NASA-STD-3001 Technical Brief

Pharmaceutical Care

OCHMO-TB-006
Rev A

Relevant Technical Requirements

NASA-STD-3001 Volume 1, Rev B

[V1 3004] In-Mission Medical Care
[V1 3005] Medical Training for In-Mission Medical Care Providers
[V1 4009] Sensorimotor Countermeasures
[V1 4016] In-Mission Hematological/Immunological Countermeasures
[V1 4021] In-Mission Nutritional Status
[V1 4027] Pre-Mission Bone Countermeasures
[V1 5001] Medical Training
[V1 5007] Support Personnel Training
[V1 6001] Circadian Shifting Operations and Fatigue Management
[V1 6007] Medical and Survival Kits
[V1 7001] Crew Health Results
[V1 7002] Crew Records Communication
[V1 7003] Crew Records Storing

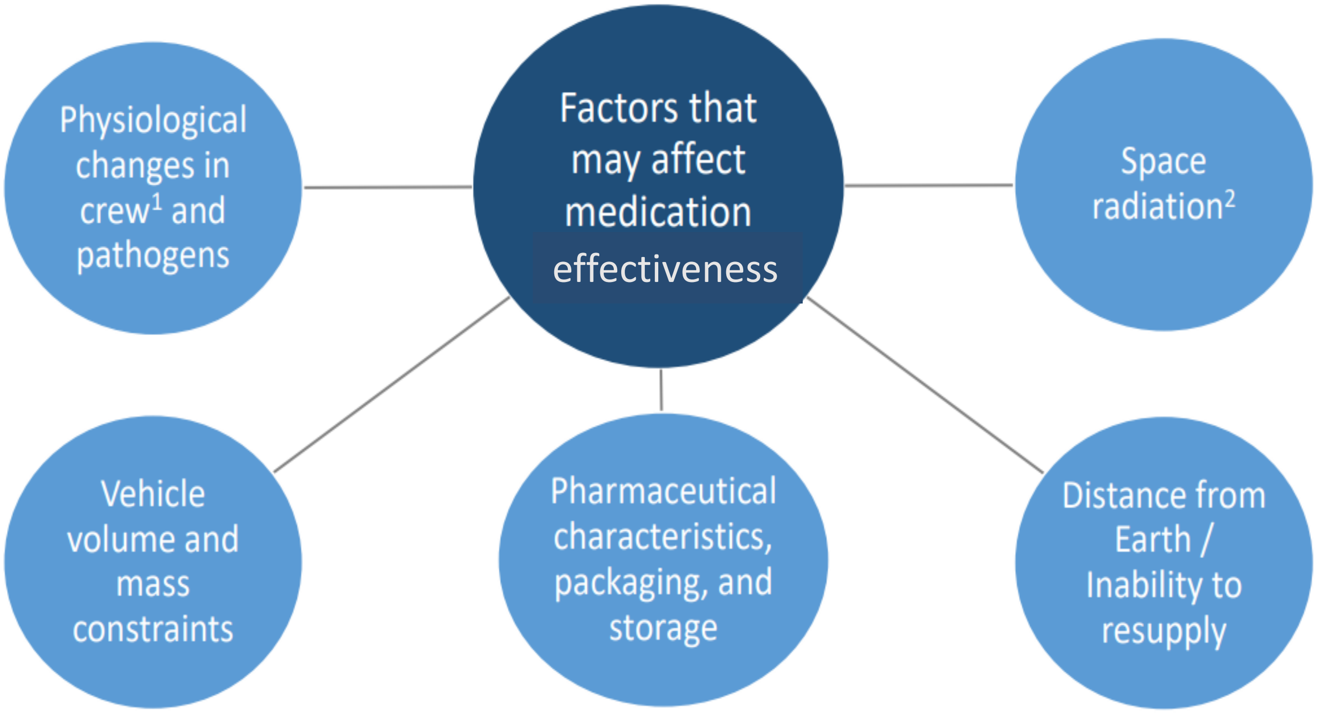
NASA-STD-3001 Volume 2, Rev C

[V2 7038] Physiological Countermeasures Capability
[V2 7042] Orthostatic Intolerance Countermeasures
[V2 7043] Medical Capability
[V2 7045] Medical Equipment Usability
[V2 7050] Stowage Provisions
[V2 7051] Personal Stowage
[V2 7052] Stowage Location
[V2 7055] Priority of Stowage Accessibility
[V2 7059] Inventory Tracking
[V2 12026] Stowage Access
[V2 11027] Suited Medication Administration

Executive Summary

Pharmaceutical Care refers to the dispensation of drug therapy to achieve outcomes that improve a patient's quality of life. Outcomes of traditional pharmaceutical care are management of a medical condition, elimination or reduction of patient symptomatology, arresting or slowing disease progression, or preventing illness. In spaceflight, pharmaceuticals and medications are used for a variety of purposes including prevention of illness, medical treatment, and countermeasures. The unique environment leads to a host of factors that must be considered when choosing treatment options. Spaceflight factors, pharmaceutical shelf life, and time to resupply could lead to ineffective medications or even the potential for toxic byproducts. Physiological changes related to spaceflight as well as alterations of pharmacokinetics and pharmacodynamics may lead to differing outcomes from pharmaceutical intervention compared to those known terrestrially. These factors, along with vehicle environment, may result in the in-mission medical capabilities and interventions to have outcomes that differ from what would be expected on Earth.

Overview



[1]Reference the Spaceflight Experience and Medical Care Technical Brief for more information
[2]Reference the Radiation Protection Technical Brief for more information

Pharmaceuticals can affect the following spaceflight human system risks as interventions or countermeasures:
Risk of Ineffective or Toxic Medications During Long-Duration Exploration Spaceflight, Risk of Bone Fracture due to Spaceflight-induced Changes to Bone, Risk of Renal Stone Formation, Risk of Cardiovascular Adaptations Contributing to Adverse Mission Performance and Health Outcomes, Risk of Performance Decrement and Crew Illness Due to Inadequate Food and Nutrition, Risk of Adverse of Health Event Due to Altered Immune Response, Risk of Adverse Cognitive or Behavioral Conditions and Psychiatric Disorders, Risk of Spaceflight-Associated Neuro-Ocular Syndrome (SANS), Risk of Performance Decrements and Adverse Health Outcomes Resulting from Sleep Loss, Circadian Desynchronization, and Work Overload, Risk of Decompression Sickness (DCS), Risk of Radiation Carcinogenesis.

Related OCHMO Technical Briefs

1. Behavioral Health
2. Bone Loss
3. Water
4. Food and Nutrition
5. Orthostatic Intolerance
6. Radiation
7. Sleep
8. Decompression Sickness

Background

Pharmacokinetics, Pharmacodynamics, and Other Factors

One of the challenges to providing pharmaceutical care in spaceflight is the lack of data regarding how medications work in space compared to how they work terrestrially. Many factors are being studied and considered to assess how space travel affects medications and how those medications affect the human body.

- **Pharmacokinetics (PK)** refers to how the body reacts to a drug, including how medications are absorbed into the body, transported throughout, and degraded or eliminated.
- **Pharmacodynamics (PD)** refers to how a drug interacts with tissues, cells, and organs as well as if the drug formulation (i.e., tablet capsule, liquid, or aerosol) produces the desired effects. The extent of absorption can depend on route of administration and physical and chemical properties.

Space Exposure: even in low Earth orbit, spaceflight introduces several factors that may affect how well medications last in space (stability) and how well they work (therapeutic value). These factors include:

Physiological changes in the human body

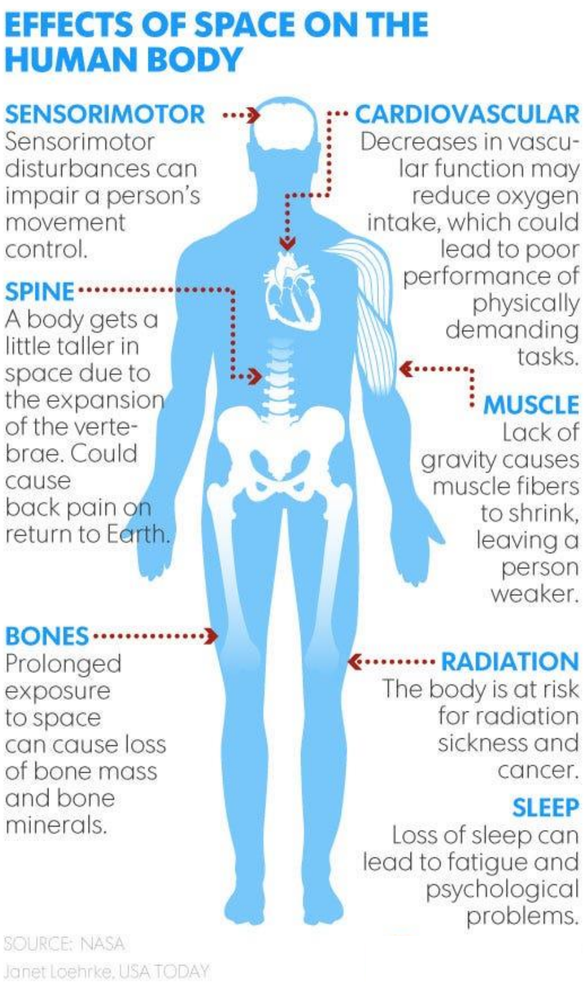
- Fluid shifts – altered volume distribution.
- Intracellular fluid alteration – altered metabolism; altered drug uptake and clearance.
- Altered plasma protein concentration – altered free drug concentration; altered renal/hepatic clearance.
- Cell membrane permeability – altered drug distribution and uptake.
- Hepatic metabolism – altered hepatic blood flow; altered hepatic enzyme expression.
- Gut motility and absorption – altered gastric emptying from space motion sickness (SMS) or medications to address SMS; faster and more variable intestinal transit rate.

Environmental changes

- CO_2 changes
- Pressure changes
- Gravity changes
- Radiation exposure
- Other atmospheric considerations (humidity, temperature, pressure, etc.)

Immunology:

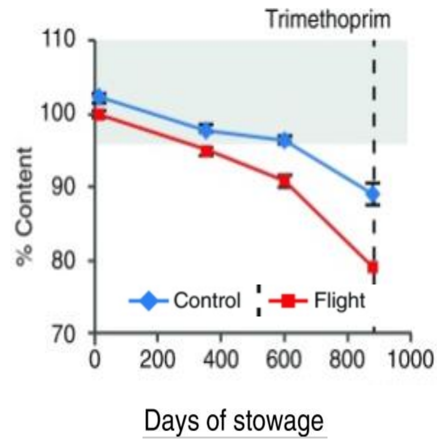
- There is evidence that pathogens may be altered or that medications may be unsuccessful in managing pathogens during spaceflight.
- Prior studies have explored increased antibiotic resistance of spaceflight cultured bacteria.

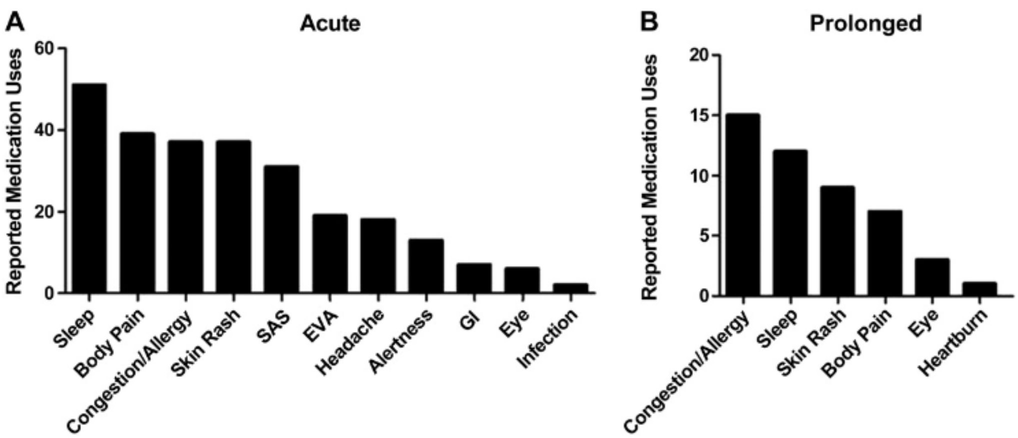


Background

Research Related to Pharmaceuticals

Spaceflight may affect the stability of certain medications by altering the concentration of the active pharmaceutical ingredient (API). NASA has not identified a definite mechanism for this phenomenon, but more research is being conducted. An example of this is shown by the graph to the right (Du et al., 2011) where the active pharmaceutical ingredient (API) of Trimethoprim decreased with longer stowage duration. Another study however, with returned samples from the ISS did not show much (if any) decline in effectiveness of the API past their expiration date. *Wotring, 2014*





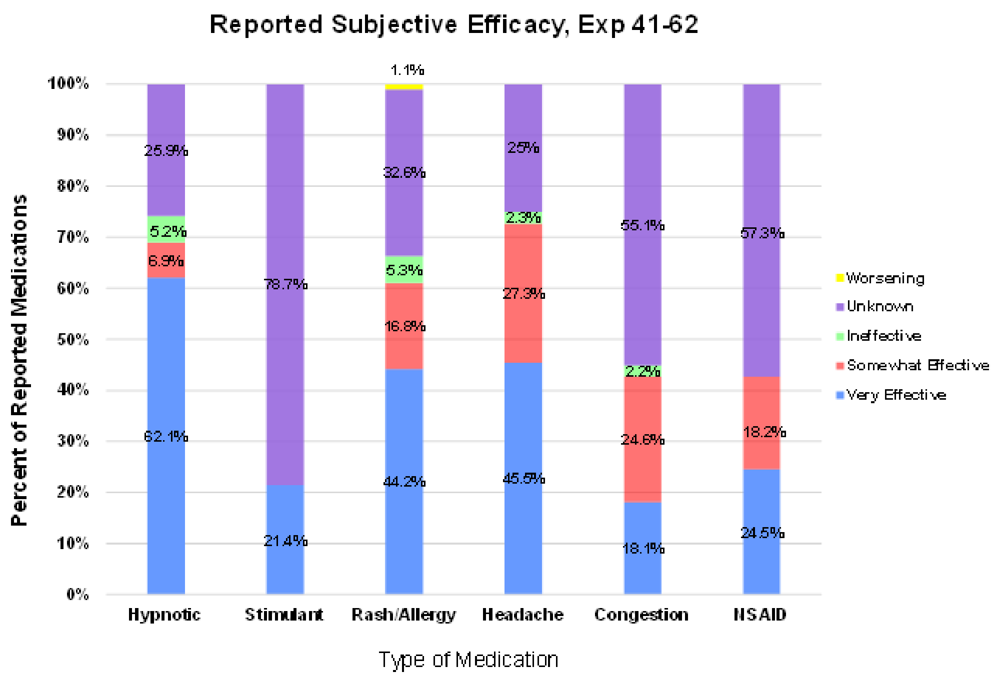
Medication Usage

- Sleep aids are the leading medications for acute use in-mission
- Congestion/allergy medications are the leading medications for prolonged use in-mission

Wotring, 2015

In-Mission Medication Effectiveness

Even though underreporting limited the Dose Tracker 2017 study dataset, a very small percentage of medications were found to be ineffective in-mission. Most medications led to at least some amount relief of symptoms. It was difficult to determine if medication recall data could have been altered by crew taking medications for an "inaccurate diagnosis".
Blue et al., 2019



Background

How to choose medications to fly

As with everything in spaceflight, onboard medications must be chosen with utmost care due to extreme weight and volume constraints, inability to resupply, distance from Earth and shelf-life considerations.

Onboard pharmacies are chosen based on many factors, including:

- Medications known to be safe, effective, and well tolerated, with a wide therapeutic range.
- Avoid on-board medications that have known intolerable side effects and prefer to use those not requiring refrigeration or other special storage requirements.
- Prefer to use medications known to be safe and effective for the journey duration. Given longer duration missions like Mars, may need to be flexible with this recommendation.

As spaceflight has evolved, so have medication kits. During the Mercury Program, the initial pharmacy kit contained 4 medications to be used for emergency only, later ISS kits contain more than 70 medications. As we plan future flights, especially long duration space flights that have extreme mass and volume constraints, we will use information gathered from historical data, data from risk assessment tools (see page 6), and flight surgeon expertise, to best inform our medication kits.

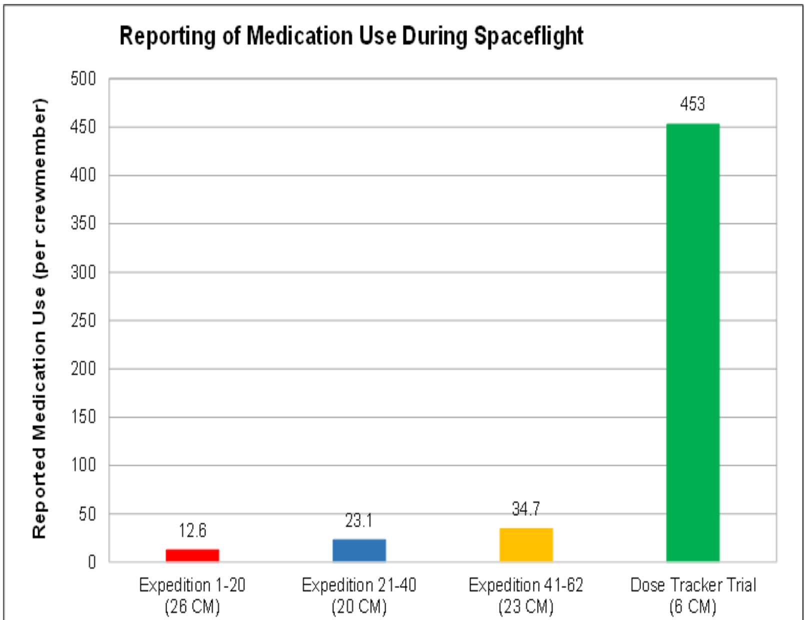
Historical information with the following considerations is used when planning a medical kit:

- Early space medicine did not include a specific reporting system for medication use.
- Most historical reporting has been ad hoc and anecdotal, with substantial recall and reporting bias.
- A 2020 study was implemented that required dose reporting of all medications and demonstrated that there was a substantial loss of medication use data when relying on ad hoc reporting methods.
- Study data suggests mandatory reporting with user friendly interfaces, may provide data to improve our understanding of pharmacy use and effectiveness.

Dose Tracker Study

Historically, we had poor capture of medication usage data (which medications, time of use, efficacy, side effects, etc.). Shuttle expeditions 21-40 had a more standardized medication usage reporting process (improvement from Expeditions 1-20). The dose-tracker project data shows a 20-60x increase in reported data points. All data presented are AVERAGE reports per crewmember.

Dose tracker trial reporting translated to 3.5 to 4.0 medications used per crew/week and a total of 453 doses of medication. *See Wotring & Smith, 2020 and Blue et.al. 2019*



Updated since Blue et al, NPJ Microgravity (2019)5:14

Background

Medication storage and packaging
In addition to determining what medications are best to include, NASA must consider other logistical factors when packing medication kits:

Considerations for medical kit content
- Volume
- Mass
- Waste (excess packaging)
- Stability and sterility
- Storage conditions
- Pharmaceutical issues - PK/PD toxic metabolites
- Drug delivery systems ability in space
- Drug availability - shortages
- Consider costs associated with mass/storage
- Astronaut personal medications
- Vehicle and Suit environmental impacts

A medical technician surrounded by medical kits for the ISS Crew. *Source: NASA*

Onboard personal medical kit Crew is allowed to bring a personal supply of medications or medical supplies. These are referred to as ISS Medical Accessory Kits (IMAKs). The medical team needs to consider this content ahead of time to evaluate any potential medication interactions.

Medical kits in-flight factors
- Shelf life is a driver of medication as expiration is a limiting factor when flying medications. We can only legally pack medications that have manufacturer expiration data.
- Need to consider time it takes to pack and transport to launch site when considering expiration date.
- Toxicology considers all medications for active and inactive ingredients as possible toxic exposure.
- Shipping happens during prelaunch timeframe, need to ensure storage chain requirements are followed.
- Predict any side effects and interactions, including personal medications.
- Provide education regarding all medications.
- Consider administration, absorption, metabolism, elimination, clinical response, toxicity, and effectiveness.
- Consider any physiological change that can cause medications to work differently.
- International medications – may need additional information such as education and storage if not familiar.
- Inventory management—ensure medications are packed to be accessible and designed to best manage expiration parameters.
- May have multiple medication packs depending on mission design.

[V2 7115] Medical treatment, including pharmaceuticals, non-pharmaceutical crew care items, and related supplies, shall be evaluated for impacts on vehicle systems.

Background

Drug expiration and shelf Life

Medication Expiration poses a big challenge to providers of health care for long duration space flight. Many medications expire within 1-5 years and without resupply, medication availability and usability is in question.

Expiration date The date at which the manufacturer can still guarantee the full potency and safety of the drug when stored under proper conditions.
Shelf-life Date determined by drug manufacturers expressed as an expiration date after which time the manufacturer cannot guarantee the stability of potency of the medication.

Neither shelf life or expiration date state that medications are harmful if used beyond identified date, and currently there is very little information regarding this topic. One medication, **Tetracycline**, is associated, but not strongly proven, with potential harm of increased risk of kidney damage **(**Fanconi syndrome) when used beyond expiration. (see *Wegienka et al., 1964*).

History of Expiration Dating

In 1979 the U.S. Food and Drug Administration passed the law "**Current Good Manufacturing practice for finished pharmaceuticals, Expiration dating"** [32] to ensure people would only use medications that were safe and guaranteed to work as intended under proper storage conditions.
This protection also caused some difficulty, The Department of Health and Human Services (HHS), which stockpiles certain medications in case of emergency, or in the interest of National health, found that they were needing to replace stockpiles of unused medications at significant expense based on expiration dates.

1986 Federal Shelf-Life Extension Program (SLEP) Developed by Department of Defense in conjunction with FDA to defer cost of drug waste by studying if drugs can be used beyond expiration. Lyon et al. (2006). The study demonstrated that many medications, when maintained in original and unbroken packaging, may last significantly longer than labeled expiration dates. Testing showed 88% of medication lots have been extended beyond their stated expiration. Stability is unknown and varied between samples of the same drug, manufacturer, and lot. As a result, some government stockpiled medications can be stored beyond there original expirations for emergency use only. A similar study occurred in the UK with the electronic Medicines Compendium (eMC), which contained drug information from UK pharmacy companies. Many eMC medication shelf lives were changed by manufactures and extended up to 3-6 years (practice is not yet adopted by FDA).

Sample of SLEP medication extensions

Drug name	Average extension time Months
Morphine Sulfate injectable	89(35-119)
Naproxen Tablets	52 (46-62)
Ciprofloxacin Tabs	55(12-142)
Doxycycline Caps	50(37-66)

Source Lyon et al 2006

Other concerns

Some medications may be more susceptible to bacterial growth or loss of stability including nitroglycerin, eye drops, liquid antibiotics, and insulin, and are less likely to qualify for extended shelf life.

Background

Radiation effect on medications

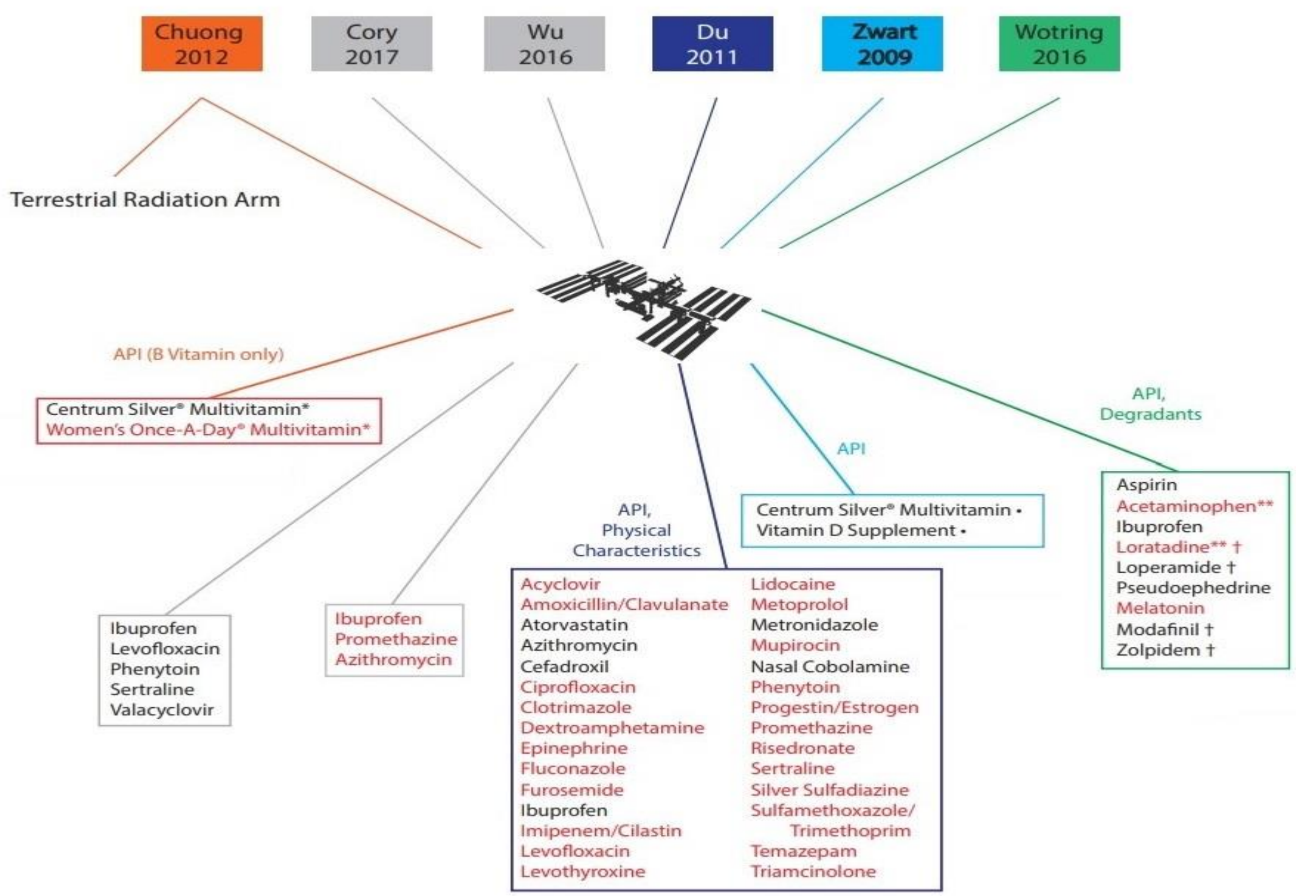
One of the challenges to long duration spaceflight is the uncertainty of the effect, radiation exposure will have on humans, including how radiation exposure will affect pharmaceuticals in space.

During spaceflight, radiation can potentially cause direct or indirect damage to biological cells, so we question if it similarly may damage pharmaceutical chemical and structural composition. Concerns include: will radiation degrade pharmaceuticals reducing the therapeutic effect, or cause release of toxic substances, and will radiation affect the human, so the pharmaceuticals no longer achieve desired results?

Example studies

Studies of pharmaceuticals exposed to simulated space radiation were found, in some circumstances, to have altered physical structure, alterations of active pharmaceutical ingredient concentration, and similar changes of unclear clinical significance. Some medications were found to have alterations of active pharmaceutical ingredient or physical characteristics, particularly after prolonged spaceflight exposure. Data may be confounded by the fact that pharmaceuticals returned to Earth and data analysis in many cases, occurred after expiration of the medications.

See summary graphic below from Blue et al., 2019.



Background

Analog and spaceflight to study medication use

- Bedrest: bone, cardiac, muscle atrophy
    - Human bedrest studies have been performed to simulate spaceflight conditions on body fluid shifts due to microgravity using head down positioning. Bedrest studies introduce elements experienced in spaceflight but do not replicate other conditions including stress or physical demands experienced, they are also limited by small numbers and variable conditions.
- Medication studies have been used to determine alterations of drug metabolism due to postural changes. Human Exploration Research Analog (HERA): software tracking what medications were used and why.
- Artificial gravity: induce motion sickness to test efficacy/dose etc. and learn-to-learn protocol.
- Variable results confirm more data is needed to determine effects spaceflight has on medication efficacy.

Source: NASA Bedrest study

Artificial Gravity *Source: Space.com May 12, 2010*

Study	Levy	Rumble	Putcha	Roberts	Schuck
Year	**1967**	**1988**	**1991**	**1980**	**2005**
Design	Head down bed rest (HDBR) study of intramuscular (IM) benzyl-penicillin.	1. Studied effect of bedrest on pharmacokinetics of intravenous (IV) Benzyl-penicillin.	Studied salivary samples of acetaminophen to characterize physiologic responses.	The pharmacokinetics of amoxicillin in normal male volunteers was studied during the states of bedrest, sleep and ambulation.	Evaluated the effects of simulated microgravity on the pharmacokinetics of ciprofloxacin after a single 250-mg oral dose in normal gravity (1G) and simulated microgravity.
Result	Increased renal clearance and decreased metabolic degradation in HDBR study compared to normal control.	1. No significant change in absorption, distribution, clearance, or half--life of benzylpenicillin in bedrest subjects.	Crew showed more pronounced changes in absorption than elimination phase. Acetaminophen showed significant decrease in absorption rate during flight.	Serum amoxicillin concentrations were found to be significantly greater during ambulation than during bedrest and sleep.	No significant change in ciprofloxacin serum concentration in simulated microgravity.

Background

History of Medication Kits

Mercury Medications were available for emergency auto injectors:

- Cyclizine for motion sickness, epinephrine for injury or shock, meperidine for pain, dextroamphetamine sulfate for alertness and response time.

Gemini Higher quantities of medications for longer missions, included a first-aid kit:

- Medications added included pseudoephedrine for congestion, as well as tetracycline for infection, diarrhea and eye drop medication.

Apollo Continued to adjust and add medications per needs assessed after each flight:

- Included lunar module kit to accommodate crew split and medication for sleep disruption, cardiac dysrhythmias, eye, ear, multivitamins, decongestant/antihistamine, antibiotics, analgesics, GI, sedative, and stimulant medications.

SKYLAB Longer missions required larger and more comprehensive med packs:

- Medications similar to Apollo, introduced additional medical kits including first dental kit, first diagnostic kit including hematology, urinalysis, and therapeutic kit including laryngoscope and airway equipment.

Space Shuttle Program Crew Medical Officer on each flight:

- Three kits including medication kit, medication and bandage kit (MBK), and emergency medical kit (EMK); kits contained subpacks to further organize and make medications accessible.

International Space Station Two medical kits, one for the Russian segment and one for the US segment

- Contains 190 medications to treat anticipated medical conditions, medical officer trained in first aid and emergency medical treatments and include personal medication kits for crew (IMAK).

Sample Medication Kit Lists

Mercury	Gemini	Apollo	Space Shuttle	ISS
Cyclizine	Cyclizine	Acetaminophen	Acetaminophen	Albuterol inhaler
Dextroamphetamine	Dextroamphetamine	Ampicillin	Acyclovir	Ambien
Epinephrine	Diphenoxylate	Aspirin	Aluminum Hydroxide	Ethinyl estradiol/norgestrel
Meperidine	Epinephrine	Atropine	Amikacin	Fluocinonide .05%
		Bacitracin	Amoxicillin	Ertapenem
		Cyclizine	Flurazepam	Nitroglycerin
		Dextroamphetamine	Ibuprofen	Phenytoin
		Simethicone	Lidocaine	Provigil
		Tetracycline	Metronidazole	Tamsulosin
		Tetrahydralazine	Naloxone	Zoloft

Background

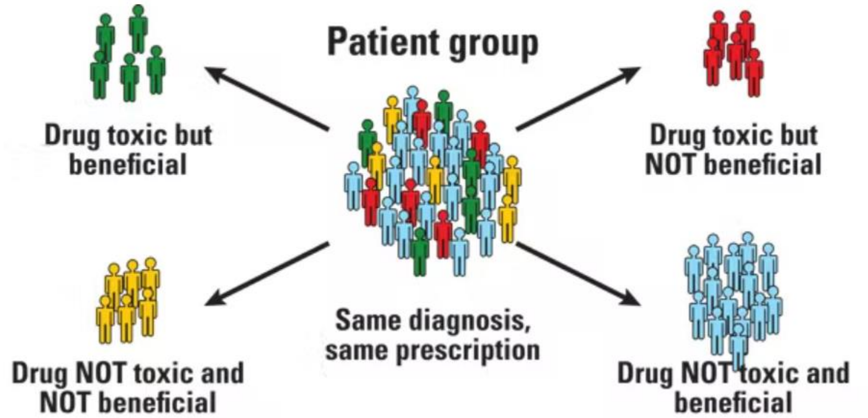
Pharmacogenomics The study of how a person's genes affect their response to medications. Medication effectiveness can vary among patients, some will attain the desired effects with no problems while others may have an adverse drug reaction or receive no benefit from taking the medication. One cause of medication reaction variability is the fact that patients can have differences in enzymes which help to metabolize medications into usable products. Patients with enzymes which are more active have increased metabolism and may break down the medication too quickly to be able to work in the manner designed. If the patient enzymes are less active, medication is not broken down quickly enough and patient may be exposed to unexpected chemicals for longer periods of time which can cause adverse or toxic effects. Studies have also found particularly strong variances among specific cultural populations.

Pharmacogenomics and Spaceflight Pharmacogenomics information is being studied as it could be helpful when choosing the optimal effective medications to include in each mission medication kit.

Pharmacogenomics Study Stengl et al (2014) study explored 78 drugs permanently available on the ISS to determine how much variability the elimination of the medications occurs among crewmembers and would this require individual dose changes in order to prevent therapy failure or exposure to toxic adverse effects. Results: 24 drugs showed metabolism is affected by polymorphic metabolizing enzymes, but not enough evidence was present on how polymorphisms affects drug exposure to predict therapeutic recommendations or dose adjustments to make genetic testing a requirement at this time.

Pharmacogenomics Examples Although we do not have enough information at present to base medical kit formula choices on pharmacogenomics, we can still be aware of possible impacts. For example, enzyme CYP2D6 has been studied and found to have significant variability with patients ranging from poor metabolizers, through ultrarapid metabolizers. CYP2D6 is involved in the metabolism of 11 medications currently on the ISS medical formulary including metoprolol, a heart medication, which when taken by poor metabolizers (PM) can lead to symptoms of bradycardia and by ultrarapid metabolizers cause twofold higher clearances, not treating patient's symptoms or disease properly. Pharmacogenomics is new in its use and not standard practice in spaceflight crews at this time but is something being studied for effectiveness for future long-distance spaceflight.

Example of Pharmacogenomics



Source. *Journal of Solid Tumors*, 2012

Application

[V2 11027] Suited Medication Administration The system shall provide a means for administration of medication to a suited, pressurized crewmember for pressurized suited exposures greater than 12 hours. *From: NASA-STD-3001 Vol 2*

Medication Challenges

In-Suit Medication Use

Historically, a crewmember would plan to spend no more than 6 hours in a pressurized spacesuit for an EVA and would not need to take medications while in-suit. In future missions, situations may arise that require crewmembers to stay suited for longer periods and take medications while suited. For example:

- Long duration missions have longer transit times (i.e., return from the Moon can take 144 hours or more). Crewmembers must have the capability to stay suited for long periods of time in the event of unplanned cabin depressurization and ability to take medication if needed.
- Crewmembers may have much longer EVA capacity or be traveling in an unpressurized rover, requiring them to be suited for long periods of time and need the capability to access medications.

[V2 11125] Pharmaceuticals, topical treatments and cleaning materials **shall** be compatible with suit materials (internally and externally).

Medication Delivery Options

NASA is studying many options to find the best way to be able to provide medications to suited crewmembers. Providing medication in suits is difficult, for example, injections and oral medications are both options being considered but each have their own unique set of challenges.(below)

Injectable Medication Challenges

- The ability to physically use the medical delivery device at the desired location while the astronaut is gloved and possibly seated is challenging.
- Not all medications are available as injectables so this method can decrease treatment options.
- Behavior of the fluid in a off nominal pressure/ temperature environment can make injections difficult, for example, when giving an injectable medication the bubble within a syringe will expand as pressure decreases.
- Require additional suit opening that can disrupt suit integrity, posing safety risks.

Toxic Off gassing Another challenge to using medications in space is to ensure that medications, while being stored, used, or broken-down, do not introduce off gassing or toxicity that may be damaging to the crew or vehicle.

Oral Medication Challenges

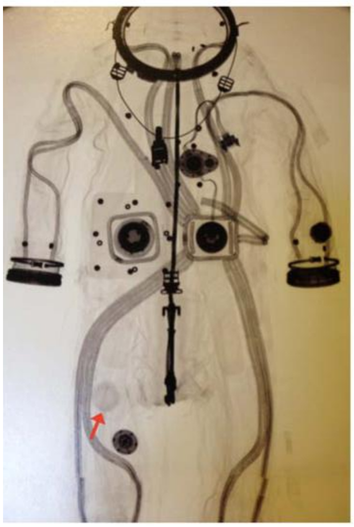
- The capability to provide an easily accessible, and administrable delivery of oral medication compatible with a pressurized suit is challenging.
- Programs are currently considering using hand-held tools to assist with oral pill port type medication delivery which can pose a challenge when the astronaut has a gloved hand.
- The oral delivery device may be limited in what sizes of pills/capsules it can use limiting medication options.
- Oral medication can potentially introduce residue contamination.

The Air Force U-2 suits had port for food and pills in the hard shell.

[V2 6047] Toxic Hazard Level Three The system shall use only chemicals that are Toxic Hazard Level Three or below, as defined in JSC-26895, Guidelines for Assessing the Toxic Hazard of Spacecraft Chemicals and Test Materials, in the habitable volume of the spacecraft. *NASA-STD-3001 Vol 2*

Application

History Apollo In-Suit Medication
When Apollo spacesuits were designed, the needs differed from the Mercury and Gemini programs because the transit time lengthened from hours to days. The suit needed to address additional risks imposed by the longer duration including if a contingency situation required the crew to remain in pressurized suits, they would have to be able to administer an injection while suited in the event of illness or injury. The Apollo Program identified a requirement (see below) for the Apollo EMU to have a biomedical injection patch to facilitate the injection while in a pressurized suit. This patch is no longer in use, however in suit medication administration options are currently being studied.



X-ray image of David Clark Apollo A-IC suit. *Source: Smithsonian Institute Image*

Right: Apollo Suit Injection Requirement. Apollo space Suit Assembly Design and Performance Specification, October 12, 1964.

> <u>Medical Injection Provisions</u> - The PGA shall provide the capability for the crewman to administer to himself hypodermic injections utilizing a spring-loaded plunger type needle, while in a pressurized PGA. The PGA shall provide, in a location to be determined by NASA, features which shall allow insertion of the needle and subsequent withdrawal, without endangering the pressure integrity or reliability of the suit, and shall be self-sealing to prevent the loss of gas at the site of the needle penetration. Best location for medical injections is on the ventrolateral aspect of the thigh, approximately half-way between the knee and the hip. An alternate location would be the deltoid area of either arm.

Apollo suit medication injection patch. *Source: NASA*

The Apollo medical kits housed pre-filled medical syringes inside a pressurized aluminum tube. Injections were activated by pressing a button at the top of the device, which caused the syringe and needle to displace, driving the needle through the seal on the device and the injection patch on the EVA suit into the muscle.

Source: *NASA*

Back-Up

Major Changes Between Revisions

Original → Rev A

- Added introduction with additional content, updated standards, added images of more current med kits.
- Deleted Back risk and Inflight medical risk for accuracy, added “other environmental factors” to space radiation bubble.
- New page with image “effects of space on the human body”, added wording regarding physiological, environmental, and immunologic changes information.
- Added additional information and graph regarding In-Mission Medication Effectiveness.
- Added additional detailed information regarding medication selection.
- Added Information and graph regarding Dose Tracker Study.
- Removed Photo of med kit.
- Added additional information regarding Medication storage, packaging, shelf life, Onboard medical kit, Federal Shelf-Life Extension Program.
- Removed inflight medical kit image.
- Removed Apollo application information.
- New slide regarding radiation effects on medication.
- Added new slide analog and spaceflight to study medication use information.
- Added new slide history of medication kits.
- Added new slide information regarding pharmacogenomics.
- Added new slide regarding medication delivery and suited medication challenges.
- Added new slide with images regarding in suited medication administration.

Referenced Technical Requirements

NASA-STD-3001 Volume 1 Revision B

[V1 3004] In-Mission Medical Care All programs shall provide training, in-mission medical capabilities, and resources to diagnose and treat potential medical conditions based on epidemiological evidence-based PRA, clinical practice guidelines and expertise, historical review, mission parameters, and vehicle-derived limitations. These analyses should consider the needs and limitations of each specific DRM and vehicles. The term “in-mission” covers all phases of the mission, from launch, through landing on a planetary body and all surface activities entailed, up to landing back on Earth. In-mission capabilities (including hardware and software), resources (including consumables), and training to enable in-mission medical care, are to include, but are not limited to: (see NASA-STD-3001, Volume 1 Rev B for full standard).

[V1 3005] Medical Training for In-Mission Medical Care Providers The level of training of in-mission medical care providers shall be commensurate with the complexity of anticipated medical, mental health, and behavioral conditions, taking into account such aspects as mission duration, destination, capabilities of the medical system, return-to-Earth capability, mission architecture, crew quantity, vehicle design, and the need for autonomous-from-Earth medical care. The term “in-mission” covers all phases of the mission, from launch, through landing on a planetary body and all surface activities entailed, up to landing back on Earth.

[V1 4009] Sensorimotor Countermeasures Countermeasures shall maintain function within performance limits.

[V1 4016] In-Mission Hematological/Immunological Countermeasures In-mission countermeasures shall be in place to sustain hematological/immunological parameters within the normal range as determined by direct or indirect means.

[V1 4021] In-Mission Nutritional Status In-mission nutritional status shall be assessed, and recommendations/countermeasures applied for any decrements below predetermined values.

[V1 4027] Pre-Mission Bone Countermeasures Countermeasures shall maintain bone mass of the hip and spine at or above 95% of pre-mission values and at or above 90% for the femoral neck.

[V1 5001] Medical Training Medical training to astronaut candidates, assigned crewmembers, flight surgeons (FSs), mission control support staff, and other ground support personnel (GSP) deemed appropriate shall be provided.

[V1 5007] Support Personnel Training Supervised training programs shall be implemented for individuals who require knowledge of space medicine or flight medical procedures, such as flight directors, medical consultants, and/or other personnel deemed appropriate as part of the Medical and Crew Health Requirements Document.

[V1 6001] Circadian Shifting Operations and Fatigue Management Crew schedule planning and operations shall be provided to include circadian entrainment, work/rest schedule assessment, task loading assessment, countermeasures, and special activities.

[V1 6007] Medical and Survival Kits Vehicle medical kits (routine and survival) shall be provided for all phases of the mission.

Referenced Technical Requirements

[V1 7001] Crew Health Results The results of all crew health monitoring shall be kept in a permanent retrievable format for evaluation, including trend analysis.

[V1 7002] Crew Records Communication The method of transmission of crewmembers' medical health data shall be in a timely manner to meet the medical operational needs of the program.

[V1 7003] Crew Records Storing The method for handling, storing, and transmission of crewmembers' medical health records shall be secured.

NASA-STD-3001 Volume 2 Revision C

[V2 3006] Human-Centered Task Analysis Each human space flight program or project shall perform a human-centered task analysis to support systems and operations design.

[V2 7038] Physiological Countermeasures Capability The system shall provide countermeasures to meet crew bone, muscle, sensorimotor, thermoregulation, and aerobic/cardiovascular requirements defined in NASA-STD-3001, Volume 1.

[V2 7042] Orthostatic Intolerance Countermeasures The system shall provide countermeasures to mitigate the effects of orthostatic intolerance when transitioning from weightlessness to gravity environments and during Gz (head-to-foot) vehicle accelerations defined in the sustained acceleration limits.

[V2 7043] Medical Capability A medical system shall be provided to the crew to meet the medical requirements of NASA-STD-3001, Volume 1.

[V2 7045] Medical Equipment Usability Medical equipment shall be usable by non-physician crewmembers in the event that a physician crewmember is not present or is the one who requires medical treatment.

[V2 7050] Stowage Provisions The system shall provide for the stowage of hardware and supplies, to include location, restraint, and protection for these items.

[V2 7051] Personal Stowage The system shall provide a stowage location for personal items and clothing.

[V2 7052] Stowage Location All relocatable items, e.g., food, EVA suits, and spare parts, shall have a dedicated stowage location.

[V2 7055] Priority of Stowage Accessibility Stowage items shall be accessible in accordance with their use, with the easiest accessibility for mission-critical and most frequently used items.

[V2 7059] Inventory Tracking The system shall provide an inventory management system to track the locations and quantities of items (including hazardous trash) throughout the mission.

[V2 12026] Stowage Access The system shall provide access for ground support personnel to spacecraft stowage volumes that require late loading and early unloading of items.

[V2 11027] Suited Medication Administration The system shall allow the ground support personnel safe operation of flight software systems for ground processing.

Reference List

1. Du, B., Daniels, V.R., Vaksman, Z., Boyd, J.L., Crady, C., and Putcha, L. (2011). Evaluation of Physical and Chemical Changes in Pharmaceuticals Flown on Space Missions. *The AAPS Journal, 13*(2): 299-308
2. Wotring, V.E. (2014). Stability Analysis of Medications from the International Space Station.. JSC Pharmacology.
3. Wotring, V.E. (2015). Medication use by U.S. crewmembers on the International Space Station. *The FASEB Journal, 29*(11): 4417-4423
4. Blue, R.S., Bayuse, T.M., Daniels, V.R., Wotring, V.E., Suresh, R., Mulcahy, R.A., and Antonsen, E.L. (2019). Supplying a pharmacy for NASA exploration spaceflight: challenges and current understanding. *npj Microgravity, 5*(15)
5. Roberts, M. & Denton, M. Effect of posture and sleep on pharmacokinetics: amoxycillin. Eur. J. Clin. Pharm. 18, 175–183 (1980).
6. Wotring, V.E. and Smith, L.K. (2020). Dose Tracker Application for Collecting Medication Use Data from International Space Station Crew. *Aerospace Medicine and Human Performance, 91*(1); 41-45
7. Putcha, L., Cintron, N.M., Tsui, J., Vanderploeg, J.M., and Kramer, W.G. (1989). Pharmacokinetics and Oral Bioavailability of Scopolamine in Normal Subjects. *Pharmaceutical Research, 6*: 481-485
8. Daniels, V.R., Bayuse, T.M., McGuire, K.M., Antonsen, E.L., and Putcha, L. (2017). Radiation Impact on Pharmaceutical Stability: Retrospective Data Review. Tech. Report No. 09940. *Proceedings of the NASA Human Research Program Investigator Workshop (2018)*. https://ntrs.nasa.gov/citations/20170009940
9. Schuck, E.L., Grant, M., and Derendorf, H. (2005). Effect of Simulated Microgravity on the Disposition and Tissue Penetration of Ciprofloxacin in Healthy Volunteers. *Journal of Clinical Pharmacology, 45*(77): 822-831
10. Putcha, L., and Cintron, N.M. (1991). Pharmacokinetic consequences of spaceflight. *Ann N Y Acad Sci, 28*(618): 615-618
11. Rumble, R.H., Roberts, M.S., and Scott, A.R. (1988). The effects of posture on the pharmacokinetics of intramuscular benzylpenicillin. *European Journal of Clinical Pharmacology, 33*(6): 629-635
12. Aunins, T.R., Erickson, K.E., Prasad, N., Levy, S.E., Jones, A., Shrestha, S., et al. (2018). Spaceflight Modifies *Escherichia coli* Gene Expression in Response to Antibiotic Exposure and Reveals Role of Oxidative Stress Response. *Frontiers in Microbiology, 16*(9)
13. Juergensmeyer, M.A., Juergensmeyer, E.A., and Guikema, J.A. (1999). Long-term exposure to spaceflight conditions affects bacterial response to antibiotics. *Microgravity Sci Technol, 12*(1): 41-47
14. Emanuelli, M. (2014). Evolution of NASA Medical Kits: From Mercury to ISS. *Space Safety Magazine*. Retrieved from: http://www.spacesafetymagazine.com/spaceflight/space-medicine/evolution-medical-kits-mercury-iss/
14. Stingl, J.C., Welker, S., Hartmann, G., Damann, V., and Gerzer, R. (2015). Where Failure Is Not an Option -Personalized Medicine in Astronauts. *PLoS One, 10*(10): e0140764
15. Human Molecular Genetics, 2012, Vol. 21, Review Issue 1 R58–R65 doi:10.1093/hmg/dds341 Advance Access published on August 19, 2012

Reference List

16. Kates R.E., Harapat S.R., Keefe D.L., Goldwater D., Harrison D.C. Influence of prolonged recumbency on drug disposition. Clin. Pharmacol. Ther. (1980) 28 624–628
17. Levy G. Effect of bed rest on distribution and elimination of drugs. J. Pharm. Sci. (1967) 56 928–929.
18. Gandia P., Bareille M.P., Saivin S. et al. Influence of simulated weightlessness on the oral pharmacokinetics of acetaminophen as a gastric emptying probe in man: a plasma and a saliva study. J. Clin. Pharmacol. (2003) 43 1235–1243.
19. Rumble R.H., Roberts M.S., Scott A.R. The effect of posture on the pharmacokinetics of intravenous benzylpenicillin. Eur. J. Clin. Pharmacol. (1986) 30 731–734.
20. Levy G. Effect of bed rest on distribution and elimination of drugs. J. Pharm. Sci. (1967) 56 928–
21. Gandia P., Bareille M.P., Saivin S. et al. Influence of simulated weightlessness on the oral pharmacokinetics.
22. Stingl JC, Welker S, Hartmann G, Damann V, Gerzer R (2015) Where Failure Is Not an Option – Personalized Medicine in Astronauts. PLoS ONE 10(10): e0140764. https://doi.org/10.1371/journal.pone.0140764
23. https://lsda.jsc.nasa.gov/Experiment/exper/12376, Spaceflight Injectable Delivery System (ISIS)
24. https://pharmaceutical-journal.com/article/feature/drugs-in-space-the-pharmacy-orbiting-the-earth
25. Shane M. McFarland Jsc and Aaron S. Weaver Breaking the Pressure Barrier: A History of the Spacesuit Injection Patch. Conference Paper International Conference on Environmental Systems January 1,2013
26. U.S. Food and Drug Administration. Don't Be Tempted to Use Expired Medicines. Feb 8,2021.
27. Lyon,R et al. Stability profiles fo drug products extended beyond labeled expiration dates. Journal of Pharmaceutical Sciences, Volume 97 issue 7 July 2006.
28. Gikonyo,D, Gikonyo,A, Luvayo,D, Ponoth<p. Drug expiry debate: the myth and the reality. African Health Sciences Sept 19.2019.
29. U.S.Food and Drug Administration. Expiration Dating Extension updated 111/8/2022
30. DoD Manual 4140.27 Volume 1 DoD Shelf-Life Management Program: Program Administration 7/6/2016, Change 2 12/11/2019.
31. Tull,K. 2018. Drug expiry standards in developing countries. University of Leeds Nuffield Centre for International Health and development June 11,2018.
32. Code of Federal Regulations , Title 21,Volume 4. Title 21- Food and Drugs, FDA of Health and Human Services, Drugs, Current Good Manufacturing Practice For Finished Pharmaceuticals.
33. Drug Expiration Dates- Do They Mean Anything? 2020. Harvard Health Publishing, Harvard Medical School Aug 29,2020.
34. Wegienka,L et al. 1964. Renal Tubular Acidosis Caused by Degraded Tetracycline. Journal of the American Medical Association August 1964.
35. Lyon et al. 2006. Stability profiles of drug products extended beyond labeled expiration dates. Journal of Pharmaceutical Sciences July 2006.
36. *USA Today "After a year in space, Scott Kelly returns 2 inches taller". Mary Bowerman March 3, 2016*