
2011 Pharmacology Risk Standing Review Panel

Research Plan Review

Final Report

I. Executive Summary and Overall Evaluation

The 2011 Pharmacology Risk Standing Review Panel (from here on referred to as the SRP) met for a site visit in Houston, TX on October 9-10, 2011 to review the Pharmacology section of the Human Research Program's (HRP) Integrated Research Plan (IRP, Rev C.). The SRP commends the progress the Pharmacology Discipline made since last year. A complete tabulation of the drugs/drug formulations that are used in space (e.g., Pharmacology Database Tool) should be a high priority for NASA. The SRP members are concerned about drug-drug interactions with the prescribed medications and particularly with OTC medications, dietary supplements and any drugs that may be in the astronaut's personal kit. For example, St. John's wort (*Hypericum perforatum L.*), a dietary supplement known to induce metabolic enzymes and drug transporters, can render other medications ineffective. The SRP reiterated that a Pharmacology Database is essential for any rational assessment of pharmacological risks in long-term spaceflights. The SRP does appreciate the confidentiality issue involved in a Pharmacology Database, but believes that privacy of medical information specific to the astronauts can be maintained, while collecting useful information on medication utilization, efficacy and safety.

The longer astronauts stay in space the greater the risk of therapeutic adverse effects. Long-term exposure in space may result in changes in efficacy and safety of the medication along with changes in physiology or pathophysiology of the astronauts. The potential for therapeutic adversity may not only involve safety and efficacy of the medications, but may impact the astronaut's, possibly compromising their mission. Lack of information on therapeutic usage by not knowing completely the drugs/drug formulations used in space and their therapeutic usage presents a potential problem.

The addition of the proposed pharmacology research projects to current research problems is useful, but appears to be more basic research oriented. The SRP thinks that some of these projects do not seem to fit into the mission of the pharmacologic risk assessment.

The SRP recommends a more formal relationship between the Johnson Space Center (JSC) Clinical Pharmacy group and the HRP Pharmacology Discipline – as both are focused on medications and therapeutic efficacy. There definitely should be some discussion about coordinating research and medical care.

The SRP also recommends in-house education of flight surgeons, research staff, and astronauts about biopharmaceutics, pharmacokinetics, pharmacodynamics, safety and efficacy of drugs and drug formulations including potential drug interactions, dosage of medications, etc. This knowledge would be beneficial for the researchers, flight surgeons, and astronauts by giving them a better understanding of their medication and the issues of possible adverse effects due to self medication.

The SRP members are still very concerned about the astronaut personal kits, whose content remains private. Although the astronauts may be allowed to have their own personal medications/dietary supplements, the contents should be known to the flight surgeons and researchers who can determine whether any personal medications/dietary supplements have the potential for an adverse event.

II. Critique of Gaps and Tasks for the Risk of Therapeutic Failure Due to Ineffectiveness of Medication

Gaps and Tasks:

PH01: Inadequate tracking of medication use, indication, efficacy, and side effects.

- The SRP thinks that this gap is extremely relevant and has been properly identified.
- This SRP thinks that this is a very urgent gap for the Pharmacology Discipline and the research under this gap should be fast tracked.

Tasks:

- Medical Consumables Tracking – PI: DeVon Griffin, NASA Glenn Research Center
 - The SRP believes that **all** medications should be tracked. The PI should count and track what comes back in the crew medical kit. Tracking of consumables should include time and dose taken and for which indications. A record of symptoms and whether the medication was effective would be useful information.
 - The SRP still thinks that access to the crew medical kit is desirable in order to track medical consumables. Individuals who have access to the crew medical kit should also be identified.
 - A personal kit is not appropriate if the contents are not known by at least the flight surgeon. All medications (including caffeine, vitamins, over the counter medications and any dietary supplements) should be tracked.
 - Taking medications that are not tracked may interfere with the results for other medical/physiological studies.
- Medication/Symptom Tracking Tool (MSTT) – PI: Virginia Wotring, Universities Space Research Association (USRA)
 - The SRP thinks that this task would benefit from comparing information obtained from subjects while on ground versus that obtained while in flight.
 - It is unclear to the SRP how this information is being tracked.
 - The drug/drug formulation taken, dose, and administration time should all be tracked.
 - Self-reported efficacy and safety would be good data to have, but is not a priority.
 - Causality assessment of adverse events by the astronaut may not be needed at this stage to help accelerate implementation of the MSTT. After processes have been streamlined and accepted, causality assessment by astronauts, and possibly flight surgeons, should be included.
 - The SRP thinks that the MSTT PI should be permitted to review the questionnaire in order to accomplish this task.

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- MSTT Flight Validation – Unfunded
 - The SRP thinks that a computer application or scan for the MSST would be helpful.
 - Pharmacology Database Tool – Unfunded
 - The SRP thinks that this task should be funded immediately.
 - New information on medications that could be used in spaceflight should be reviewed systematically, including formulations, pharmacokinetics, and pharmacodynamics.
 - Potential interactions with other medications, diet, food supplements should be included in this database.
 - The drugs should be placed in three levels of risk, as recommended by this SRP in 2010.

PH02: What drug interactions may adversely affect clinical care?

- The SRP agrees with the Pharmacology Discipline and is in favor of moving this gap to the JSC Clinical Pharmacy group. However, there should be a formal relationship with regular interactions between Clinical Pharmacy and Pharmacology.
- The SRP thinks that the Pharmacology Database Tool should contain drug interaction information.

Tasks:

- Data Mining (Polypharmacy) – Unfunded
 - This is an appropriate task because a complete drug utilization assessment is needed.
 - The SRP is not clear on what is being planned, the aims of the task, or the expected results.
- Pharmacology Database Tool – Unfunded
 - The SRP thinks that it is very important to have this task completed as soon as possible.

PH04: What diagnostic, therapeutic, and laboratory technologies are necessary to predict and manage medication side effects, interactions, and toxicity during spaceflight?

- The Pharmacology Discipline proposes to move this gap to the hardware group and the SRP agrees with this since much of it is technology development.

Tasks:

- In-flight Blood Analysis Technology for Astronaut Health Monitoring – PI: Yu-Chong Tai, California Institute of Technology
 - The SRP thinks that this task is appropriate.
- Nanoscale Test Strips for Multiplexed Blood Analysis – PI: Eugene Chan, DNA Medicine Institute
 - The SRP thinks that this task is appropriate.
- Reusable Handheld Electrolytes and Lab Technology for Humans – PI: Eugene Chan, DNA Medicine Institute

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- The SRP thinks that this task is appropriate.

PH06: Can a standard procedure for prospective analyses of drugs to be considered for flight and periodic analyses of drugs that are used for flight be developed?

- The SRP agrees with the Pharmacology discipline and is in favor of moving this gap to Space Medicine. However, there should be a formal relationship with regular interactions between Clinical Pharmacy and Pharmacology.

Tasks:

- Medication/Symptom Tracking Tool – PI: Virginia Wotring (USRA)
 - The SRP thinks that this task is appropriate.
- Pharmacology Database Tool - Unfunded
 - The SRP thinks that this task would be appropriate.

PH07: What are the effects of spaceflight on pharmacokinetics and pharmacodynamics?

- The SRP thinks that this is clearly identified as a gap but you need to know what drug is being taken and at what dose to answer this question.
- Nothing is currently tasked specifically for pharmacokinetics/pharmacodynamics (PK/PD).
- The SRP suggests changing the gap wording to “What are the effects of spaceflight on pharmacokinetics?” All tasks are PK, but not PD. Should take PD out of the gap wording.

Tasks:

- BHP Medications – Spaceflight Concerns – Unfunded
 - The SRP likes the individuality of this study and it is important to know this information from ground-based studies, as well as during spaceflight in order to determine if there are differences.
- Determine Effect of Spaceflight Environment on Drug Distribution and Metabolism – Planned
 - The SRP thinks the term “absorption” should be added to the task title.
 - The SRP thinks it will be very difficult to directly translate the data from this task into practice.
 - This is a task that will be added onto another funded task and is not a high priority. The aims do not match the task and the title of task does not match the proposed aims. There is a definite disconnect.
- Determine Oxidative Gene and Protein Expression Changes Involving the Enzymes that Metabolize Drugs – Unfunded
 - This is another task that will be added onto an already planned task, so there is no harm to complete it.
 - The SRP thinks it will be very difficult to directly translate the data from this task into practice.
 - The SRP questions what NASA would do operationally with the data from this task.

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- Medication/Symptom Tracking Tool – PI: Virginia Wotring (USRA)
 - The SRP thinks that this task is appropriate.
 - Pharmacology Database Tool - Unfunded
 - The SRP thinks that this task would be appropriate.
 - **PROPOSED NEW TASK:** Flight research is needed. A task should be added where a blood draw is done to measure drug levels. This should be taken in flight and the results should be compared to ground results. Metabolism and renal excretion should be looked at also.

PH09: What is the stability of drugs during long duration spaceflight?

- The SRP thinks that the stability issue was better addressed this year than last year and that drug ionization is not as big of a problem as it originally thought.

Tasks:

- Determine the Useful Lifespan of the ISS Medications – Unfunded
 - The SRP thinks that this task would be appropriate.
- Pharmacology Database Tool - Unfunded
 - The SRP thinks that this task would be appropriate.
 - The SRP suggests that the Pharmacology Discipline focus on drugs that are known to be unstable.
- Spaceflight Effects on the Useful Lifespan of ISS Medications – Unfunded
 - The SRP thinks that this task should be a high priority and that this should be in the budget since a medication kit is already being flown.
 - The SRP thinks that this should be easy to measure before and after spaceflight.

PH10: What are the effects of in-flight drugs on exercise, orthostatic tolerance, motor control, cognitive function, or other performance-determining aspects of physiology? Can novel multidisciplinary therapeutic approaches be used to enhance efficacy and reduce side effects?

- The SRP thinks that this gap is appropriate.

Tasks:

- Develop New Motion Sickness Treatments - Planned
 - The SRP thinks that anticholinergic burden should be investigated and that cognitive impairment may occur. There are algorithms that survey medication use (drug and dose) to assess anticholinergic burden.
 - Alternatively/complementarily, blood samples could be drawn in flight to assess serum anticholinergic activity.
- Effect of anti-motion sickness medication combinations on QTc Interval – PI: Virginia Wotring, USRA

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- The SRP thinks this task should be integrated with the Cardiovascular Discipline.
 - The SRP thinks that more frequent ECG measurements should be taken during the ground-based QTc study.
 - The SRP thinks that the PI should consider adding a positive control (moxifloxacin) to the ground-based QTc study.

 - Medication/Symptom Tracking Tool – PI: Virginia Wotring (USRA)
 - The SRP thinks that this task is appropriate.

 - Pharmacology Database Tool – Unfunded
 - The SRP thinks that this task would be appropriate.

PH13: Which sleep aid is best in flight in terms of efficacy? In terms of limited side effects?

- The SRP thinks that this gap is appropriate.

Task:

- No current tasks are planned.

PH15: Are the antimicrobials carried on board effective against microbes that exhibit spaceflight-related changes?

- The SRP thinks that this gap is appropriate.

Task:

- Determine efficacy of antimicrobial agents in the MedOps kit against microbes that have undergone virulence changes seen in spaceflight analogs – Planned
 - Clinical question: What are the clinicians concerned about? Only bacteria?
 - Viral and fungal infections may need to be added based on this answer.

M14: What anabolic or anti-catabolic drugs can be used to mitigate muscle loss?

- The SRP thinks that this gap is appropriate.

Tasks:

- Anabolic/Anti-Catabolic Pharmaceutical(s) with or without Exercise Studies – Planned
 - The SRP thinks that this task is appropriate.

- Flight Validation Studies of Exercise + Pharmaceutical or Nutritional Supplements – Unfunded
 - The SRP thinks that this task would be appropriate.

- Testosterone Supplementation as a Countermeasure against Musculoskeletal Losses during Space Exploration – PI: Randall Urban, University of Texas Medical Branch at Galveston
 - The SRP thinks that this is a good pilot study on Earth but there is no rush for this to be performed in flight.

III. Discussion on the strengths and weaknesses of the IRP

Is the Risk addressed in a comprehensive manner?

- Yes, the SRP thinks that the Risk of Therapeutic Failure Due to Ineffectiveness of Medication is addressed in a comprehensive manner.

Are there obvious areas of potential integration across disciplines that are not addressed?

- The SRP strongly urges more collaboration among the JSC Clinical Pharmacy group, research pharmacology, and medical practitioners.
 - Review what is in formulary and what may be in the formulary in the future to help identify pharmacology risks.
 - A multidisciplinary group should look at the formulary.
- The SRP suggests a continuing education with the NASA flight surgeons and even the astronauts. The SRP members are willing to help with this.
- The QTc task should be integrated with Cardiovascular Discipline.
- The Pharmacology Discipline should be integrated with the Bone Discipline Gap B3: What pharmaceuticals against bone loss are best used and how?

IV. Additional Comments

- The SRP strongly urges that the Pharmacology Database Tool get completed immediately.
- The SRP recommends a better tracking of drug utilization by the astronauts.
- The SRP suggests expanding the definition of “therapeutic failure” to include both a lack of effectiveness/change in efficacy and increased risk of toxicity/lack of safety.

IV. Pharmacology Risk SRP Research Plan Review Statement of Task

The 2011 Pharmacology Risk Standing Review SRP (SRP) is chartered by the Human Research Program (HRP) Program Scientist at the NASA Johnson Space Center (JSC). The purpose of the SRP is to review the Pharmacology section of the HRP's Integrated Research Plan (IRP). Your report will be provided to the HRP Program Scientist.

The 2011 Pharmacology Risk SRP is charged (to the fullest extent practicable) to:

1. Evaluate the ability of the IRP to satisfactorily address the risk by answering the following questions:
 - A. Have the proper Gaps been identified to address the Risk?
 - i) Are all the Gaps relevant?
 - ii) Are any Gaps missing?
 - B. Have the proper Tasks have been identified to fill the Gaps?
 - i) Are the Tasks relevant?
 - ii) Are any Tasks missing?
2. Identify the strengths and weaknesses of the IRP, *and* identify remedies for the weaknesses, including answering these questions:
 - A. Is the risk addressed in a comprehensive manner?
 - B. Are there obvious areas of potential integration across disciplines that are not addressed?
3. Address (as fully as possible) the questions provided in the charge addendum and to provide comments on any important issues that are not covered in #1 or #2 above.

Additional Information Regarding This Review:

1. Expect to receive review materials at least four weeks prior to the site visit.
2. Participate in a 2011 Pharmacology Risk SRP teleconference to discuss any issues, concerns, and expectations of the review process approximately three weeks prior to the face-to-face meeting.
 - A. Discuss the 2011 Pharmacology Risk SRP Statement of Task and address questions about the SRP process.
 - B. Identify any issues the 2011 Pharmacology Risk SRP would like to have answered prior to the site visit.
3. Attend the 2011 Pharmacology Risk SRP at NASA JSC in October 2011.
 - A. Attend Element presentations, question and answer session, and briefing.
 - B. Prepare a draft report, including any recommendations. Debrief the HRP Program Scientist on what will be included in final report and should address #1, #2, and #3 above.

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4. Prepare a final report that contains a detailed evaluation of the risks organized by Items #1, #2, and #3 above and provides specific recommendations that will optimize the scientific return to the HRP. The report will be sent to the HRP Program Scientist. A copy of the report will be provided to the Human Health Countermeasures Element at NASA JSC that sponsors the Pharmacology discipline. Once the report is finalized it will be made available to the public.
 5. Consider the possibility of serving on a non-advocate review SRP of a directed research proposal or on a solicited research peer review SRP; or otherwise advise the Program Scientist.

VII. Pharmacology Risk SRP Roster

SRP Chair:

Jürgen Venitz, MD, Ph.D.

Medical College of Virginia
Virginia Commonwealth University

Department of Pharmaceutics

Room 450B

R.B. Smith Building

410 N. 12th Street

Richmond, VA 23298-0533

Ph: 804-828-6249

Email: jvenitz@vcu.edu

SRP Members:

Hartmut Derendorf, Ph.D.

Department of Pharmaceutics

University of Florida

1600 SW Archer Road, P3-27

Gainesville, FL 32610

Ph: 352-273-7856

Email: hartmut@ufl.edu

Leon Shargel, Ph.D., R. Ph.

Applied Biopharmaceutics, LLC

1535 Caraleigh Mills Court, Suite 228

Raleigh, NC 27603

Ph: 919-846-5509

Email: lshargel@appliedbiopharmaceutics.com