0 |
| Step I | 0 | 27 | 15 | 0 | 18 | 5 |
| Total | 13 | 244 | 19 | 30 | 241 | 5 |
| Steps A and C do not directly classify drugs<br>Insufficient data exists to inform classification by Step H<br>DRM; design reference mission | | | | | | |




***Appendix 3 Figure 2. Drug classification by Mission Duration.*** *The fraction of formulary drugs classified as green, yellow, or red based on the length of the design reference mission. The large fraction of drugs classified as yellow is primarily attributable to data missingness.*

## *3. CHANGES FROM THE 5/22/2022 VERSION*

- *This stoplight classification is no longer a time-consuming manual process. Drugs are now classified using a curated machine-readable database. The classification algorithm is coded in R software. A clean, SME-curated database is essential for this process.*

- *Empirical spaceflight data are now given priority in the decision tree. It is assumed that if experimental testing is the gold standard for qualifying drugs for exploration spaceflight, then these data, when available, should be the default.*
- *"Unknown" option is added to step G.*
- *Step C (previously step F) is no longer a terminal step. A "yes" decision sends the drug to Step D to evaluate relative shelf life. This is justified because the drug was repackaged and empirically tested in a spaceflight study but failed to meet quality standards.*
- *Step G now includes separate options for not stable (No = Red) and Unknown (unknown = Yellow), which distinguishes observed drug instability from absence of data.*

### *4. NOTES ON THE STOPLIGHT CLASSIFICATIONS*

#### a. *General comments*

- *The color classification of the drugs is primarily determined by data availability. Drugs assigned yellow typically have inadequate data to classify them as green or red. For this reason, the number of drugs classified as yellow has low correlation with DRM length; drugs classified as green or red are associated with DRM length.*
- *Steps A and D are decision steps that do not classify the drugs. The stoplight chart does not have results for these 2 steps.*

#### b. *Step A – Spaceflight empirical testing results*

- *Very few drugs are classified by spaceflight studies because there is only one controlled spaceflight stability study and most of the drugs tested in that study are not included on the CRT drug list.*
- *Empirical classification is only applicable to the formulation of the drug that was tested (e.g., tablet, solution).*
- *Caution should be used when extrapolating empirically measured stability of one brand of drug product to other equivalent brands. Different brands of equivalent drugs are usually formulated with different excipients, and excipients can significantly affect the shelf life of drug products. For this reason, the shelf life of one manufacturer's product does not necessarily predict the shelf-life of equivalent products from other manufacturers.*
- *Data from the SLEP are only available from a 2006 publication. The FDA has collected at least 16 years of additional data since that publication and on a broader range of drugs. These data should be obtained to reduce data missingness.*

c. Step D - shelf life

- *None of the formulary drugs have actual shelf-life information. Current data are functional expiration times estimated by NASA's operations pharmacy for a small fraction of the ECF. These data were collected opportunistically through ad hoc expiration date tracking of medications sent to the ISS, or European drug products manufactured by European companies under approval of the EMA, not the U.S. FDA. Shelf-life data for US drug products are not publicly available. The U.S. FDA has shelf-life data that has not been shared with NASA.*

d. *Step G Radiostability*

- *Extraction of radiostability data from public literature is a time-consuming process that requires some SME experience (see methods below). Most drugs in the DDR have not undergone radiostability testing. Label storage instruction "protect from light", which is based on non-ionizing radiation exposure, is not used due to high misclassification rates, as discussed in the Drug Stability Evidence Report (Reichard, 2023).*

e. *Step H. Toxic degradation products*

- *No data have been collected or curated on toxic degradation products in aged medications. No drugs are currently classified on this criterion. It is expected that very few drugs will "fail" on this criterion because drugs undergo accelerated testing at elevated temperature and humidity prior to market approval by the FDA, and clinical reports of adverse effects attributable to drug degradation products are exceptionally rare. World-wide, adverse effects due to adulterated medications are far more common. Logistically, this strategic goal can be achieved through SME literature search, collaborative partnership with pharmaceutical manufacturers and/or the FDA, and predictive cheminformatics (Zeneth®) predictions.*

f. *Step I Repackaging*

- *The removal of solid oral medications from manufacturer's packaging exposes medications to humidity, $O_2$, and potentially other atmospheric factors that mediate chemical and physical degradation. It is assumed that most solid oral drugs (e.g., tablets, capsules, lozenges) will be repackaged into non-protective packaging. Drugs that have adequate manufacturer shelf life in manufacturer packaging may not have adequate shelf life when this protection is removed. Validated protective packaging procedures should remove this step.*

*5. DATA CURATION METHODS*

a. *Combination Drug Products (i.e., Drugs with More than One API)*

Combination drug products are classified as "failed" either when the drug product does not meet physical requirement (i.e., dissolution, hardness) or when any of the individual APIs fail to meet content specifications. Impurities are not used for evaluation because these data are generally unavailable. Combination drugs are classified based on the step when the first ingredient fails. If none of the ingredients fail (i.e., all ingredients are classified as "green"), then the first step where an ingredient is assigned "green" is identified. If even one API is not classified as "green", then the earliest step that classifies the drug as "yellow" or "red" is identified.

b. *Shelf life*

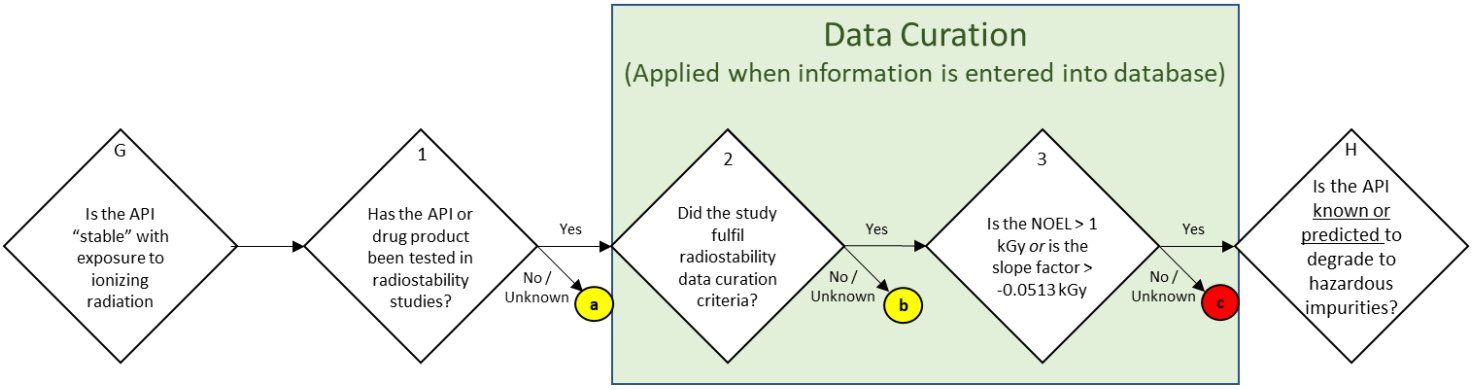
Shelf lives are not publicly available for U.S. drug products. For classification, shelf lives are estimated from 2 sources of information: the UK Electronic Medicines Compendium (emc®) and NASA operational shelf lives.

- Emc®. Shelf lives from the emc® are genuine shelf lives because the EMA requires disclosure of shelf life in addition to expiration dates for drug products sold in Europe. A limitation of emc® data is that drugs sold in Europe are not identical to those sold in the US; they have different manufacturers and regulatory environment. In the absence of evidence, shelf lives of European medications are assumed to be similar to equivalent products marketed in the US.
- NASA operational shelf life. The NASA operations pharmacy has tracked and recorded the dates that medications are prepared for each space mission and the corresponding expiration date. The operation shelf life is calculated as the difference between the time a drug product is prepared for a space mission and the expiration date. Limitations of this estimate are (1) estimates are not manufacturer specific and therefore do not provide information regarding relative stability of different brands; (2) variance of the estimates have not been tracked, which means that the range and precision of these measurements are unknown; and (3) measurements can significantly underestimate actual shelf life because they do not include the period of time from drug production to processing by the pharmacy. Because manufacturers typically produce a run of drug during a manufacturing campaign and then store and release the product over time, the time in the supply chain could mean operational shelf life is substantially shorter and more variable than actual shelf life. It is important to better understand the accuracy of these values.

c. *Radiation Stability*

"Stable" is subjective and depends on several assumptions. For the Stoplight Framework, stability classification depends on 2 key thresholds: the effective dose of radiation mediating chemical change and the degree of chemical change in the drug. No established guidelines exist for the acceptable degree change in a drug product or substance due to ionizing radiation exposure, aside from USP quality specifications. Therefore, criteria are used to classify radiation "stability" for the purpose of a Mars Exploration mission. The curation process for determining figures of merit is depicted in Figure 3.3. Radiostability assumptions are as follows:

- ***Radiation thresholds.*** *A cutoff of 1 kGy is assumed for the effective dose of ionizing radiation mediating chemical change (see below) in a drug product. This dose is 1000-fold greater than the cumulative dose (~1 Gy) expected during a Mars mission. This dose is 200–250-fold greater than the human acute lethal dose of ionizing radiation. According to the Nuclear Regulatory Commission, the dose of radiation expected to cause death to 50% of an exposed population*




***Appendix 3 Figure 3. Decision logic to classifying drug stability to ionizing radiation.*** *This sequence is accomplished programmatically as part of step G in the stoplight chart discussed above (Appendix 3 Figure 1), prior to step H and based on curated data input.*

Step 1. Quantitative analytical radiostability studies are identified for the drug API.

Step 2. Study results are collected for inclusion in the DDR if the study satisfies inclusion/exclusion criteria.

Step 3. A NOEL is assigned if there is no change (<5% change from untreated control) in drug content at 1 kGy (1000-times the estimated radiation dose for humans during a Mars transit mission) or an exponential slope factor of > 0.0513.

*Outcome footnotes*

- *Risk benefit analysis and/or market survey should be performed to determine if the loss of drug quality presents an unacceptable risk, if the drug is required for treatment of the intended medical condition(s), or if there are different marketed brands or formulations that may provide a better stability profile (i.e., a formulation that includes antioxidant ingredients or excludes ingredients that contribute degradation).*
- *Not all radiostability studies can be used to quantify drug stability. These studies are excluded from curation according to preset rules.*
- *Drugs that undergo precipitous degradation after radiation exposure may not be suitable for exploration missions. The basis for drug disqualification should be reviewed, and if it is determined that the data supporting disqualification are not applicable or not justifiable based on risk/benefit analysis, then the drug may reenter the decision logic for further consideration.*

API; active pharmaceutical ingredients: NOEL; no observed effect level

*within 30 day is 4–5 Gy (4– 5 Sv assuming a quality factor of 1). The 1kGy threshold dose is also 20,000-time greater than the acceptable occupational exposure limit for ionizing radiation, which is 0.05 Gy (0.05 Sv) set by the Occupational Safety and Health Administration, and 1666-fold greater than the NASA career limit for radiation exposure. A change in drug content at a dose of ionizing radiation ≤ 1 kGy classifies the drug as "unstable" (Appendix 3 Figure 3).*

- *Chemical change threshold. A cutoff of 5% loss of API is used to define chemical change. The following described why a 5% decrease in drug content is justified:*
    - *5% is more protective than most USP quality specifications for drug content, which are typically set at ±10% of label strength. Most ECF drugs that undergo a 5% decrease in label strength will still meet USP quality standards with a few exceptions. Exceptions can be dealt with on an individual case-by-case basis.*
    - *A 5% threshold is a statistically pertinent change that allows for reasonable measurement variability and is the amount of change typically regarded as significant.*
    - *A 5% threshold allows margin for additional effects associated with time-dependent drug aging that are independent of radiation.*
- *The thresholds applied for chemical change in drug products, and/or drug substances, are protective in terms of both drug potency (i.e., API content) and radiation dose. Together, the protective threshold provides a reasonable margin for uncertainty.*
- *Stability Classification. The classification of "stability" uses one of 2 approaches: the NOEL and the slope of the dose response line.*
    - *The preferred approach for classifying stability uses the full range of dose-response data to calculate the slope of the best-fit regression (or trend) line. For all drugs evaluated so far, drug stability from exposure to ionizing radiation is well characterized by an exponential function:*

$$A_1 = A_0 e^{-k * x}$$

Where $A_0$ is the initial amount of the drug substance and $A_1$ is the amount of the drug remaining at some dose (x) of ionizing radiation. The slope factor, k, is the proportionality factor between radiation dose and API content of the exposed drug.

    - *The alternative approach when dose-response data are not available uses a NOEL. The NOEL is defined as the highest dose of radiation (in Gy or rads) that does not elicit a 5% change. The lowest dose of radiation that elicits a change in drug content ≥5% is defined as a LOEL. This*

*approach is similar to the methods used in toxicology and chemical risk assessment to characterize chemical toxicity.*

- *Radiation study rule in/ rule out criteria used for SME curation. Experience has shown that it is critically important to establish criteria for the types of studies used to characterize radiostability of drugs. The following rule in/rule out criteria are used to simplify the classification task and establish a reasonable standard to compare results across different studies.*
  - *Measurement metric. Radiostability of chemicals is measured in many ways. ESR characterizes and measures persistence of radicals in an irradiated drug substance. Thermal analysis provides information on drug crystal melting temperature due to lattice rearrangements. Minimum inhibitory concentration can indicate a loss of antibiotic drug potency. Thin-layer chromatography is a semi-quantitative method for identifying the presence of chemical reaction products, among other uses. Many studies report the results of infrared, UV, and nuclear magnetic resonance spectroscopy measurements of molecular structural changes. To classify drug stability, the fraction of the drug that changed at a discrete radiation dose is required to meet the criteria discussed above. Therefore, acceptable studies must report drug content and are reasonably assumed to be stability indicating base on the analytical method used, such as ultra-high-performance liquid chromatography with UV/vis or mass spectrometer detection.*
  - *Acceptable studies must report discrete radiation doses applied to the drug substance. The drug content should be reported for the applied dose(s) of radiation in tabulated or figure formats. The study must include a nonirradiated control. When dose-response data are provided as a figure, the figure is digitized for data extraction.*
  - *Acceptable studies must report the form of the drug that was irradiated, i.e., whether it was irradiated in solid form or in liquid suspension/solution. If the drug was in solid form, information must be provided on whether it was the active drug substance or finished drug product. If the drug was in a liquid form, the solvent matrix (usually water) and any additives must be specified.*
  - *The types and source of radiation must be specified. Acceptable type of radiation includes gamma, proton beam, and electron beam (e-beam or beta partial beam). X-ray can be considered however these studies are typically low dose, in the range of doses provided by*

*medical or security equipment and are therefore not very informative. Photons in the non-penetrating wavelengths, and non-ionizing radiation are excluded.*

- *The method of irradiation must be described including the temperature at which irradiation was performed and under what type of atmosphere (i.e., ambient air, argon, nitrogen, oxygen).*
- *The study should NOT be focused on wastewater remediation. Wastewater studies typically focus on very dilute drug substances, often in non-standardized solutions that often contain organic chemicals and perhaps reactive metals. The exception are studies that measure drug stability in solutions that are at a concentration similar to a drug product in pure water or a clearly defined matrix reflective of a drug solution (i.e., containing polyethylene glycols, glycerol, or alcohol). It is cautioned that several studies show that radiostability of drug solutions decreases with concentration, so studies of very dilute drug substances, in the range of those typically found in the environment (surface water and wastewater) can significantly overestimate the effect of ionizing radiation. For this reason, when alternative studies are available, studies related to water treatment and ecotoxicology should be avoided.*

*6. LIMITATIONS*

a. *Biotechnology drugs*

The current ECF consists primarily of small molecule drugs. It is anticipated that the meteoric increase in New Drug Applications for biotechnology products submitted to the FDA likely means that future iterations of the formulary will include protein-, RNA-, and DNA-based medications. Information should be acquired for representative biotechnology products.

b. *Product selection*

Stoplight decision outcomes depend heavily on product selection and NASA risk tolerance. Product selection influences shelf life and radiostability. Risk tolerance influences classification cutoffs, such as the degree to which a drug might depart from USP standards, acceptable daily dose of impurities, etc. Sensitivity analysis can be performed to determine the extent to which uncertainty in the input data influences output classification. The results of such evaluations should inform prioritization of future work on data curation.

c. *Predictive vs. Empirical testing*

Not every drug can be evaluated for interplanetary DRMs. Predictive models and literature data can be used to mitigate risk by quantify margins of safety. The extent to which non-empirical evaluations can substitute for direct studies is uncertain and may not be accepted by clinical personnel who are responsible for the crew's health and performance.

d. *Subject Matter expert (SME) support to achieve strategic goals*

During FY22 it became apparent that current support provided by contractors included personnel who were not equipped to achieve the strategic goals outline in the Pharmaceutical Drug Stability Strategy. It is expected that significant progress can be made during FY23 to acquire shelf-life toxic impurity and radiostability data for formulary drugs if appropriate SME support are available. If drug stability remains a concern for the ExMC Element, assurance of logistical support from the Element is required to ensure the strategic goals to mitigate risk are met.

D. APPENDIX 4: DRUG STABILITY TESTING PROPOSAL FROM THE U.S. FDA

U.S. FOOD & DRUG ADMINISTRATION

## Memorandum

**Date:** April 07, 2020

**To:** Jorge L. Sotomayor, ExMC Deputy Element Manager, NASA Johnson Space Center

**From:** Patrick J. Faustino, Ph.D. Lab Chief, Division of Product Quality Research
Office of Testing and Research, Office of Pharmaceutical Science, CDER/FDA

**Subject:** NASA-FDA Budget 2020-2022

### Background

Representatives from NASA and FDA have been in discussions since February 2019 to develop a plan to evaluate the stability and extended shelf-life of drug products and for FDA to conduct laboratory studies to evaluate the stability of the drug products. A statement of work has been drafted by NASA and reviewed by FDA scientists. To complete the SOW a draft budget was prepared by NASA and FDA for review by NASA.

Discussion between NASA (Jorge L. Sotomayor) and FDA (Patrick Faustino) developed criteria that includes equipment, ORISE Staff fellows, drug products, official reference standards, bulk standards, reagents/buffers/organic solvents, training and ORISE travel. Three draft budgets are listed below:

Appendix 4 Table 1

| Budgets | CY2020 (USD) | CY2021 (USD) | CY2022 (USD) |
|---|---|---|---|
| Budget 1 proposal<br>Two PHD Fellows | 141,100.00 | 280,200.00 | 285,200.00 |
| Budget 2 proposal with UPLC instrument | 291,100.00 | 280,200.00 | 285,200.00 |
| Budget 3 proposal<br>One PHD and One Technician Fellow | 141,100.00 | 252,200.00 | 258,200.00 |

- Proposal #1 is broken out in Appendix 4 Table 2 listed below.
- *Proposal #2 is broken out in Appendix 4 Table 2 listed below with the additional of the cost of the ultra-high-performance liquid chromatography (UPLC)-mass spectrometer (MS) ($150,000) in CY2020.*

- Proposal #3 is broken out in Appendix Table 3 listed below.

Appendix 4 Table 4. Proposal FDA Budget #1 and #2.

Dollar amount are projections from 2019. Values will be updated when the interagency agreement negotiations resume.

| Column1 | Column2 | Column3 | Column4 | Column5 | Column6 |
|---|---|---|---|---|---|
| **Budget Item** | **CY 2020** | **CY 2021** | **CY 2022** | | |
| | | | | | |
| ORISE Fellow 1 | 60,000.00 | 108,000.00 | 110,000.00 | | |
| PHD | | | | | |
| ORISE Fellow 2 | 60,000.00 | 108,000.00 | 110,000.00 | | |
| PHD | | | | | |
| Drug Products | 2,000.00 | 8,000.00 | 8,000.00 | | |
| | | | | | |
| USP Reference Standards | 3,000.00 | 10,000.00 | 10,000.00 | | |
| | | | | | |
| Bulk API | 600.00 | 1,200.00 | 1,200.00 | | |
| | | | | | |
| Instrument standards | 2,000.00 | 3,000.00 | 3,000.00 | | |
| | | | | | |
| UPLC columns | 4000 | 6000 | 6000 | | |
| | | | | | |
| Solvents, reagents,water | 3000 | 5000 | 5000 | | |
| | | | | | |
| UPLC PM Kits | 0.00 | 12,000.00 | 12,000.00 | | |
| | | | | | |
| UPLC Repair Supplies | 0.00 | 6,000.00 | 6,000.00 | | |
| | | | | | |
| UPLC Service | 0.00 | 9,000.00 | 10,000.00 | | |
| | | | | | |
| Training-Instrument/software | 5000 | 1000 | 1000 | | |
| | | | | | |
| ORISE Travel to NASA | 1500 | 3000 | 3000 | | |
| | | | | | |
| | | | | | |
| **TOTAL** | **141,100.00** | **280,200.00** | **285,200.00** | | |

Appendix 4 Table 5. Proposal FDA Budget #3.

Dollar amount are projections from 2019. Values will be updated when the interagency agreement negotiations resume.

| Budget Item | 2020 | 2021 | 2022 | | |
|---|---|---|---|---|---|
| | | | | | |
| ORISE Fellow 1 | 60,000.00 | 108,000.00 | 110,000.00 | | |
| PHD | | | | | |
| ORISE Fellow 2 | 60,000.00 | 80,000.00 | 83,000.00 | | |
| Techician | | | | | |
| Drug Products | 2,000.00 | 8,000.00 | 8,000.00 | | |
| | | | | | |
| USP Reference Standards | 3,000.00 | 10,000.00 | 10,000.00 | | |
| | | | | | |
| Bulk API | 600.00 | 1,200.00 | 1,200.00 | | |
| | | | | | |
| Instrument standards | 2,000.00 | 3,000.00 | 3,000.00 | | |
| | | | | | |
| UPLC columns | 4000 | 6000 | 6000 | | |
| | | | | | |
| Solvents, reagents,water | 3000 | 5000 | 5000 | | |
| | | | | | |
| UPLC PM Kits | 0.00 | 12,000.00 | 12,000.00 | | |
| | | | | | |
| UPLC Repair Supplies | 0.00 | 6,000.00 | 6,000.00 | | |
| | | | | | |
| UPLC Service | 0.00 | 9,000.00 | 10,000.00 | | |
| | | | | | |
| Training-Instrument/software | 5000 | 1000 | 1000 | | |
| | | | | | |
| ORISE Travel to NASA | 1500 | 3000 | 3000 | | |
| | | | | | |
| | | | | | |
| **TOTAL** | **141,100.00** | **252,200.00** | **258,200.00** | | |