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A FRAMEWORK APPROACH FOR EVALUATION OF POTENTIAL DEGRADATION OF APIs FOR LONG-DURATION SPACEFLIGHTS

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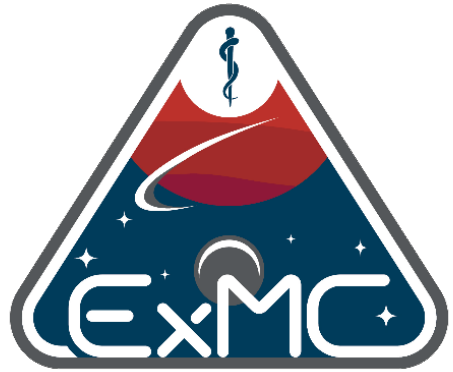
Context

- **HRP Risk:**
  - Ineffective or *Toxic* Medications during Long Duration Exploration Spaceflight
- **HRP Roadmap Gap:**
  - Pharm-401: We need to perform further research to understand and characterize the active pharmaceutical ingredient and ***degradation profiles*** *of medications* for which we have low to moderate confidence in their ***safety*** and effectiveness for exploration missions.
- **Support:**
  - Exploration Medical Capability (ExMC) Element



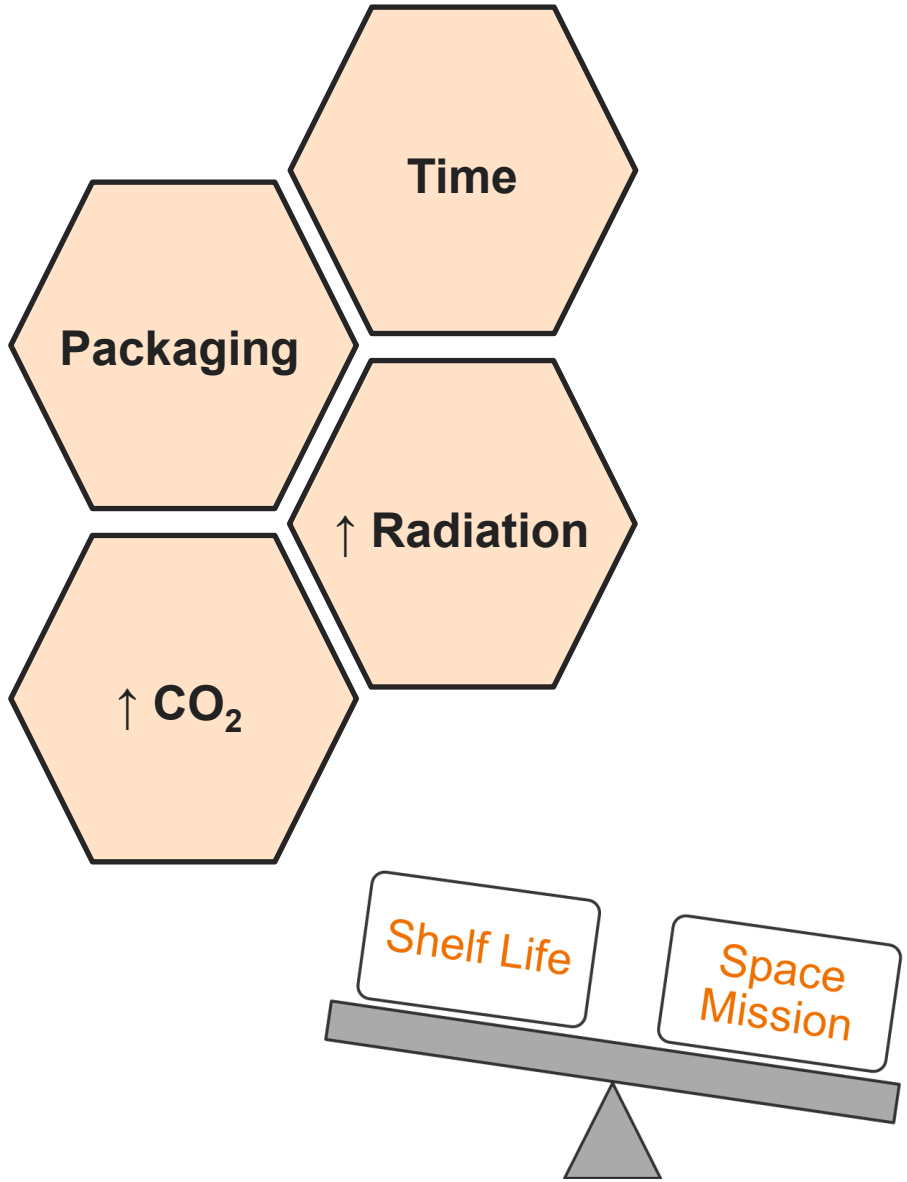
Exploration Medical Capability

Outline

- Problem formulation
- Framework development
- Framework application
- Results
- Conclusions & Next steps

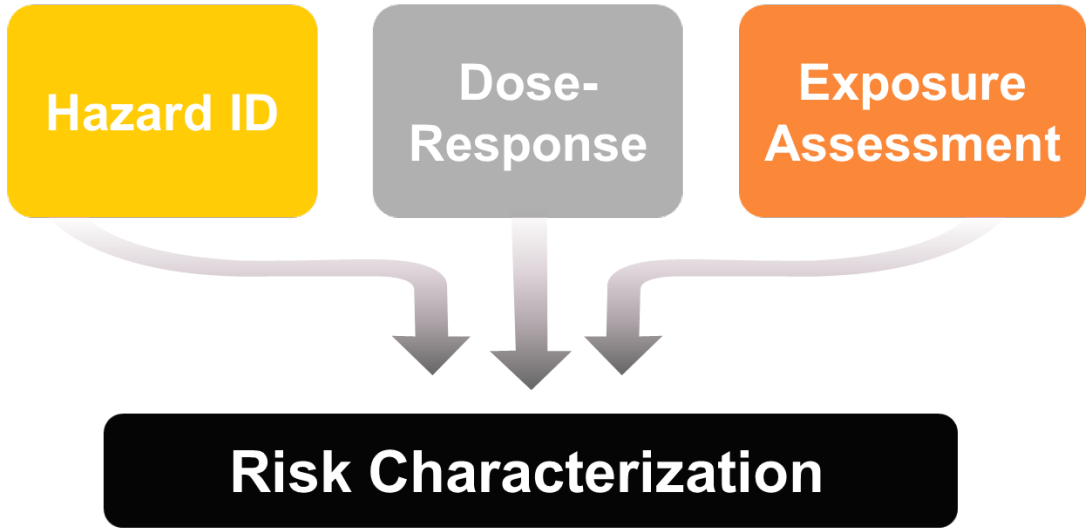
Problem Formulation

- Active pharmaceutical ingredients (APIs) may contain impurities/degradants
- A degradant/impurity may pose a safety concern
  - E.g., Nitrosamines are associated with genotoxicity/carcinogenicity concerns
- Degradation rate in spaceflight is ~1.5x higher *vs.* on Earth
- Limited number of studies on API degradation in spaceflight

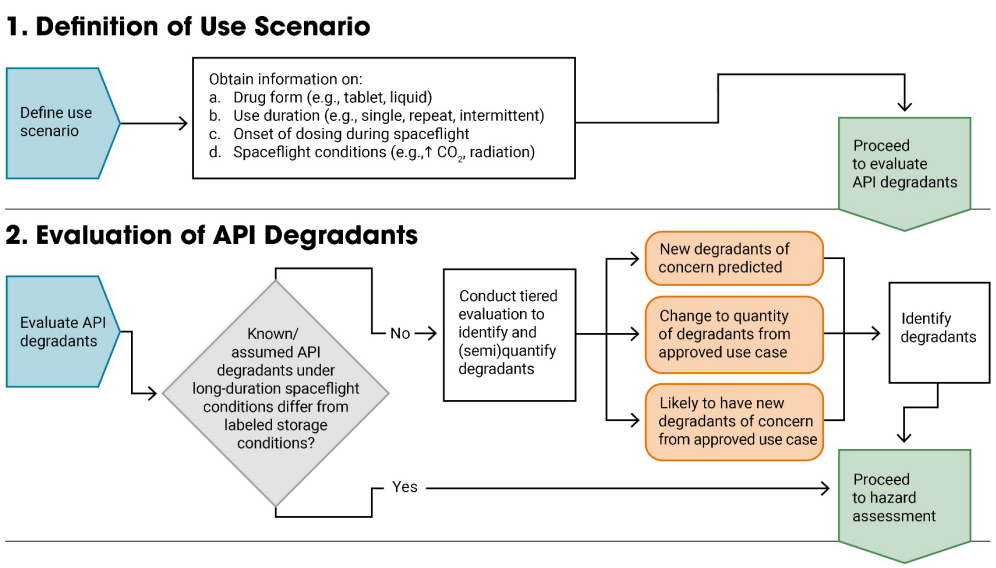


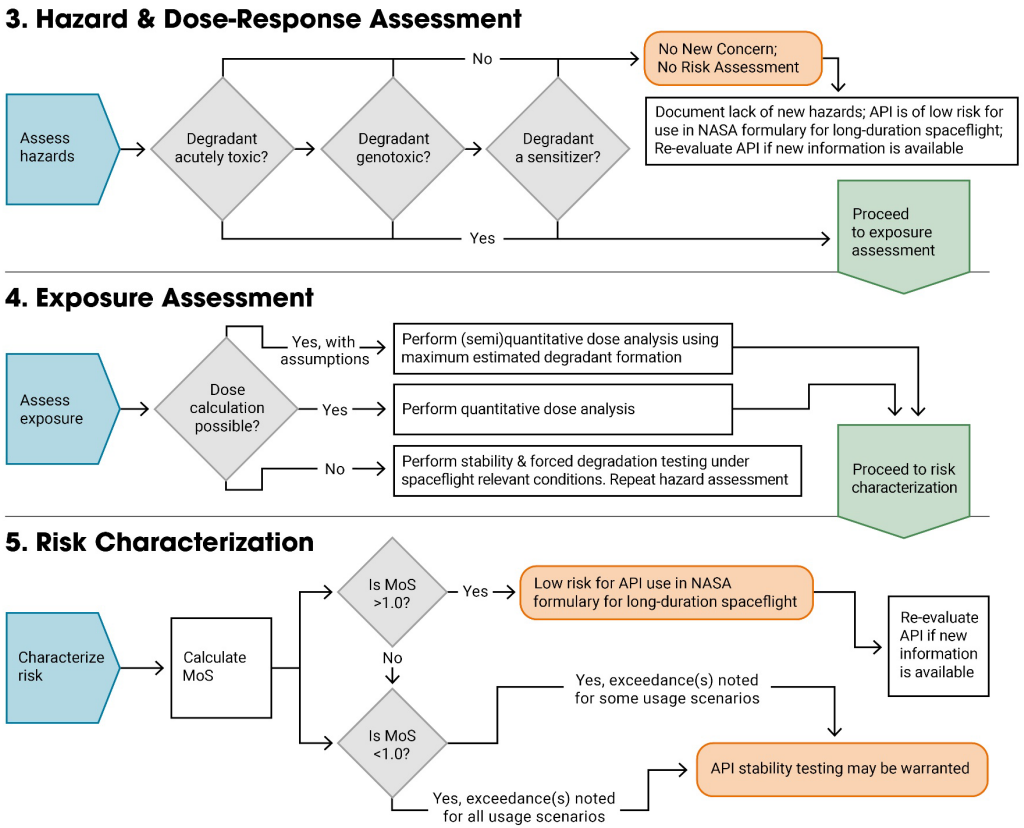
Framework Development

- Leveraging:
  - Considerations for degradant ID:
    - Known degradation pathways and API chemistry
    - Stability and forced degradation study results
    - *In silico* prediction tools
    - Available spaceflight studies
  - Principles of risk assessment



Framework Development (cont.)





Step 1. Definition of Use Scenario

- Aims to define API use scenario
- Several characteristics considered:
  - Clinical indication
  - Form (e.g., tablet, capsule, solution)
  - Labeled strength
  - Known or anticipated onset of dosing during spaceflight
  - Frequency of use
  - Labeled expiration date
  - Long-duration spaceflight conditions

Step 2. Evaluation of API Degradants

- Aims to identify degradants
- If specific API degradants differ from labeled storage conditions, proceed to Step 3
- If no known/assumed API degradants identified, conduct tiered evaluation, then proceed to Step 3

Tier	Resource
1	FDA Stability Testing FDA SLEP EMC Database
2	Lhasa Zeneth Moiety-based expert predictions
3	Peer reviewed literature

Step 3. Hazard Assessment

- Aims to assess acute toxicity, genotoxicity, and sensitization potential
- Empirical data (if available) along with *in silico* predictions
  - OECD QSAR Toolbox
  - Lhasa DEREK/SARAH Nexus
  - Etc.
- If hazards identified, proceed to Step 4
- If no hazards identified, API considered safe and no need to proceed further

GHS Classification	LD_{50} (mg/kg)
Category 1	≤5
Category 2	>5 to ≤50
Category 3	>50 to ≤300
Category 4	>300 to ≤2000
Category 5	>2,000 to ≤5,000

		Is degradant genotoxic?	
		Yes	No
Is degradant a sensitizer?	Yes	Conduct Risk Assessment	Conduct Risk Assessment
	No	Conduct Risk Assessment	No New Concern; No Risk Assessment

Step 4. Exposure Assessment

- Aims to calculate degradant dose
- Five cases considered

Case		Equation(s)
1	Long-duration spaceflight scenario-relevant data	Eq. 1. $Degradant\ (\%) = \frac{Degradant\ Amount\ (mg)}{Labeled\ API\ Amount\ in\ Study\ (mg)} \times 100$ Eq. 2. $Degradant\ (mg/dose) = Labeled\ API\ Content\ on\ NASA\ Formulary\ (mg/dose) \times Degradant\ (\%)$
2	Short-duration spaceflight scenario-relevant data	Eq. 3. $Slope(\%/year) = \frac{Degradant\ (\%)\ at\ T_{Sample} - [100\% - Labeled\ API\ (\%)\ at\ T_0]}{T_{Sample} - T_0}$ Eq. 4. $Degradant\ (\%) = Slope(\%/year) \times 3\ years$
3	Spaceflight scenario-relevant data from read-across	Eq. 5. $Degradant\ (\%) = \frac{Degradant\ Amount\ (mg) \times F_{RA}}{Labeled\ API\ Amount\ in\ Study\ (mg)} \times 100$
4	Stability study data	Eq. 6. $Degradant\ (\%) = \frac{Estimated\ Degradant\ Amount\ at\ 3\ Years\ (mg) \times 1.5}{Labeled\ API\ Amount\ in\ Study\ (mg)} \times 100$
5	Forced degradation study data	Eq. 7. $Slope(\%/year) = \frac{Degradant\ (\%)\ at\ T_{Shelf\ life} - [100\% - Labeled\ API\ (\%)\ at\ T_0]}{T_{Shelf\ life} - T_0}$ Eq. 8. $Degradant\ (\%) = Slope(\%/year) \times 3\ years \times 1.5$

Step 5. Risk Characterization

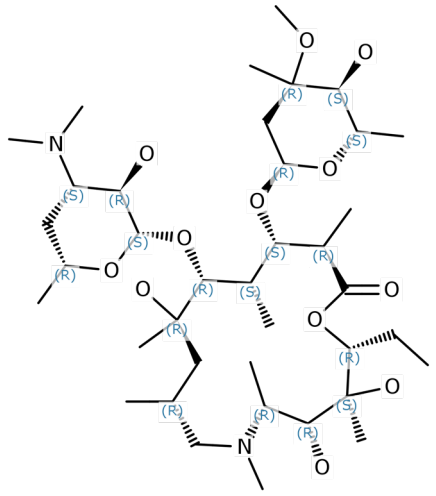
- Aims to characterize risk
- Degradant doses compared to:
  - Health-based exposure limits (HBELs)
  - Thresholds of toxicological concern (TTCs)

$$MoS = \frac{HBEL\ or\ TTC}{Dose}$$

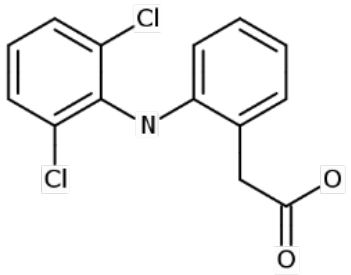
MoS > 1.0 (no concern); MoS < 1.0 (concern)

Framework Application

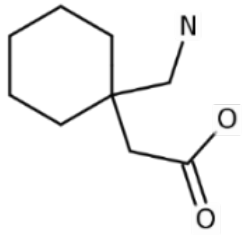
- Framework applied to four APIs on the NASA exploration candidate formulary (ECF):



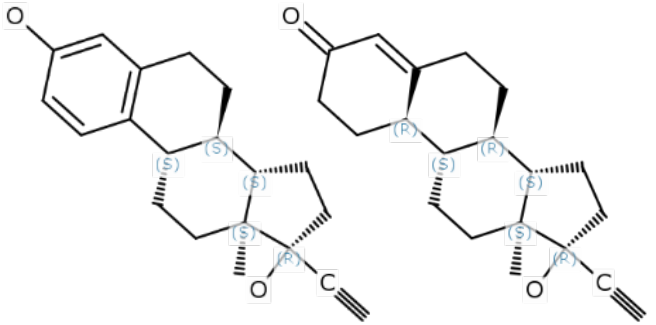
Azithromycin



Diclofenac



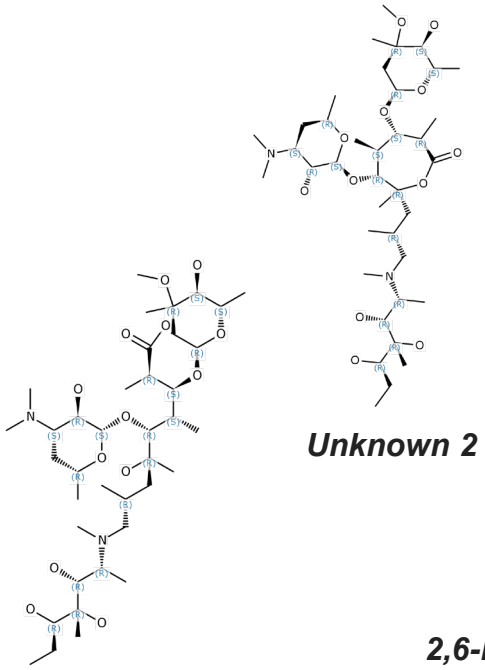
Gabapentin



Oral contraceptive (ethinyl estradiol & norethindrone)

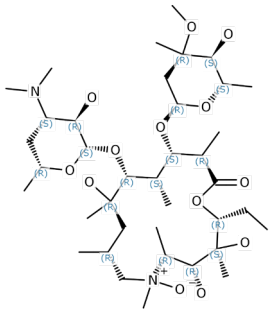
Use and Degradants

- Step 1 (Definition of Use Scenario)
  - Dosage forms listed on NASA ECF:
    - 250 and 500 mg oral tablets
    - 500 mg lyophilized powder for intravenous injection
- Step 2 (Evaluation of API Degradants)
  - 8 impurities measured in samples from spaceflight but were not different from ground control
    - Not considered for hazard assessment
  - 7 degradants considered for hazard assessment:
    - 5 predicted degradants
    - 2 degradants from peer-reviewed studies



Unknown 1

Unknown 2



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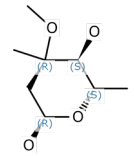
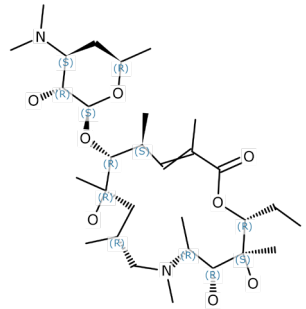
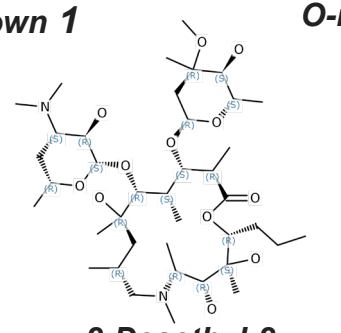


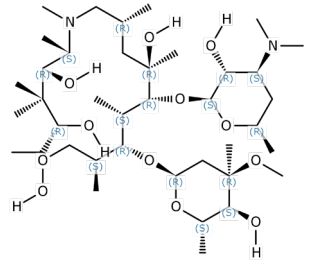
2,6-Dideoxy-3-C-methyl-3-O-methylhexopyranose



Unknown 4



2-Desethyl-2 propylazithromycin



Impurity X

Hazards

- Step 3 (Hazard Assessment)

Table A12. Hazard assessment summary for azithromycin degradants.

Degradant Name	Acute Toxicity	Sensitization	Genotoxicity[1]
Unknown 1	-	+	+ (C)
Unknown 2	-	+	+ (C)
Unknown 3	-	+	-
Unknown 4	-	+	-
2,6-Dideoxy-3-C-methyl-3-O-methylhexopyranose	-	+	-
2-Desethyl-2 propylazithromycin	-	+	-
Impurity X	-	+	+ (C)

[1] Letter C in parenthesis indicates a carcinogenicity concern
Color codes: Light orange: Hazard (+); Gray: No hazard (-)

Doses

- Step 4 (Exposure Assessment)

Table A13. Daily doses of a single azithromycin degradant.

Dosing Regimen	Degradant Amount (Treatment Course Duration in Days)	Average Degradant Daily Dose over Treatment Course	Time-Weighted Degradant Daily Dose over 3 Years
Scenario 1: a 500 mg tablet on Day 1 followed by a 250 mg tablet once daily on Days 2-5[1]	2.1 mg (5 days)	0.43 mg/day	2.0 µg/day
Scenario 2: (1) a 500 mg tablet on Day 1 followed by a 250 mg tablet once daily on Days 2-5 or (2) a 500 mg tablet once daily for 3 days[2]	(1) 2.1 mg (5 days) or (2) 2.9 mg (4 days)	(1) 0.43 mg/day or (2) 0.71 mg/day	(1) 2.0 µg/day or (2) 2.6 µg/day
Scenario 3: a 500 mg tablet once daily for 3 days[3]	2.1 mg (3 days)	0.71 mg/day	2.0 µg/day
Scenario 4: a single dose of 500 mg administered by IV for at least two days[4]	1.4 mg (2 days)	0.71 mg/day	1.3 µg/day

[1] Scenario 1 calculations: Degradant amount: $0.71mg + 4 \times 0.36mg = 2.1mg$, Average degradant daily dose: $2.1mg \div 5d = 0.43mg/d$, Time-weighted degradant daily dose: $2.1mg \div 1095d \times 1000 = 2.0\mu g/d$

[2] Scenario 2 calculations: (1) same as Scenario 1; (2) Degradant amount: $0.71mg \times 4 = 2.9mg$, Average degradant daily dose: $2.9mg \div 4d = 0.71mg/d$, Time-weighted degradant daily dose: $2.9mg \div 1095d \times 1000 = 2.6\mu g/d$

[3] Scenario 3 calculations: Degradant amount: $0.71mg \times 3 = 2.1mg$, Average degradant daily dose: $2.1mg \div 5d = 0.43mg/d$, Time-weighted degradant daily dose: $2.1mg \div 1095d \times 1000 = 2.0\mu g/d$

[4] Scenario 4 calculations: Degradant amount: $0.71mg \times 2 = 14.3mg$, Average degradant daily dose: $1.4mg \div 2d = 0.71mg/d$, Time-weighted degradant daily dose: $1.4mg \div 1095d \times 1000 = 1.3\mu g/d$

Risks

- Step 5 (Risk Characterization)

Table A14. Risk characterization for azithromycin degradants.

Degradant Name	Daily Limit (Reason)[1]	Highest Time-Weighted Daily Dose	MoS[2]
Unknown 1	5 µg/day (sensitization)	2.6 µg/day	1.9
Unknown 2	5 µg/day (sensitization)	2.6 µg/day	1.9
Unknown 3	5 µg/day (sensitization)	2.6 µg/day	1.9
Unknown 4	5 µg/day (sensitization)	2.6 µg/day	1.9
2,6-Dideoxy-3-C-methyl-3-O-methylhexopyranose	5 µg/day (sensitization)	2.6 µg/day	1.9
2-Desethyl-2 propylazithromycin	5 µg/day (sensitization)	2.6 µg/day	1.9
Impurity X	5 µg/day (sensitization)	2.6 µg/day	1.9

[1] The TTC of 5 µg/day for sensitizers is based upon the qualification threshold developed for orally inhaled and nasal drug products developed by PQRI (https://pqri.org/wp-content/uploads/2022/03/PQRI-PDP-Recommendation-2022.pdf)
[2] MoS is the daily limit divided by the daily dose (i.e., 5 µg/day divided by 2.6 µg/day)

Results

- No additional stability testing was recommended for:
  - Azithromycin (hazards identified for degradants but MoS values >1.0)
  - Gabapentin (no hazards identified for degradants)
  - Diclofenac (hazards identified for degradants but MoS values >1.0
- Additional testing was warranted for oral contraceptive
  - Hazards identified for ethinyl estradiol but MoS values >1.0
  - Hazard identified for norethindrone (sensitization) and MoS values <1.0
  - Testing for norethindrone degradants could be warranted

Conclusions & Next Steps

- Framework enables "toxicity" evaluation of degradants and quantitative analysis of API degradant formation in long-duration spaceflights
- Framework flexibility accommodates evaluation of any drug form or use scenario, application to APIs or drug products with excipients, and utilization in unique environments outside of long-duration spaceflights

- Apply framework to additional APIs on NASA ECF
  - Particularly APIs that may contain/generate nitrosamines
    - A nitrosamine-specific framework needed?

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Exploration Medical Capability

Questions?

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