NASA 2010 Pharmacology Evidence Review

Final Report

March 2011

I. Executive Summary:

The 2010 Pharmacology Evidence Risk Report and supporting documents including the Human Research Program (HRP) Integrated Research Plan (IRP) from the NASA Johnson Space Center (JSC) were submitted for review on October 6, 2010. A Pharmacology Evidence Review panel (The Panel) chaired by Dr. Jürgen Venitz, M.D., Ph.D. from the Virginia Commonwealth University (see roster, section VI), was convened to review the HRP documentation and provide a detailed evaluation of the pharmacology risk. The Panel members were provided copies of all the review materials on October 8, 2010. The Panel had their first teleconference on October 21, 2010 to review their charge (see charge, section VII) and discuss the review process. Each Panel member was assigned the following focus areas: Pharmaceutical Risks, Dr. Leon Shargel; Pharmacological Risks, Dr. Hartmut Derendorf; Therapeutic Risks, Dr. Jürgen Venitz. On November 18, 2010 the Panel held a second teleconference to discuss the review documents, disuss their individual reviews, and formulated their initial recommendations. A draft prelimary report of the Panel's findings and recommendations was provided to the HRP Program Scientist, Dr. John Charles, on November 29, 2010. Drs. Leon Shargel and Jürgen Venitz attended a site visit at JSC on December 1, 2010 for a debriefing and detailed discussions with the appropriate HRP staff on the Panel's comments and recommendations.

Overall, the Panel believes the 2010 Pharmacology Evidence Risk Report should be adopted and implemented along with the recommendations listed below:

Integration with Therapeutics:
Both pharmacology and therapeutics should be considered when implementing the proposed comprehensive astronaut medication use survey. The Panel is aware of issues that may make such a survey difficult (e.g., ethical issues regarding private health information, inconsistent medical record keeping, and permission for astronauts to keep personal items including medications and supplements). However, given the glaring lack of this essential information that should drive the focus of pharmacology research, the Panel believes there is a need for a strong appropriate collaboration between NASA staff in pharmacology and therapeutics.

Furthermore, for future pharmacology reports and activities, the increased prevalence of chronic mild diseases (hypertension, hyperlipidemias, thyroid dysfunction, etc.) and chronic medication use for these conditions, along with older astronauts need to be considered and emphasized.

Prioritization of Pharmacology-Risk Activities:
Based on available evidence, pharmacology research activities in the near future should be prioritized towards the following endeavors:

1. Evaluation of Pharmacokinetics/Pharmacodynamics (PK/PD) of antibacterials/antivirals;

2. Assessment of long-term spaceflight on drug distribution including *in-vivo* drug metabolism and renal drug clearance;

3. Risk assessment of promethazine-induced QT_c prolongation;

4. Testing of shelf-life/potentially protective packaging of prototypical medications (e.g., L-thyroxine) in ground-based studies.

In addition, pharmacology staff at JSC should be involved in the training and education of flight surgeons and astronauts on pharmacology-related risks in medication use.

II.   Overall Impression:

The 2010 Pharmacology Evidence Risk Report is a comprehensive, well-written, well-organized, and well-referenced document. The 2010 Pharmacology Evidence Risk Report appears to be in sync with the HRP IRP. Most of the risks are properly identified and explained, with the remaining knowledge gaps clearly delineated (see section IV. Missing Topics and Specific Comments below).

The supporting curriculum vita provided per the request of the Panel during the review shows that the author of the report is well qualified and has the expertise for the pharmacology risk evidence assessments.

The 2010 Pharmacology Evidence Risk Report is of high quality and very readable. However, as outlined under section III. General Comments and Recommendation section of this final report, additional efforts should be undertaken to comprehensively tabulate all in-space drug products, survey their current use, and rationally assign a pharmacological risk priority score to help direct future pharmacology research.

III.   General Comments and Recommendations:

1. The Panel strongly recommends that a complete tabulation of all therapeutic agents that are currently being used/provided in in-flight kits be added to the 2010 Pharmacology Evidence Risk Report. In particular, the drug product names, routes of administration, dosage forms, doses and amounts (dose units and quantities) should be explicitly listed.

2. Furthermore, the Panel strongly advocates a systematic, comprehensive survey of medication use in all future spaceflights (drug, dose, self-reported and/or flight-surgeon-assessed clinical effects) in section I. Executive Summary of this report. The Panel believes that insufficient progress had been made on compiling this essential information.

3. In order to rationally allow appropriate resource allocations for the study of in-space pharmacology risk assessment and mitigation, the Panel proposes explicitly a risk-based approach for the future study of medications.

Therefore, each medication (listed above, #1) should be assigned its pharmacological risk priority as follows:

Priority 1:   Critical dose (narrow therapeutic index (NTI)) drugs, frequently used medication for acute conditions and/or potent medication taken chronically for long-term clinical conditions in long-duration spaceflight (i.e., lack of efficacy or toxicity);

Priority 2:   Drugs/formulations with suspected pharmaceutical/PK/PD changes due to long-term spaceflight;

Priority 3:   Drugs/formulations unlikely impacted by long-term spaceflight.

This prioritization should help focus the study of pharmacological risk to top priority drugs.

To facilitate such a risk prioritization a compilation of each of the therapeutic agents should be provided (e.g., as a table, listing the pharmaceutical route of administration, dosage form, excipients, PK/PD properties, and absorption, distribution, metabolism, and excretion (ADME) properties). The ADME properties should include classification according to Biopharmaceutics Classification System (BCS), class 1-4). Both quantitative (e.g., F_{oral}, CL_{tot}, Vd_{ss}, f_u, CL_{ren}) and qualitative (e.g., routes of metabolism, presence of active metabolites) information should be listed. Finally, evidence of pharmacological risk and/or reason to suspect pharmacological risk should be tabulated for each drug product.

The 2010 Pharmacology Evidence Risk Report should discuss in more detail the biopharmaceutic aspects of drug delivery and provide a tabulation of various drug products such as conventional (immediate release), extended release, delayed release, orally disintegrating tablets, transdermal systems, etc. Alterations in human physiology in spaceflight that affect blood flow, gastrointestinal pH, motility and transit time may determine whether the desired drug should be given in a dosage form that has higher probability of absorption and subsequent therapeutic efficacy.

The existing 2010 Pharmacology Evidence Risk Report tends to emphasize the lack of efficacy possibly due to the lack of drug absorption; there is also the possibility of increased drug bioavailability in space. For example, an enteric coated product would cause dose dumping in the stomach if the pH is higher due to taking an anti-cholinergic drug or a drug such as omeprazole. Various efflux transporters such as P-glycoprotein (P-gp) could also be affected in the gastrointestinal (GI) tract leading to greater bioavailability.

4. As long-term spaceflight is in the future for NASA, the potential for drug-drug interactions and chronic medication drug use should be considered. Therefore, a discussion of

intermittent/chronic use versus acute use of medications is needed as most existing evidence is obtained from single dose (PK, PK/PD) studies in humans.

IV.   Missing topics:

1.   Antibacterial/antiviral PK/PD changes in long-term spaceflight;

2.   Potential pharmacological risk of symptomatic treatments of acute conditions (e.g., decongestants, anti-diarrheals); H_2-blockers, analgesics (nonsteroidal anti-inflammatory drugs), etc.

V.   Specific Comments:
(Note: The page numbers in this section correspond with those of the 2010 Pharmacology Evidence Risk Report)

Page 7:
The astronauts have the opportunity to consult with ground-based flight surgeons, but they also have free access to the medication kit and can self-administer as they see fit. This means that records of medication use may not always be complete. Attempts are made to capture information about medication use with post-flight debriefings, but it is understandably difficult for crewmembers to recall all medication use, indications, and side effects extending back over weeks or months.

Hospital pharmacies use a unit dose system. When each dose is removed the person initials the unit and provides the time and date. A bar code and scanning device might be easier to use. Side effects are more difficult to ascertain. However, a generic adverse event form that can be scanned could list large number of adverse events that are most probable for all medications. In addition, self-scoring as to the severity of the adverse event could be also on the form. All of this could be in electronic media.

Page 10, line 4:
The term 'pill' is now a common generic term for all oral drug products (delayed release tablets, conventional tablets, conventional capsules, beads in capsule, extended release tablets, oral disintegrating tablets, etc.). Each of these products has advantages and disadvantages for oral absorption. In addition, these oral dosage forms are differently affected by food, gastric pH, GI transit time, etc. A tabulation of these products would help to differentiate these products.

Page 11:
A tabulation of the route of administration and drug absorption would be helpful. Are transdermal patches a viable dosage form in space? Blood flow at the absorption site is an important consideration. Different muscle groups have different blood flows and drug absorption after intramuscular (IM) injection varies.

Page 13:
Scopolamine and promethazine have anticholinergic activity that slows GI motility, but also affects secretions in the GI tract. How does this affect enteric coated drug products or extended release drug products?

The 2010 Pharmacology Evidence Risk Report should discuss the steepness of the dose response curve as part of NTI.

Page 14:
The 2010 Pharmacology Evidence Risk Report should discuss the BCS as a foundation of risk-based assessment of potential spaceflight effects on drug absorption.

Pages 14 - 15:
Acetaminophen is absorbed very rapidly (t_{max} around one hour or less), and small changes in absorption rate can easily be observed. Drugs that are normally absorbed maximally at t_{max} of three to four hours are less affected by small changes in absorption rate. This may be a characteristic for BCS class 1 drugs only (high GI solubility and permeability). What is the effect on poorly orally absorbed drugs (e.g., bisphosphonates)?

A table of the usual drugs that are used in spaceflight would be helpful. Include PK parameters, therapeutic plasma drug concentrations, probability of drug interaction, affect of food, etc. The table would demonstrate which drugs would be more likely to lose or gain efficacy due to physiologic changes (see section III. General Comments).

Page 18:
The risk associated with drug absorption changes fall under the HRP risk: Risk of Therapeutic Failure Due To Ineffectiveness of Medication.

There is a need to also consider increased bioavailability due to dose dumping of enteric coated drug products, interaction or loss of GI efflux transporter such as P-gp. If the therapeutic window is wide, there is less risk of therapeutic failure or higher than anticipated drug absorption. Another risk is a change at the drug receptor (pharmacodynamic). Does the sensitivity to the drug change in space?

Page 19:
The following HRP gaps are associated with absorption changes:
   1. PH7: What are the effects of spaceflight on pharmacokinetics or pharmacodynamics?
   2. PH 1: Inadequate tracking of medication use, indication, efficacy and side effects.

The panel had no specific questions or recommendations for these gaps.

Pages 19 - 23:
Small changes in volume of distribution are unlikely to affect PK parameters. However, changes in permeability and protein binding for potent drugs could have an effect on the PD response.

It is not clear whether hematocrit (HCT) changes in spaceflight. Some drugs highly bind to red blood cells and changes in HCT might have an influence on the PD response.

It would be helpful to have a table of drugs, PK values, therapeutic drug concentrations and the probability of which physiological change (e.g., metabolism, renal clearance, etc) would have the most effect on the PD of these drugs (see section III. General Comments).

Page 25:
Are physiological volume shifts only important for low volume of distribution (polar?) drugs?

Discuss perfusion-limited versus permeability-limited drug distribution.

Page 26:
The risks associated with distribution changes fall under the HRP risk: Risk of Therapeutic Failure Due To Ineffectiveness of Medication.

An additional risk may be the increased risk of adverse event due to drug penetration into tissues due to increased drug permeability through capillaries.

The following HRP gaps are associated with distribution changes:
1. PH7: What are the effects of spaceflight on pharmacokinetics or pharmacodynamics?
2. PH 1: Inadequate tracking of medication use, indication, efficacy and side effects.

Justify the use of erythromycin and propranolol as model drugs to assess drug distribution?

Pages 26 - 27:
There is no discussion of hepatic clearance, intrinsic clearance and blood flow relationship. Moreover, polymorphism of the Cytochrome P-450 enzymes may lead to drug-drug interactions.

There have been some studies that stress affects drug metabolism.

Page 30:
The risks associated with metabolism changes fall under the HRP risk: Risk of Therapeutic Failure Due To Ineffectiveness of Medication.

An additional risk may be the increased risk of an adverse event caused by a decrease in intrinsic clearance due to changes in enzymes responsible for drug metabolism.

The following HRP gaps are associated with metabolism changes:
1. PH7: What are the effects of spaceflight on pharmacokinetics or pharmacodynamics?
2. PH 1: Inadequate tracking of medication use, indication, efficacy and side effects.
3. PH11: What potential polypharmacy problems exist in current spaceflight medical practice?

Apparently, there is no information on human *in-vivo* metabolism in spaceflight – this should be a high priority area of future research; discuss the significance of *in-vitro*/animal PK findings.

Discuss the role of active metabolites (which seems common for most current drugs in spaceflight).

Pages 31 - 32:
There is no quantitative discussion of renal clearance.   Does blood flow to the kidneys change? This could be reflected in an estimate in glomerular filtration rate (GFR) using creatinine clearance.

Page 33:
Can estimates be made about the possible contamination of the urine processor assembly (UPA) with drug/metabolites (considering doses, amounts excreted and total UPA volume balance) to better assess this risk? If not, should samples be taken to measure actual drug and/or metabolite concentrations?

The risks associated with excretion changes fall under the HRP risk: Risk of Therapeutic Failure Due To Ineffectiveness of Medication.

It is important to note which drugs would be more likely to be affected by changes in renal clearance. Small changes in renal clearance my not have a clinically significant affect on the PD of the drug.

The following HRP gaps are associated with excretion changes:
    1. PH7: What are the effects of spaceflight on pharmacokinetics or pharmacodynamics?
    2. New gap: What is the effect of drugs used frequently in flight on the UPA?

The recycling system process could remove drugs from waste water by passage through an adsorption column. This could be tested in the laboratory.

Page 41:
Consider the use of lorazepam/Ativan® (short-acting benzodiazepine (BZD) without active metabolites) as a hypnotic as well as the use of flumazenil to reverse BZD-induced sedation.

Tryptophan (1 gm) has sleep inducing qualities without "hangover" affect if awakened. For awakening under emergency, some medicinal plants have been reported to be effective and might be considered to counteract sleep aids and some of the effects of the BZDs and other agents better than caffeine. In addition, zolpidem (Ambien) has a short elimination half-life. Given as an extended release product, zolpidem would remain in the body if awakened. However, a transdermal patch containing a short acting sleep aid would give the effects of extended activity and could be removed if subject needs to be awakened in an emergency.

The risks associated with the central nervous system fall under two established HRP risks:
1. Risk of Performance Errors Due To Fatigue Resulting from Sleep Loss, Circadian Desynchronization, Extended Wakefulness, and Work Overload
2. Risk of Therapeutic Failure Due To Ineffectiveness of Medication

Alternate drugs for sleep and alertness could be used.

The following HRP gaps are associated with the central nervous system:
1. Sleep 3: Does sleep loss continue on long-duration spaceflight or is there adaptation? What is the nature of circadian desynchronization, extended wakefulness and work overload over long-duration missions?
2. Sleep 6: How can individual crew members most effectively and safely use sleep and alertness medications prior to and during spaceflight?
3. Sleep 9: What are the countermeasures needed to recover from chronic partial sleep loss, work overload, and/or slam sleep shifting, and that permit recycle back into the same sleep-restricted schedules?
4. PH11: What potential polypharmacy problems exist in current spaceflight medical practice?

Which drugs have circadian rhythms that are of PD consequence? Have alternative sleep aids (e.g., tryptophan) and stimulant alternatives to d-amphetamine or caffeine been considered? A tabulation of drugs and patient profile records would help determine the possibility of a drug-drug interaction.

Page 47:
The 2010 Pharmacology Evidence Risk Report should justify concerns about cardiac arrhythmia; which particular medications are currently used that carry such as risk? If this is considered a major risk, would telemetry of cardiac rhythm be justified?

The risks associated with the cardiovascular system fall under three established HRP risks:
1. Risk of Orthostatic Intolerance During Re-exposure to Gravity
2. Risk of Cardiac Rhythm Problems
3. Risk of Therapeutic Failure Due To Ineffectiveness of Medication

Have the use of over-the-counter sympathomimetic drugs such as pseudoephedrine or phenylpropanolamine been considered as mild pressor agents?

The following HRP gaps are associated with the cardiovascular system:
1. CV 3: Is orthostatic intolerance a potential hazard?
2. PH 10: What are the performance effects of in-flight drugs on exercise, orthostatic tolerance, motor control, cognitive function, etc.?
3. PH 7: What are the effects of spaceflight on pharmacokinetics/pharmacodynamics?
4. PH 11: What potential polypharmacy problems exist in current spaceflight medical practice?

The panel had no specific questions or recommendations for these gaps.

Page 48:
Motion sickness can affect gastric emptying time, pH, and GI transit. There is a need to consider the effects of various dosage forms on *in vivo* performance (e.g., conventional capsules/tablets and modified release products such as extended release and delayed (enteric coated) release products).

Pages 54 - 58:
Many of these drugs have anticholinergic affects and affect gastric emptying time, pH, and GI transit. There is the potential for drug-drug interactions.

Consider other non-sedating H_1-receptor antagonists (e.g., loratidine and fexofenadine), without cardiac arrhythmia risk.

Improved SMS treatment approaches (other than promethazine) should be a high priority area of research.

Page 58:
The risks associated with gastrointestinal systems changes fall under two established HRP risks:
    1. Risk of Therapeutic Failure Due To Ineffectiveness of Medication
    2. Risk of Orthostatic Intolerance during Re-exposure to Gravity

The panel had no specific questions or recommendations for these risks.

Page 59:
The HRP gaps associated with gastrointestinal systems changes are:
    1. PH 10: What are the performance effects of in-flight drugs on exercise, orthostatic tolerance, motor control, cognitive function, etc?
    2. PH 1: Inadequate tracking of medication use, indication, efficacy and side effects.
    3. PH11: What potential polypharmacy problems exist in current spaceflight medical practice?

The panel had no specific questions or recommendations for these gaps.

Page 63:
The risks associated with multisystem radiation exposure fall under three established HRP risks:
    1. Risk of Accelerated Osteoporosis
    2. Risk of Bone Fracture
    3. Risk of Renal Stone Formation

The HRP gaps associated with the skeletal system are:
    1. B 3: What pharmaceuticals against bone loss are best used and how?
    2. MO 5: Determine how osteoporosis treatments can be employed?
    3. B 8: Do pharmaceuticals work effectively in spaceflight to prevent renal stones?

There is a need to consider novel, long-acting bisphosphonates for the prevention/treatment of osteoporosis. Supplemental calcium and vitamin D in diet or as a food supplement should also be addressed.

Has the chemistry of the renal stones been identified? If so, there may be some suggested diet and fluid intake that would be beneficial.

Page 66:
The risks associated with the muscular system fall under the established HRP risk: Risk of impaired performance due to reduced muscle mass, strength and endurance.

The HRP gap associated with muscular system changes is: M14: What anabolic or anti-catabolic drugs can be used to mitigate muscle loss?

What affect does muscle atrophy have on IM injections?

Page 71:
The risks associated with alterations of the immunological system fall under three established HRP risks:
1. Risk of Therapeutic Failure Due To Ineffectiveness of Medication
2. Risk of Crew Adverse Health Event Due To Altered Immune Response
3. Risk of Adverse Health Effects Due To Alterations in Host-Microorganism Interactions

The HRP gaps associated with immunological system changes are:
1. PH 15: Are the antimicrobial agents carried on board effective against microbes that exhibit spaceflight-related changes in virulence?
2. IM 1: Does spaceflight alter immune function?
3. AEH 8: What changes are occurring to host susceptibility during human exploration of space that could affect crew health?

Stress and the immune system are inter-related and this may affect glucose metabolism (corticosteroid effects) and drug metabolizing enzymes, and other physiologic changes.

Will stress cause activation of viruses in the body? Should acyclovir be used as a prophylactic to viral infection? What are the effects of alterations in GI flora on the absorption of drugs?

In-vitro antibiotic sensitivity studies for relevant bacteria should be a high priority area of research given the potential risk based on the available evidence.

Pages 76 - 77:
The risks associated with multisystem radiation exposure fall under three established HRP risks:
1. Risk of Therapeutic Failure Due To Ineffectiveness of Medication
2. Risk of Acute Radiation Syndromes Due To Solar Particle Events
3. Inability to Adequately Treat an Ill or Injured Crew Member

The HRP gaps associated with multisystem radiation exposure are:
1. PH 9: What is the stability of drugs during long duration spaceflight?
2. CNS 4: What are the most effective biomedical or dietary countermeasures to mitigate CNS risks? By what means are the countermeasures likely to work?
3. ExMC 4.17: Lack of Adequate Protection for Medications to preserve Stability and Shelf-life in long duration spaceflight missions.

Drug products should be packaged under nitrogen gas to eliminate oxygen and oxidation.

A stability program in a terrestrial laboratory should be initiated using various exposures of radiation.

VI.   Pharmacology Evidence Review Panel Roster

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VII.   Pharmacology Evidence Review Panel Charge

This review panel is chartered by the Human Research Program (HRP) Program Scientist at the NASA Johnson Space Center (JSC) to review the evidence base for potential astronaut health and performance risks on future exploration missions that may result from the risk of therapeutic failure due to ineffectiveness of medication. The Panel will generate a report of their analysis of the Pharmacology evidence, including any recommendations on how to improve the Pharmacology Evidence Report, and submit it to the HRP Program Scientist. A copy of the report will be provided to the Human Health and Countermeasures Element at JSC that sponsors the Pharmacology discipline. Once the report is finalized it will be made available to the public.

In 2008, the Institute of Medicine reviewed NASA's Human Research Program Evidence in assessing the Pharmacology risk identified in NASA's Human Research Program Requirements Document (PRD). Since this review there was a major reorganization of the Pharmacology discipline within the HRP, as well as a re-evaluation of the Pharmacology evidence. This panel is being asked to review the latest version of the Pharmacology Evidence Report.

 Specifically, this panel will:
- Appraise the descriptions of the human health-related risk in the HRP PRD.
- Assess the relevance and comprehensiveness of the evidence in identifying potential threats to long-term space missions.
- Assess the associated gaps in knowledge and identify additional areas for research as necessary.

The Panel should:

1. Evaluate the Pharmacology Evidence Report based on the following criteria:
    A. Does the Pharmacology Evidence Report provide sufficient evidence that the risk is relevant to long-term space missions?
    B. Is the risk properly stated in the HRP Program Requirements Document (PRD)?
    C. Is the text of the short description of the risk provided in the HRP PRD clear?
    D. Does the evidence make the case for the knowledge gaps presented?
    E. Are there any additional gaps in knowledge that should be considered for this specific risk?
    F. Does the Pharmacology Evidence Report address relevant interactions between this risk and others in the HRP PRD/IRP (Integrated Research Plan)?
    G. Is the expertise of the author sufficient for the given risk?
    H. Is there information from other disciplines that need to be included in the Pharmacology Evidence Report?
    I. Is the breadth of the cited literature sufficient?
    J. What is the overall quality and readability?

2. Comment on any additional information provided to the Panel that is not addressed in #1 above.

3. Once the panel members have received the review materials and had the opportunity to look over the documents, participate in a teleconference to discuss any issues, concerns, and expectations of the review process to start the review.
   A. Discuss the charge and answer questions about the process.
   B. Identify any issues/concerns the Panel would like to have addressed.

4. The Panel will prepare a draft report, including any recommendations that will be briefed to the HRP Program Scientist by the chairperson or panel during a site visit at JSC. The report should address #1 and #2 above and any other information considered relevant by the panel.

5. The Panel will provide the HRP Program Scientist with an Executive Summary of their report one week prior to the debrief.

6. Finalize the panel report (within one month of the debrief) that contains a detailed evaluation of the risk.

7. This review panel will become the Pharmacology Standing Review Panel for the HRPs research plan in 2011. To facilitate this transition, the panel chair or a panel member will attend (or participate via WebEx or teleconference) the HRP Standing Review Panel site visit at NASA JSC on December 7, 2010, that will focus on HRP Element cross-disciplinary integration.

8. Consider serving on a non-advocate review panel to evaluate a NASA directed research proposal or on peer review panels that evaluate proposals submitted in response to NASA Research Announcements; and otherwise advise the HRP Program Scientist.