



The Research Plan: Closing the ExMC Med02 “Pharmacy” Gap

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HRP Human Research Roadmap: Risk and Gap

- Risk of Adverse Health Outcomes and Decrements in Performance due to Inflight Medical Conditions.
 - Med02 “Pharmacy” Gap: We do not have the capability to provide a safe and effective medication formulary for exploration missions.

Med02 Gap Mitigation Research Plan

- The new ExMC Med02 Gap Mitigation Research Plan was completed in July, 2016.
- The goal of this research plan is to provide a **research strategy** aimed at mitigating the Med02 “Pharmacy” Gap by:
 - delivering a recommendation for a chemically stable, safe, and effective medication formulary that will support the operational needs of exploration space missions.

Research Strategy

- **Content:**
 - evidence-based formulary and models
 - innovative analytical tools and methodologies
 - novel treatments and preventive measures
- **External Review:**
 - Planned review by a panel of experts from the pharmaceutical industry, regulatory, and academic scientific communities
(March 20, 2017)

Research Aim:

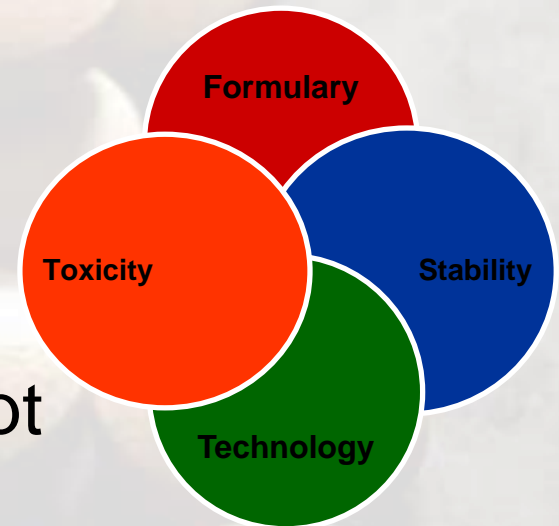
Target 7 Critical Questions

1. What medications do we think we will need to provide for a specific Design Reference Mission (DRM)?
2. Which of the medications selected will be effective throughout the journey, (and which will not)?
3. Of the medications that are not certain to be effective for the full mission duration, can we characterize what their likely effective shelf life will be?
4. Can we provide the crew a way to determine if the medication is chemically stable, still active, or degraded in real-time?
5. As the formulary medications degrade, will they remain safe and effective, or will they become toxic?
6. Are there alternative methods for supplying formulary medications for an extended deep space mission?
7. Can we modify or replace existing pharmaceuticals to minimize the resource footprint or improve tolerance to the deep spaceflight environment?

Research Portfolio Focus Areas:

The proposed approach to building a research portfolio aimed at mitigating the Med02 Gap, would be to target research in four major focus areas:

- Formulary Selection
- Formulary Potency and Shelf life
- Formulary Safety and Toxicity
- Novel Technology Proof-of-Concept
 - Portable real-time chemical analysis
 - Innovative drug development / design



Formulary Selection:

Question 1: What medications do we think we will need to provide for a specific Design Reference Mission (DRM)?

Projects:

- List of medications from targeted therapeutic classifications aimed at addressing anticipated medical events as suggested by:
 - Data mining common medical events experienced during previous missions (EMR Tracking)
 - Dose Tracker
 - Medical Consumables Tracker
 - Predictions obtained from the MONSTR
- Ongoing pharmaceutical product surveillance / technology watch
 - Surveillance of clinical / scientific literature
 - Potomac Institute Pilot Project

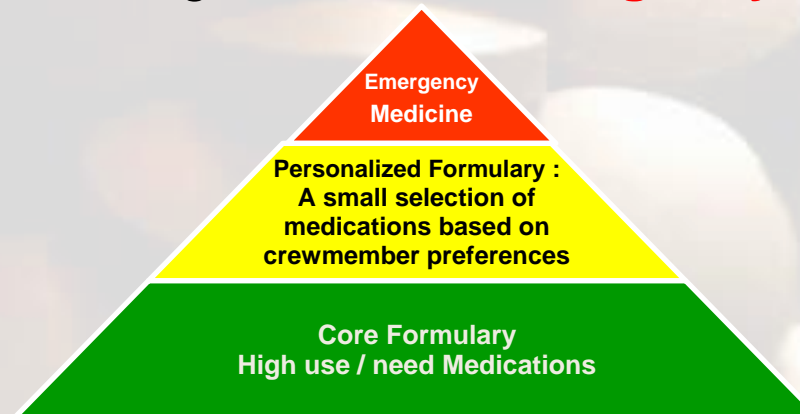
Deliverables:

- Lists of promising formulary medication candidates for further evaluation
- Annual reports highlighting promising product development and technology

Formulary Design:

The conceptual design of the exploration space formulary would consist of three components:

- Core Formulary: **Centralized**, shared inventory consisting of those medications identified as **high use or of significant or priority need** (*i.e.* “Top 20”)
- Personalized Formulary: **Small** selection of medications used for chronic condition maintenance or based on **personal therapeutic preferences**, as selected by each individual crewmember (*i.e.* around 5 selections)
- Emergency Medicine Formulary: **Even smaller** selection of medications consisting of **critical emergency** medications



Formulary Potency and Shelf life:

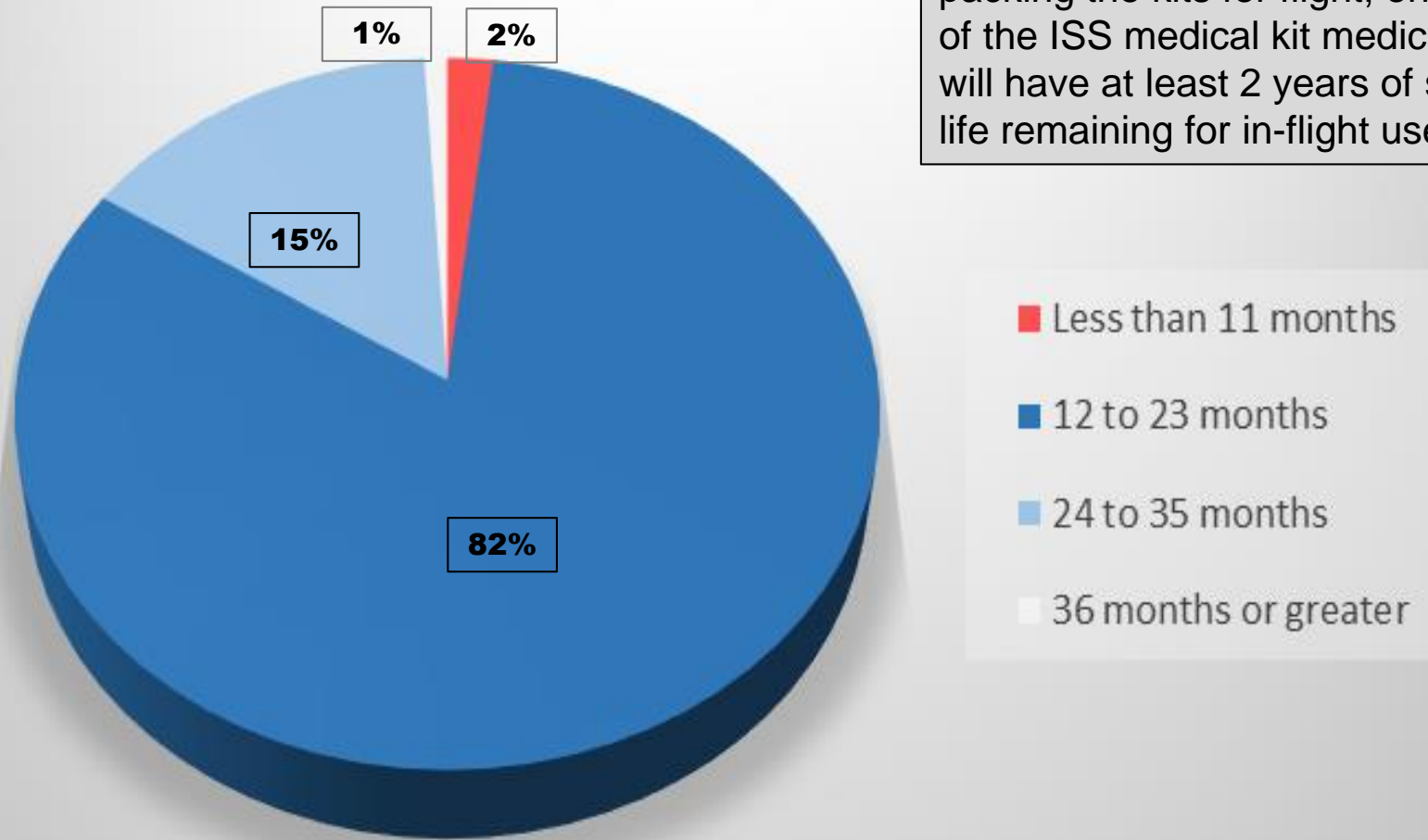
- 2. Which of the medications selected for an exploration space mission formulary will be effective throughout the journey, (and which will not)?*
- 3. Of the medications that are not certain to be stable for the full mission duration, can we characterize what their likely effective shelf life will be?*

What do we currently know?

ISS Operational Medication Kit Shelf-life Duration Observational Study:

- Shelf-life duration data was compiled by the JSC Pharmacy from multiple operational ISS medication kits, over a 3 year period (9/2013 - 9/2016).
- The ISS medication formulary observed consisted of 107 different medications.
- Shelf-life duration was determined by subtracting the time lost while preparing the operational medication kits for flight, from the manufacturer's labeled expiration date.
 - The Food and Drug Administration (FDA) requires that medications removed from the manufacturer's original packaging be assigned an expiration date of only 1 year from the date of repackaging.

ISS Medical Kit Medication Shelf-life Duration Results



Including the time lost when packing the kits for flight, only 16% of the ISS medical kit medications will have at least 2 years of shelf-life remaining for in-flight use.

Formulary Potency and Shelf life:

2. *Which of the medications selected for an exploration space mission formulary will be effective throughout the journey, (and which will not)?*
3. *Of the medications that are not certain to be stable for the full mission duration, can we characterize what their likely effective shelf life will be?*

Projects:

- Pharmaceutical stability studies
 - **Ground-based**
 - Cory Stability Study: College of Charleston, Charleston, SC (**Completed**)
 - Wu Stability Study: University of Houston, Houston, TX (**Completed**)
 - **Flight**
 - JSC Pharmacy “Dribble” Project (Maintain flight controls for opportunistic flight medication samples retrieved)
- Predictive stability modeling programs (Linear, non-linear, quantile regression)
- **Surveillance of clinical / scientific literature** (i.e. SLEP study; eMC drug monographs)

Deliverables:

- **Final project reports** characterizing tested drug’s shelf life (*Delivered*), and portable technology validation

The Shelf Life Extension Program (SLEP):

- The federal SLEP Program was established in 1986, and administered by the U.S. Department of Defense (DoD) in cooperation with the FDA, to defer replacement costs of stockpiled medications and materials by extending their expiration dates.
 - The FDA conducted all quality testing and medication evaluations for the SLEP Program, and discovered that the **actual shelf life of products tested may be longer than their labeled expiration dates**, dependent on their storage conditions.

SLEP Study

Methods:

- 122 Medications stored in original packaging from 3005 different lots were tested using US pharmacopeia and FDA stability testing standards to determine shelf life extension data

Results:

- Overall, 2650 (88%) of the 3005 lots tested were extended past their original expiration dates with an **average extension** of 66 months (*Lyon et al, 2006*).
 - Only 7 medications tested in the SLEP program are included in the current ISS operational flight formulary.

The Electronic Medicines Compendium (eMC)

- The electronic Medicines Compendium (eMC) contains up to date information about medicines licensed for use in the United Kingdom (UK).
- All information on the eMC website comes directly from the 200 pharmaceutical companies that subscribe to the eMC; of which many have corporate headquarters in the United States.
- Pharmaceutical companies submit and update the Summaries of Product Characteristics (SPCs) provided by the eMC.
 - Within the SPC, the maximum shelf-life, or maximum amount of time the medication meets regulatory standards for potency based on drug stability testing, is provided.

Formulary Potency and Shelf life:

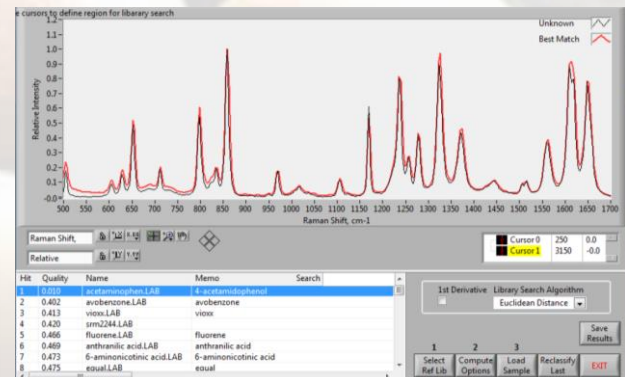
4. *Can we provide the crew a way to determine if the medication is chemically stable, still active, or degraded in real-time?*

Projects:

- Portable Technology Assessment Proof-of-Concept
 - Handheld Raman Spectroscopy: Real Time Analyzers
 - Liquid Chromatography (HPLC or UPLC) validation of portable technology: University of Houston, Houston, TX

Deliverables:

- **Reports** characterizing tested drug's shelf life, and portable technology validation



Formulary Safety and Toxicity

5. *As the formulary medications degrade, will they remain safe and effective, or will they become toxic?*

This category to be investigated on an as-needed basis

Projects:

- In-vitro / In-vivo pharmaceutical degradation / toxicology studies
- Modeling technology studies designed to generate dosing monographs adjusted for VAS medications with decreasing API content

Deliverables:

- A report summarizing results of in-vitro / in-vivo toxicity studies
- A final list of tested medications now VAS
- Dosing monographs for VAS medications with reduced API

Future Needs:

Novel Technology and Innovation

6. *Are there alternative methods for supplying formulary medications for an extended deep space mission?*
7. *Can we modify or replace existing pharmaceuticals to minimize the resource footprint or improve tolerance to the deep spaceflight environment?*

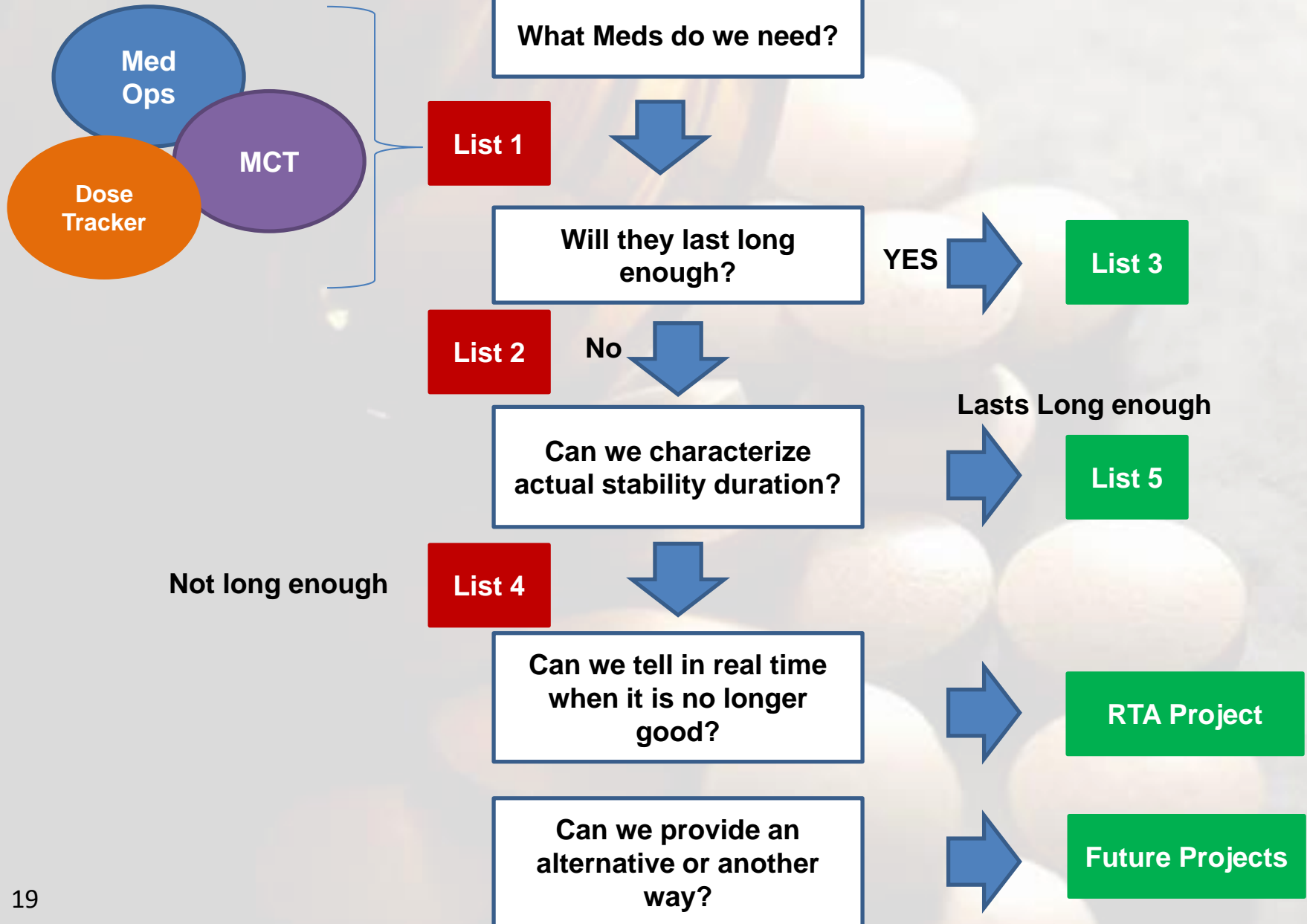
Projects:

- Technology Watch (Element-directed Research)
 - Novel drug development techniques, dosage forms, and delivery systems to improve performance outcomes
 - Research Pharmacist Surveillance
 - Potomac Institute Technology Watch Pilot Project (**Completed**)

Deliverables:

- Annual surveillance reports
- Potomac Institute pilot project report (**Delivered**)

Logic Diagram



Dedicated to the memory of
Lakshmi Putcha, PhD
Former Technical Monitor
Pharmacotherapeutics Discipline

***“Explore the unexplored,
create the unimaginable”***

A Favorite Quote of Dr. Putcha

Author Unknown