ExMC GROUND-BASED SPACE RADIATION ANALOG PILOT DRUG STABILITY STUDY:

PRELIMINARY DATA REVIEW

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Presentation Outline

- Introduction:
  - Historical Significance
  - Purpose
  - Research Objectives

- Materials / Methods

- Results
  - Time-point I Review
  - Time-point II Update

- Preliminary Conclusions

Historical Significance

- Historical NASA drug stability studies suggested that spaceflight conditions compromise medication safety and efficacy (Putcha et al, 2001 – 2011).

- Historical NASA ground analog experiments designed to simulate the effects of high-energy radioactive particles on medications during spaceflight, suggested that radiation exposure during spaceflight could threaten drug quality and potency on long-duration exploration missions (Putcha et al, 2006).

- Follow-on NASA flight studies revealed reduced active pharmaceutical ingredient (API) concentrations, and altered drug release; when compared to matching ground controls (Putcha et al, 2006 – 2011).

Purpose

- Uncertainty remains regarding space radiation impacts on drug stability and shelf life

- Space environmental analog and ground-based targeted radiation research could reveal valuable insight into drug safety and effectiveness

  - In 2017, the Exploration Medical Capability (ExMC) Element designed a three-year pilot analog experiment to expose medications to a series of simulated Galactic Cosmic Radiation (GCR) mixed-species beam exposures at the NASA Space Radiation Laboratory (NSRL) at Brookhaven National Laboratory (BNL)
    - First time-point analysis completed 2018; presented IWS 2019
    - Second time-point analysis completed 2019; presented IWS 2020

Research Objectives

- Evaluate if the effects of ground-based rapid-switching radiation beam exposures can effectively reproduce previously observed effects of spaceflight radiation on drug stability and shelf life.

- Further evaluate the utility of simulated GCR beam exposures as an effective ground-based analog for predicting the impacts of GCR exposure on drug stability and shelf life during spaceflight.

Materials and Methods

Study Drugs:

- Four medications were prioritized and selected based on:
  - Pharmaceutical **stability profiles** confirmed by **previous research** / **literature**
  - **Clinical relevance** for exploration spaceflight

Table A. Experimental Drug List

Test Product	Drug	Expiration Date
A	Acetaminophen 500 mg Tablets	01/31/21
B	Amoxicillin 500 mg Capsules	12/31/19
C	Ibuprofen 400mg Tablets	11/30/19
E	Promethazine 25mg Tablets	02/29/20

- Sets (identical brands / lots) of each drug product procured for each experimental arm
  - Sufficient quantities to provide a statistically significant number of replicates
    - 50-100 dosage units / package
    - 4 different drugs x 2 packages each x 4 different study conditions = 32 packages of drugs
- Packaged (as closely as possible) to resemble flight medical systems operational packaging (e.g. drug flight bottles / plastic bags / unit-dose strips, etc.).

Materials and Methods

Study Design: Four Experimental Arms

1. Non-irradiated JSC Control Group
2. Non-irradiated Traveling Control Group
3. Irradiation Group I (Mixed-beam 0.5Gy Total Dose)
4. Irradiation Group II (Mixed-beam 1.0Gy Total Dose)

Environmental Monitoring

- **Temperature / RH:**
  - Shipment / Storage: USP <659> "Packaging and Storage Requirements" defined conditions for "controlled room temperature" (15 - 30˚ C, 30 - 65% RH)
    - Environmental condition tracking
    - Environmentally controlled storage chambers

- **Radiation:**
  - Detection and Monitoring: Thermoluminescence Dosimeters (TLD-100 LiF:Mg,Ti)
    - TLDs enclosed in clear gelatin capsules, attached to front and / or back, of each drug product package

RH = Relative Humidity *USP = United States Pharmacopeia*

Materials and Methods

Irradiation:

- First experiment at NSRL to utilize the mixed-species simulator:

- Exposure dose: Two mixed-beam radiation doses
  - 0.5 Gy
  - 1.0 Gy

- GCR-like beam profile:
  - ^{1}H, ^{4}He, ^{12}C, ^{16}O, ^{28}Si, ^{48}Ti, and ^{56}Fe

- Dose detection and monitoring: Thermoluminescence Dosimeters (TLD-100 LiF:Mg,Ti)
  - TLDs enclosed in clear gelatin capsules, attached to front and / or back, of each drug product package

Ion	Energy (MeV/n)	Range (cm)	LET (keV/μm)	Dose (mGy)
^{1}H	100	*Polyethylene degrader to*		
^{1}H	150	15.9	0.54	35.0
^{1}H	250	38.1	0.39	68.9
^{1}H	1000	326.6	0.22	123.6
^{4}He	100	*Polyethylene degrader to*		
^{4}He	150	16.0	2.17	7.5
^{4}He	250	38.3	1.56	16.4
^{4}He	1000	327.8	0.88	24.9
^{12}C	1000	110.1	7.95	11.7
^{16}O	350	17.0	20.8	15.4
^{28}Si	600	22.7	50.2	8.1
^{48}Ti	1000	32.5	109.5	4.5
^{56}Fe	600	13.1	175.1	4.1
Total				*500.0*

Ion	Energy (MeV/n)	Range (cm)	LET (keV/μm)	Dose (mGy)
^{1}H	20.0	0.43	2.59	30.4
^{1}H	23.3	0.56	2.29	6.7
^{1}H	27.2	0.75	2.02	7.4
^{1}H	31.7	0.98	1.79	8.0
^{1}H	37.0	1.30	1.58	8.7
^{1}H	43.2	1.72	1.39	9.3
^{1}H	50.3	2.26	1.23	10.0
^{1}H	58.7	2.99	1.09	10.6
^{1}H	68.5	3.95	0.97	11.1
^{1}H	79.9	5.20	0.86	11.2
^{1}H	100.0	7.76	0.73	**27.2**

Ion	Energy (MeV/n)	Range (cm)	LET (keV/μm)	Dose (mGy)
^{4}He	20.0	0.43	10.34	**11.0**
^{4}He	23.3	0.57	9.14	**2.1**
^{4}He	27.2	0.75	8.06	**2.2**
^{4}He	31.7	0.99	7.12	**2.3**
^{4}He	37.0	1.31	6.29	**2.5**
^{4}He	43.2	1.73	5.56	**2.6**
^{4}He	50.3	2.28	4.92	**2.7**
^{4}He	58.7	3.01	4.36	**2.7**
^{4}He	68.5	3.97	3.86	**2.7**
^{4}He	79.9	5.23	3.43	**2.7**
^{4}He	100.0	7.81	2.90	**6.1**

Figure 2.0: NSRL GCR Simulation Beam Composition

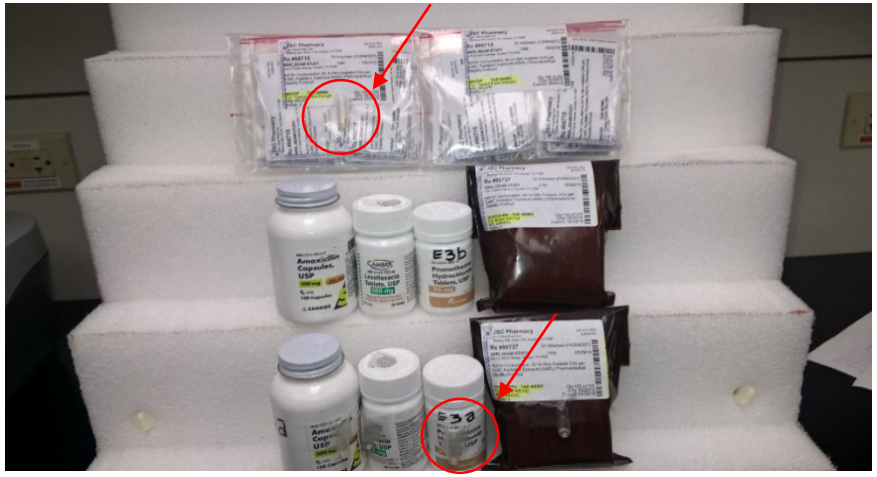


Figure 3.0: Irradiation Dose Measurement_TLD Placement

Image from R. Gaza, "SRAG Radiation Dosimetry Report", June 2018, courtesy of Dr. Tony Slaba, NSRL

Materials and Methods

Drug Stability Analyses: USP monograph Test methods developed for all analyses

- **API chemical content** (Liquid Chromatography: UPLC H-Class System with PDA Detector)
  - Trial runs to validate USP method suitability
  - Assay methods validated using commercial chemical reference standards

- **Presence of impurities or degradation products**
  - Assessment of chromatographic peak percentages
  - Drug formulation component chromatogram overlays

- **Dissolution** testing to determine API release characteristics
  - Hanson Vision Elite 8 dissolution apparatus
  - Ultraviolet–visible (UV / Vis) Spectrophotometer to assist with dissolution assessments

Preliminary Results

➢Irradiation Dose Measurements

- Entrance dose for irradiated drugs at the 500 mGy dose: 422.7 ± 5.7 - 465.3 ± 6.3 mGy
  - a measured dose of 7-15% lower than the expected nominal dose (500 mGy)
- Entrance dose for irradiated drugs at the 1000 mGy dose: 856.8 ± 11.6 - 932.4 ± 12.7 mGy
  - a measured dose of 7-14% lower than the expected nominal dose (1000 mGy)
- A dose-decreasing trend between the front and back TLDs of 7 – 16% was observed for each drug group.

Table C: Summary of TLD-100 Dose Measurement Results

Drug Type	Exposure	TLD-100 Measured Dose (mGy)	TLD-100 Mean Dose (mGy)	TLD-100 Ratio Back/Front	Nominal NSRL Dose (mGy)
Acetaminophen 500mg	A3a_Front	465.3 ± 6.3	448.1 ± 6.1	0.93 ± 0.02	500
	A3a_Back	431.0 ± 5.9			500
	A3b_Back	412.7 ± 5.6	412.7 ± 8.8	N/A	500
Acetaminophen 500mg	A4a_Front	932.4 ± 12.7	899.2 ± 9.8	0.93 ± 0.02	1000
	A4a_Back	866.0 ± 11.8			1000
	A4b_Back	843.9 ± 11.5	843.9 ± 11.5	N/A	1000
Amoxicillin 500mg	B3a_Front	436.2 ± 5.9	400.7 ± 5.5	0.84 ± 0.02	500
	B3a_Back	365.2 ± 5.0			500
	B3b_Back	371.9 ± 5.1	371.9 ± 5.1	N/A	500
Amoxicillin 500mg	B4a_Front	864.4 ± 11.7	804.4 ± 9.0	0.86 ± 0.02	1000
	B4a_Back	744.4 ± 10.1			1000
	B4b_Back	747.0 ± 10.2	747.0 ± 10.2	N/A	1000
Ibuprofen 400mg	C3a_Front	422.7 ± 5.7	405.7 ± 5.5	0.92 ± 0.02	500
	C3a_Back	388.8 ± 5.3			500
	C3b_Back	394.4 ± 5.4	394.4 ± 5.4	N/A	500
Ibuprofen 400mg	C4a_Front	871.5 ± 11.8	822.6 ± 9.2	0.89 ± 0.02	1000
	C4a_Back	773.7 ± 10.5			1000
	C4b_Back	733.3 ± 10.0	733.3 ± 10.0	N/A	1000
Levofloxacin 500mg	D3a_Front	432.0 ± 5.9	412.6 ± 5.6	0.91 ± 0.02	500
	D3a_Back	393.2 ± 5.3			500
	D3b_Back	384.0 ± 5.2	384.0 ± 5.2	N/A	500
Levofloxacin 500mg	D4a_Front	856.8 ± 11.6	855.5 ± 9.0	1.00 ± 0.02	1000
	D4a_Back	854.2 ± 11.6			1000
	D4b_Back	711.0 ± 9.7	711.0 ± 9.7	N/A	1000
Promethazine 25mg	E3a_Front	448.4 ± 6.1	413.8 ± 5.6	0.85 ± 0.02	500
	E3a_Back	379.2 ± 5.2			500
	E3b_Back	400.4 ± 5.4	400.4 ± 5.4	N/A	500
Promethazine 25mg	E4a_Front	923.6 ± 12.6	847.5 ± 9.7	0.84 ± 0.02	1000
	E4a_Back	771.5 ± 10.5			1000
	E4b_Back	769.4 ± 10.5	769.4 ± 10.5	N/A	1000

Note: The TLD measured dose values include the control dose subtraction, no additional corrections needed.

Preliminary Results

API Content Analysis: API content for all irradiated and control study medications tested at time-points (t_1- t_2) met the USP acceptance criteria for potency, or percentage of label claimed API content:

SAMPLE	PRODUCT NAME	STUDY ARM	% LABEL CLAIM API 2018	% LABEL CLAIM API 2019	% CHANGE IN POTENCY (t2-t1 / t1)	% API USP REQUIREMENT	RESULT OUTCOME
A1A	Acetaminophen 500 mg Tablet	Non-Irradiated JSC Control	95.3	103.22	↑8.31	90-110	Pass
A1B	Acetaminophen 500 mg Tablet	Non-Irradiated JSC Control	100.4	101.85	↑1.44	90-110	Pass
A2A	Acetaminophen 500 mg Tablet	Non-Irradiated Travel Control	97.08	102.18	↑5.25	90-110	Pass
A2B	Acetaminophen 500 mg Tablet	Non-Irradiated Travel Control	97.73	102.81	↑5.2	90-110	Pass
A3A	Acetaminophen 500 mg Tablet	Irradiation Group I (Mixed-beam 0.5 GY	100.18	102.45	↑2.27	90-110	Pass
A3B	Acetaminophen 500 mg Tablet	Irradiation Group I (Mixed-beam 0.5 GY	96.51	99.86	↑3.47	90-110	Pass
A4A	Acetaminophen 500 mg Tablet	Irradiation Group II (Mixed-beam 1.0 GY	95.76	102.4	↑6.93	90-110	Pass
A4B	Acetaminophen 500 mg Tablet	Irradiation Group II (Mixed-beam 1.0 GY	103.67	99.32	↓4.2	90-110	Pass

SAMPLE	PRODUCT NAME	STUDY ARM	% LABEL CLAIM API 2018	% LABEL CLAIM API 2019	% CHANGE IN POTENCY (t2-t1) / t1	% API USP REQUIREMENT	RESULT OUTCOME
B1a	Amoxicillin 500 mg Capsules	Non-Irradiated JSC Control	100.16	102.08	↑1.92	90-120	Pass
B1b	Amoxicillin 500 mg Capsules	Non-Irradiated JSC Control	97.44	98.58	↑1.17	90-120	Pass
B2a	Amoxicillin 500 mg Capsules	Non-Irradiated Travel Control	100.96	101.51	↑0.54	90-120	Pass
B2b	Amoxicillin 500 mg Capsules	Non-Irradiated Travel Control	100.04	100.02	↑0.02	90-120	Pass
B3a	Amoxicillin 500 mg Capsules	Irradiation Group I (Mixed-beam 0.5 GY	101.57	99.68	↓1.86	90-120	Pass
B3b	Amoxicillin 500 mg Capsules	Irradiation Group I (Mixed-beam 0.5 GY	99.31	97.11	↓2.25	90-120	Pass
B4a	Amoxicillin 500 mg Capsules	Irradiation Group II (Mixed-beam 1.0 GY	98.74	98.97	↑0.23	90-120	Pass
B4b	Amoxicillin 500 mg Capsules	Irradiation Group II (Mixed-beam 1.0 GY	102.42	93.72	↓8.49	90-120	Pass

SAMPLE	PRODUCT NAME	STUDY ARM	% LABEL CLAIM API 2018	% LABEL CLAIM API 2019	% CHANGE IN POTENCY (t1-t2 / t1)	% API USP REQUIREMENT	RESULT OUTCOME
C1a	Ibuprofen 400 mg Tablets	Non-Irradiated JSC Control	103.85	98.24	↓5.40	90-110	Pass
C1b	Ibuprofen 400 mg Tablets	Non-Irradiated JSC Control	106.6	102.94	↓3.43	90-110	Pass
C2a	Ibuprofen 400 mg Tablets	Non-Irradiated Travel Control	109.32	97.21	↓11.08	90-110	Pass
C2b	Ibuprofen 400 mg Tablets	Non-Irradiated Travel Control	103.84	101.37	↓2.38	90-110	Pass
C3a	Ibuprofen 400 mg Tablets	Irradiation Group I (Mixed-beam 0.5 GY	106.6	96.98	↓9.02	90-110	Pass
C3b	Ibuprofen 400 mg Tablets	Irradiation Group I (Mixed-beam 0.5 GY	109.31	96.96	↓11.3	90-110	Pass
C4a	Ibuprofen 400 mg Tablets	Irradiation Group II (Mixed-beam 1.0 GY	104.38	95.15	↓8.84	90-110	Pass
C4b	Ibuprofen 400 mg Tablets	Irradiation Group II (Mixed-beam 1.0 GY	106.43	95.37	↓10.39	90-110	Pass

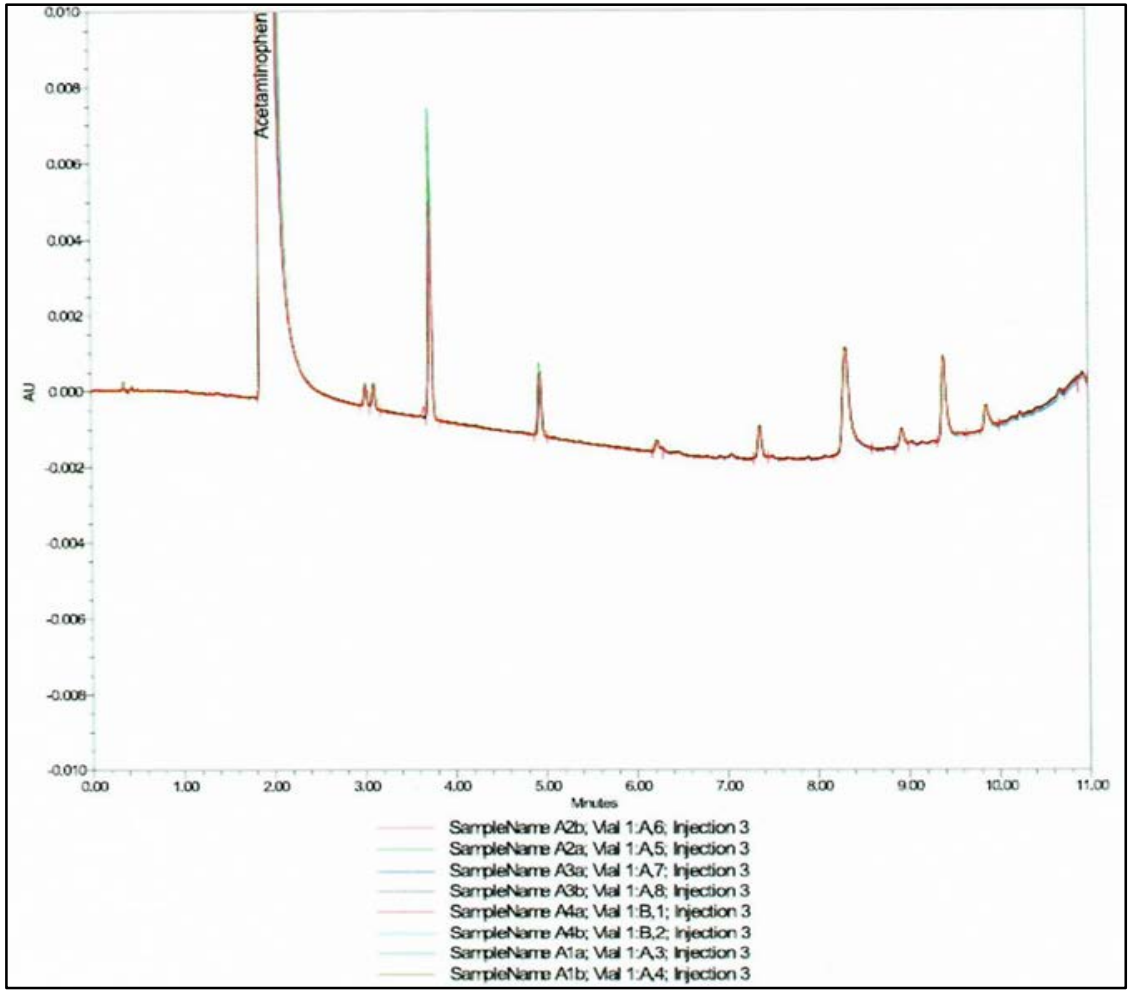
SAMPLE	PRODUCT NAME	STUDY ARM	% LABEL CLAIM API 2018	% LABEL CLAIM API 2019	% CHANGE IN POTENCY (t2-t1 / t1)	% API USP REQUIREMENT	RESULT OUTCOME
E1a	Promethazine 25 mg Tablets	Non-Irradiated JSC Control	99.17	100.2	↑1.04	95-110	Pass
E1b	Promethazine 25 mg Tablets	Non-Irradiated JSC Control	104.66	101.39	↓3.12	95-110	Pass
E2a	Promethazine 25 mg Tablets	Non-Irradiated Travel Control	107.32	100.09	↓6.73	95-110	Pass
E2b	Promethazine 25 mg Tablets	Non-Irradiated Travel Control	104.33	100.68	↓3.49	95-110	Pass
E3a	Promethazine 25 mg Tablets	Irradiation Group I (Mixed-beam 0.5 GY	103	104.02	↑0.99	95-110	Pass
E3b	Promethazine 25 mg Tablets	Irradiation Group I (Mixed-beam 0.5 GY	109.53	101	↓7.79	95-110	Pass
E4a	Promethazine 25 mg Tablets	Irradiation Group II (Mixed-beam 1.0 GY	108.33	102.3	↓5.57	95-110	Pass
E4b	Promethazine 25 mg Tablets	Irradiation Group II (Mixed-beam 1.0 GY	107.3	100.53	↓6.31	95-110	Pass

The specification limit for change in potency usually ≤ 10%. (Waterman KC, Swanson JT, Lippold BL. A scientific and statistical analysis of accelerated aging for pharmaceuticals. Part 1: accuracy of fitting methods. J Pharm Sci 2014 Oct;103(10):3000-6).

Preliminary Results

Drug Stability Analyses: Assessment of drug component chromatograms at $t_1 - t_2$ revealed no new or foreign peaks in any of the irradiated drug product samples

Acetaminophen



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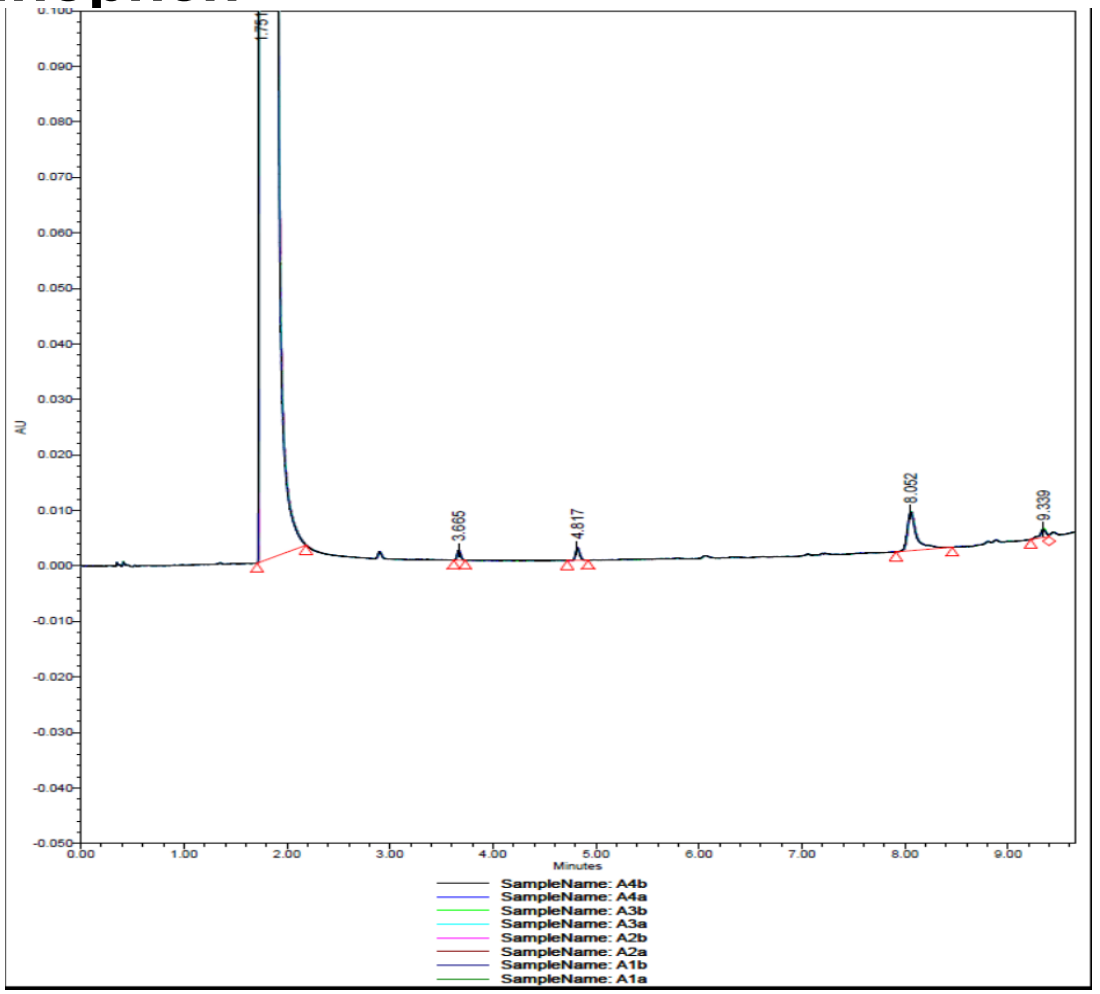
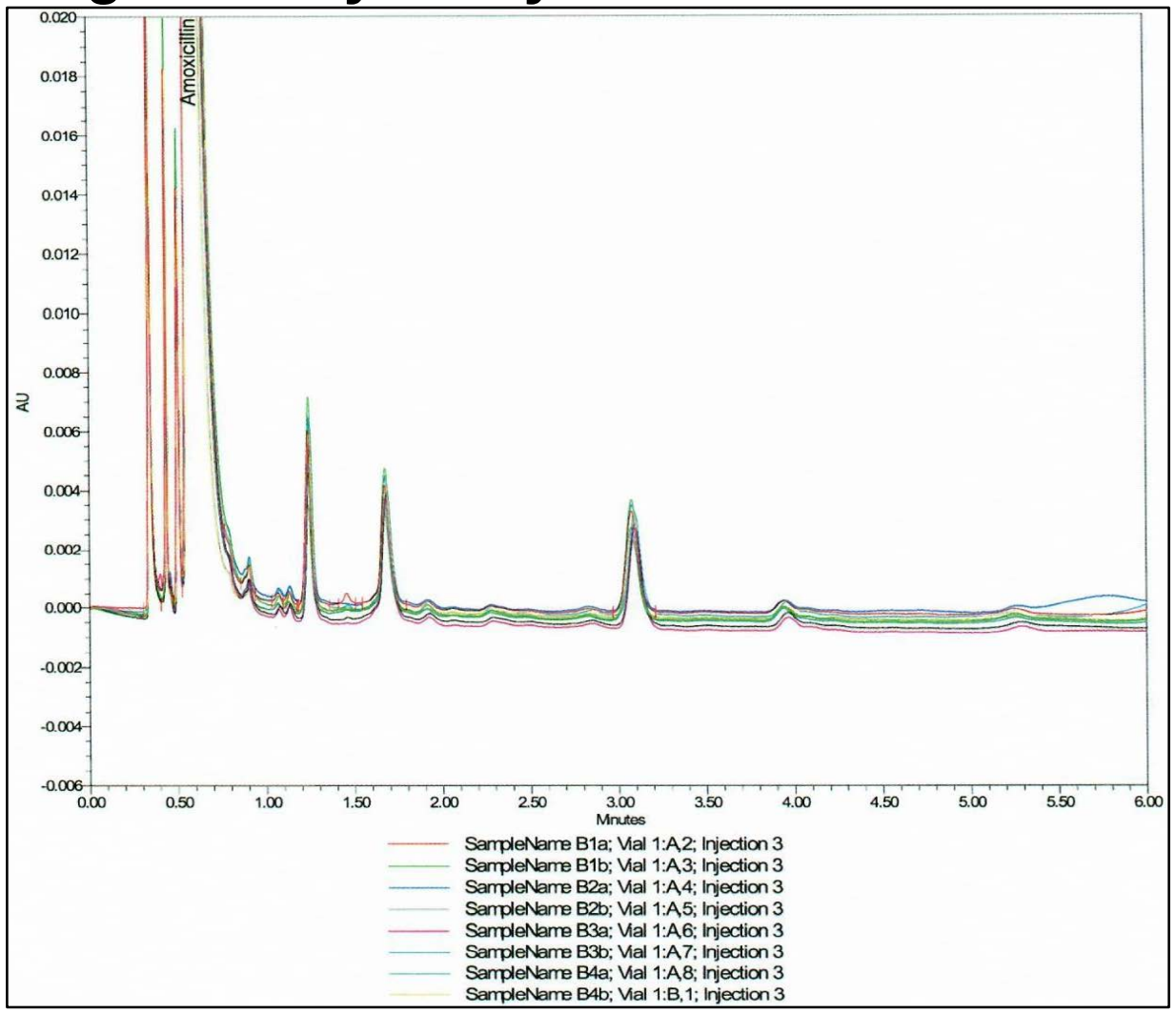


2019

Preliminary Results

Drug Stability Analyses Continued: Amoxicillin



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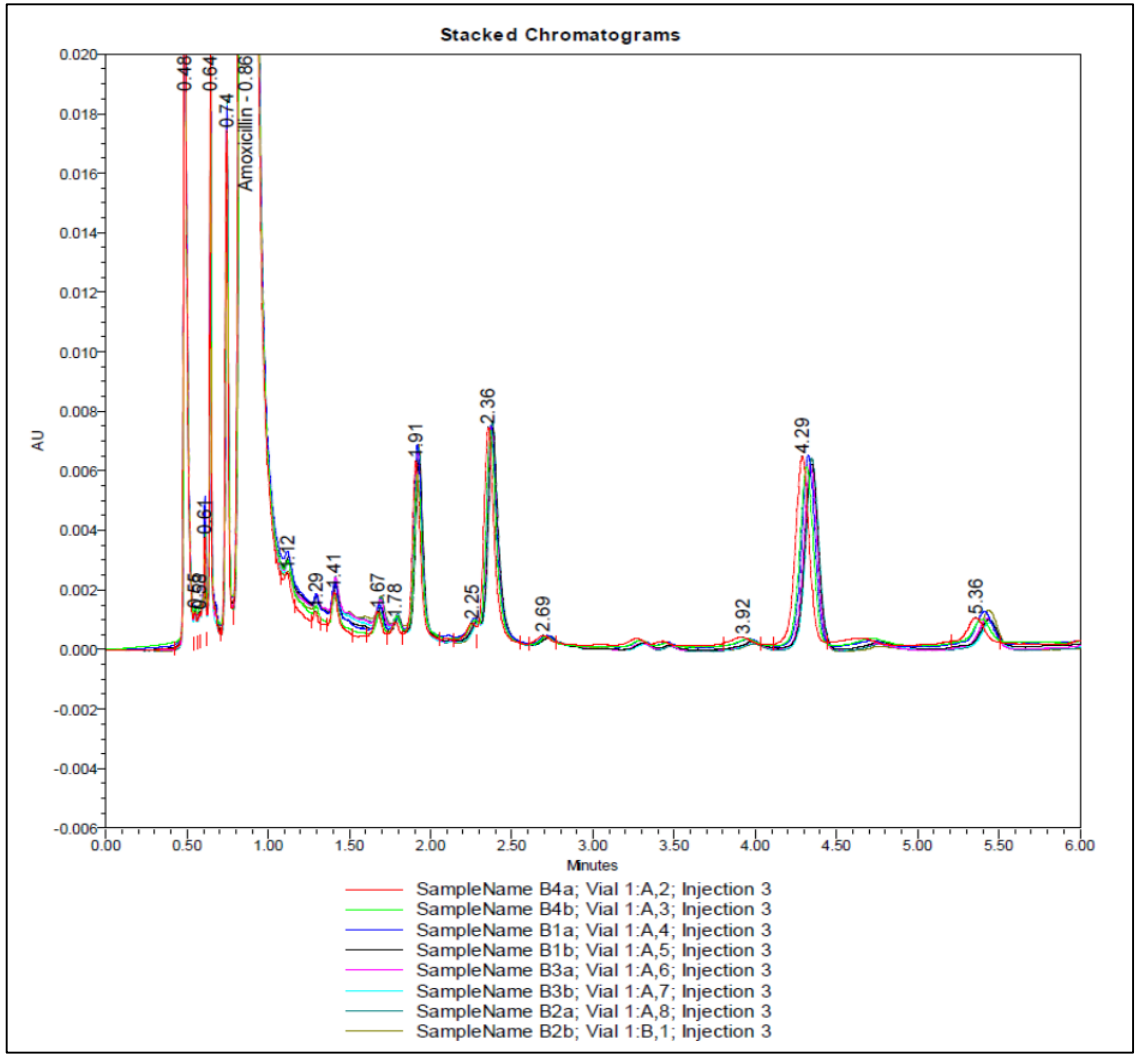
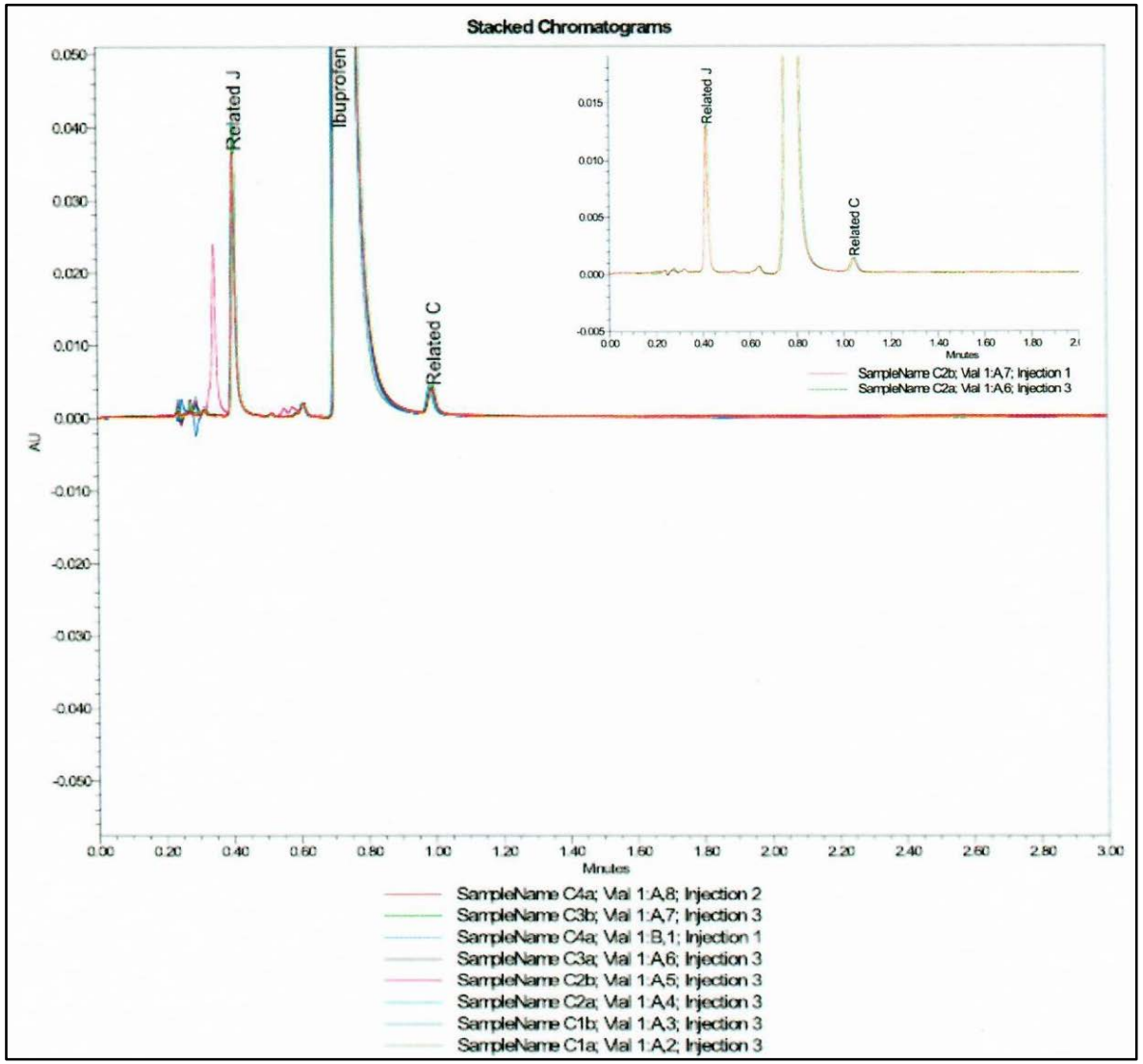


2019

Preliminary Results

Drug Stability Analyses Continued: Ibuprofen



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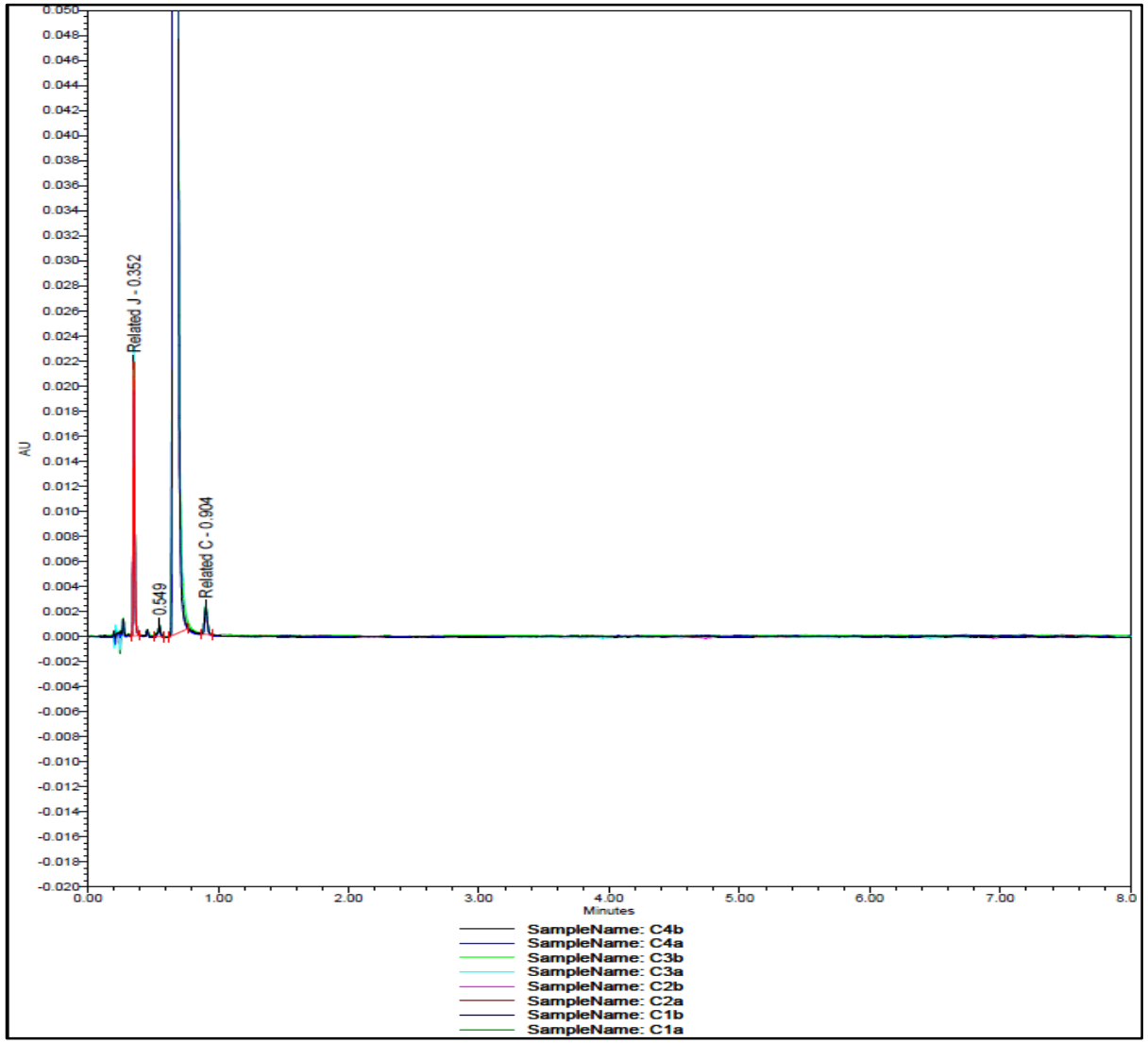
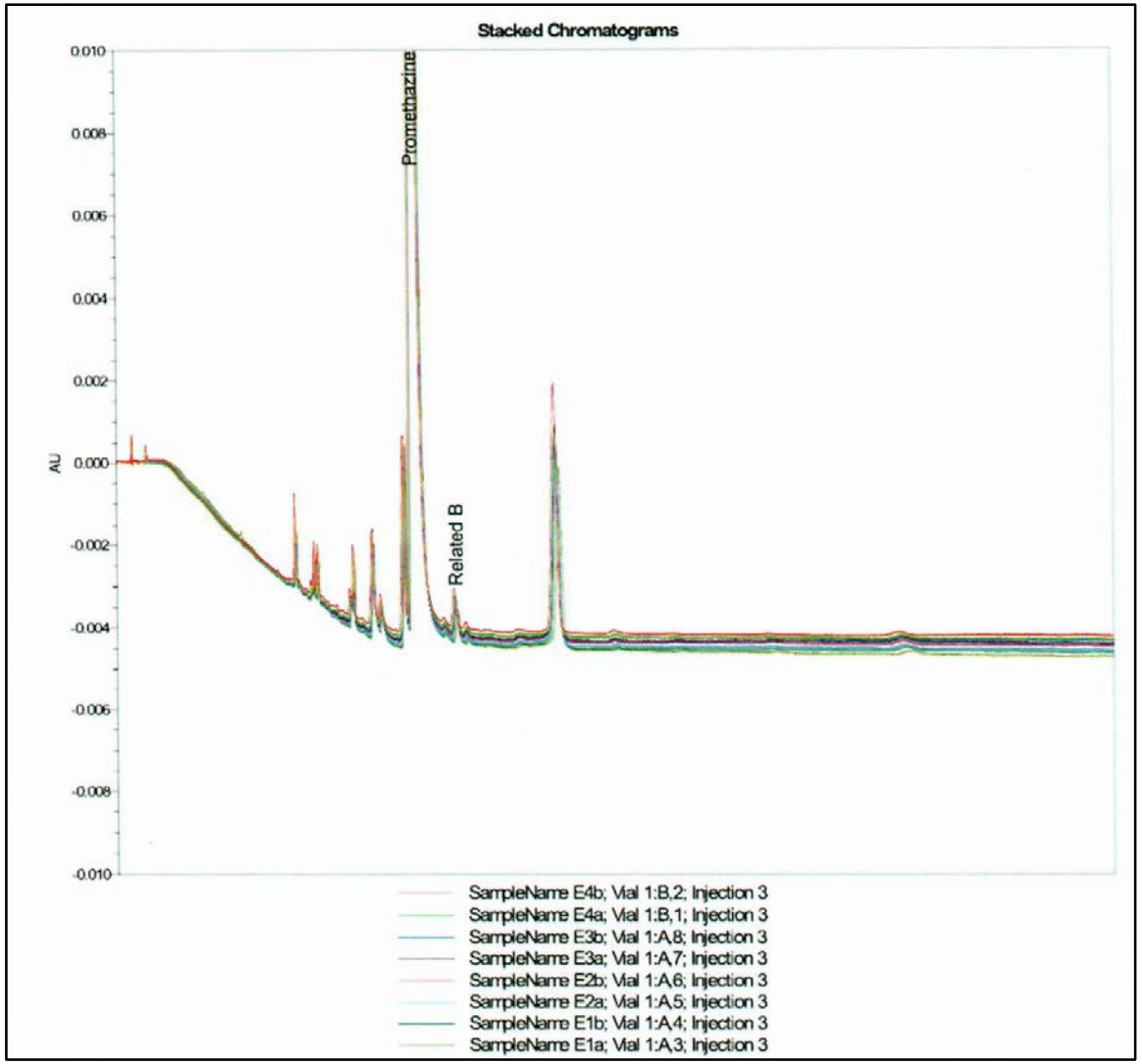


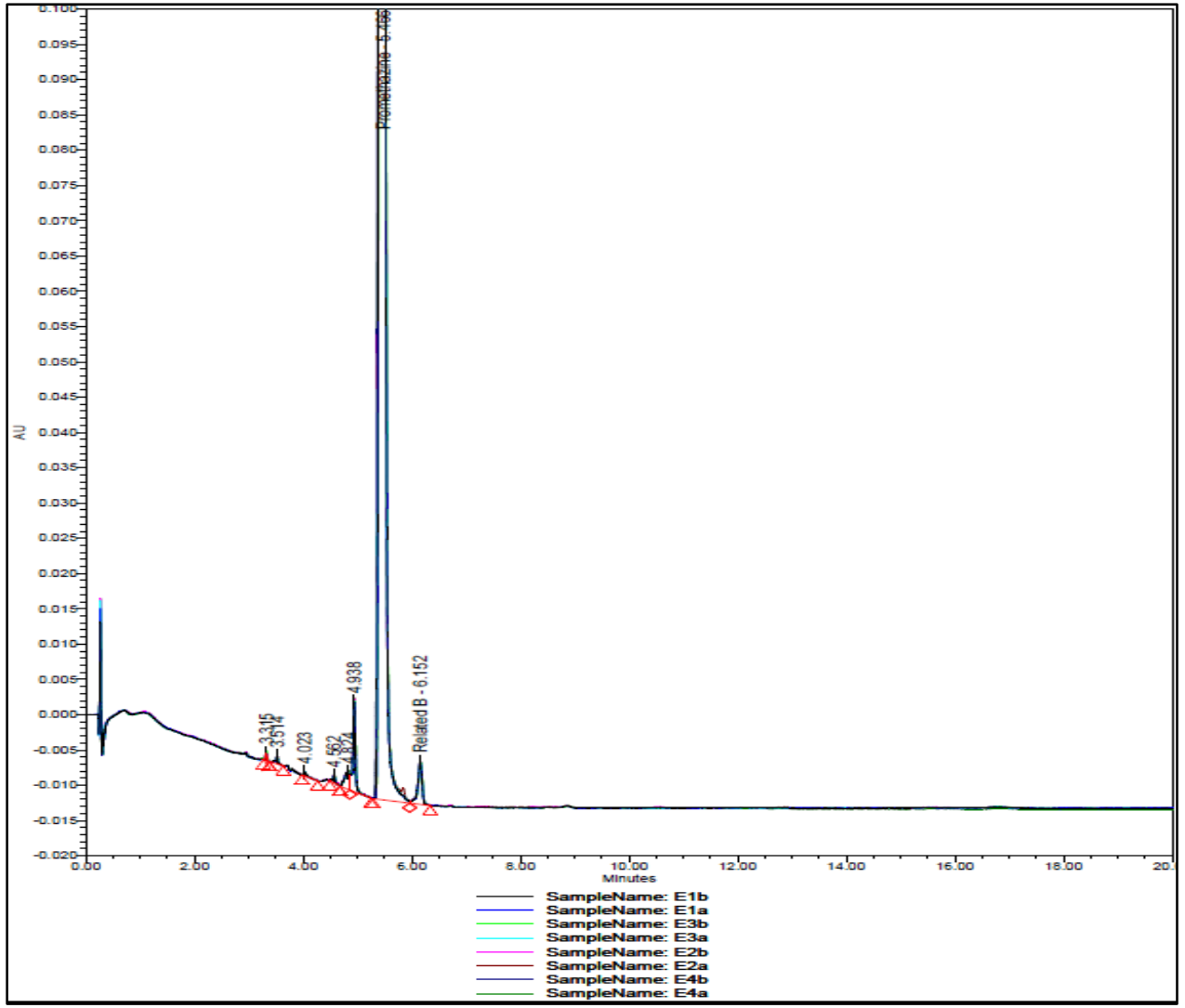
2019

Preliminary Results

Drug Stability Analyses Continued: Promethazine



2018



2019

Preliminary Results

Dissolution: All samples met the USP requirement for Dissolution.

- Some amoxicillin samples revealed "significant changes" in release between t_1 and t_2

Acetaminophen:

Sample	Product Name	Sample Name	% Dissolved 2018	2018 Standard Deviation (n=6)	% Dissolved 2019	2019 Standard Deviation (n=6)	% Change in Dissolution	USP Standard (≥ 80%)
A1a	Acetaminophen 500 mg Tablets	Non-irradiated JSC Control Group	99.51	1.10%	102.54	1.07%	3.04	Pass
A1b	Acetaminophen 500 mg Tablets	Non-irradiated JSC Control Group	100.71	3.56%	100.4	1.24%	0.31	Pass
A2a	Acetaminophen 500 mg Tablets	Non-irradiated Traveling Control Group	100.12	2.95%	101.09	1.49%	0.97	Pass
A2b	Acetaminophen 500 mg Tablets	Non-irradiated Traveling Control Group	100.77	4.48%	99.47	2.08%	1.29	Pass
A3a	Acetaminophen 500 mg Tablets	Irradiation Group I (Mixed-beam 0.5Gy	102.75	4.01%	100.49	1.67%	2.2	Pass
A3b	Acetaminophen 500 mg Tablets	Irradiation Group I (Mixed-beam 0.5Gy	100.85	2.19%	101.19	0.86%	0.34	Pass
A4a	Acetaminophen 500 mg Tablets	Irradiation Group II (Mixed-beam 1.0Gy	99.51	2.81%	100.43	1.56%	0.92	Pass
A4b	Acetaminophen 500 mg Tablets	Irradiation Group II (Mixed-beam 1.0Gy	95.45	4.47%	100.74	2.08%	5.54	Pass

Amoxicillin:

Sample	Product Name	Sample Name	% Dissolved 2018	2018 Standard Deviation (n=6)	% Dissolved 2019	2019 Standard Deviation (n=6)	% Change in Dissolution	USP Standard (≥ 80%)
B1a	Amoxicillin 500 mg Capsules	Non-irradiated JSC Control Group	100.16	5.78%	93.43	2.12%	↓6.72	Pass
B1b	Amoxicillin 500 mg Capsules	Non-irradiated JSC Control Group	97.44	5.06%	92.18	4.53%	↓5.4	Pass
B2a	Amoxicillin 500 mg Capsules	Non-irradiated Traveling Control Group	100.96	4.63%	89.69	3.16%	↓11.16	Pass
B2b	Amoxicillin 500 mg Capsules	Non-irradiated Traveling Control Group	100.04	4.70%	92.80	1.65%	↓7.24	Pass
B3a	Amoxicillin 500 mg Capsules	Irradiation Group I (Mixed-beam 0.5Gy Total	101.57	6.17%	91.25	3.89%	↓10.16	Pass
B3b	Amoxicillin 500 mg Capsules	Irradiation Group I (Mixed-beam 0.5Gy Total	99.31	5.46%	91.05	5.43%	↓8.32	Pass
B4a	Amoxicillin 500 mg Capsules	Irradiation Group II (Mixed-beam 1.0 Gy Total	98.74	4.53%	86.13	2.77%	↓12.78	Pass
B4b	Amoxicillin 500 mg Capsules	Irradiation Group II (Mixed-beam 1.0 Gy Total	102.42	2.49%	88.59	5.18%	↓13.5	Pass

Preliminary Results

Drug Stability Analyses Continued:

Ibuprofen:

Sample	Product Name	Sample Name	2018% Dissolved	2018 Standard Deviation (n=6)	2019% Dissolved	2019Standard Deviation (n=6)	% Change in Dissolution	USP Standard (≥ 80%)
C1a	Ibuprofen 400 mg Tablets	Non-irradiated JSC Control Group	100.64	1.32%	98.23	0.20%	↓2.39	Pass
C1b	Ibuprofen 400 mg Tablets	Non-irradiated JSC Control Group	100.97	0.95%	98.17	0.16%	↓2.77	Pass
C2a	Ibuprofen 400 mg Tablets	Non-irradiated Traveling Control Group	100.38	1.52%	98.11	0.00%	↓2.26	Pass
C2b	Ibuprofen 400 mg Tablets	Non-irradiated Traveling Control Group	100.58	2.39%	98.55	0.38%	↓2.02	Pass
C3a	Ibuprofen 400 mg Tablets	Irradiation Group I (Mixed-beam 0.5Gy	100.49	1.92%	98.74	0.40%	↓1.74	Pass
C3b	Ibuprofen 400 mg Tablets	Irradiation Group I (Mixed-beam 0.5Gy	100.59	3.26%	98.86	0.42%	↓1.72	Pass
C4a	Ibuprofen 400 mg Tablets	Irradiation Group II (Mixed-beam 1.0 Gy	100.53	1.36%	98.99	0.71%	↓1.53	Pass
C4b	Ibuprofen 400 mg Tablets	Irradiation Group II (Mixed-beam 1.0 Gy	100	2.66%	99.05	0.86%	↓0.95	Pass

Promethazine:

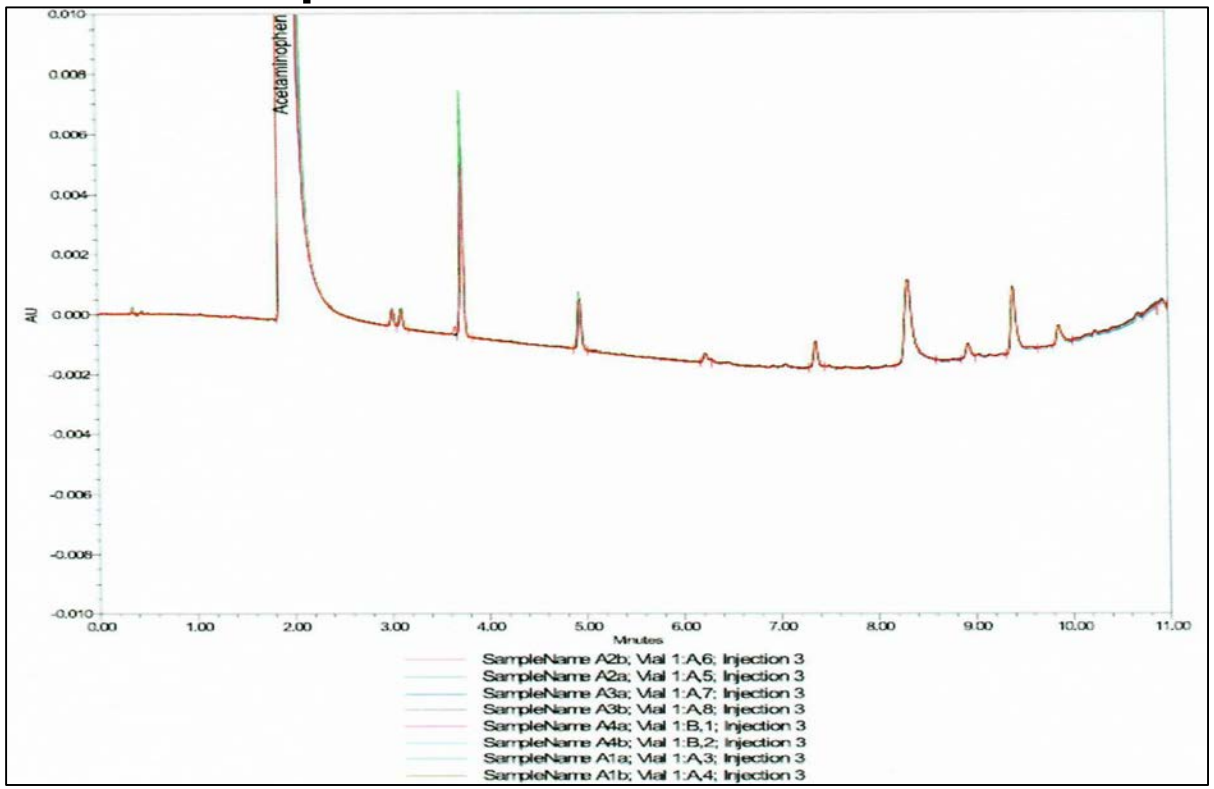
Sample	Product Name	Sample Name	2018 % Dissolved	2018 Standard Deviation (N=6)	2019 % Dissolved	2019 Standard Deviation (N=6)	% Change in Dissolution	USP Standard (≥ 80%)
E1a	Promethazine 25 mg Tablets	Non-irradiated JSC Control Group	98.48	0.92%	103.46	0.53%	↑5.05	Pass
E1b	Promethazine 25 mg Tablets	Non-irradiated JSC Control Group	98.38	0.58%	103.95	0.68%	↑5.66	Pass
E2a	Promethazine 25 mg Tablets	Non-irradiated Traveling Control Group	98.21	2.13%	102.94	0.46%	↑4.82	Pass
E2b	Promethazine 25 mg Tablets	Non-irradiated Traveling Control Group	98.69	1.35%	103.93	0.36%	↑5.31	Pass
E3a	Promethazine 25 mg Tablets	Irradiation Group I (Mixed-beam 0.5Gy Total	98.12	1.69%	103.90	0.32%	↑5.89	Pass
E3b	Promethazine 25 mg Tablets	Irradiation Group I (Mixed-beam 0.5Gy Total	98.58	0.80%	104.03	0.59%	↑5.53	Pass
E4a	Promethazine 25 mg Tablets	Irradiation Group II (Mixed-beam 1.0 Gy Total	98.41	1.47%	103.50	0.51%	↑5.17	Pass
E4b	Promethazine 25 mg Tablets	Irradiation Group II (Mixed-beam 1.0 Gy Total	98.48	0.62%	103.46	0.53%	↑5.05	Pass

Preliminary Results

Drug Degradation Products / Impurities:

- Impurities peak percent calculations, and overlay chromatograms revealed no foreign or new peaks in any of the irradiated samples during the first two time-point analyses.

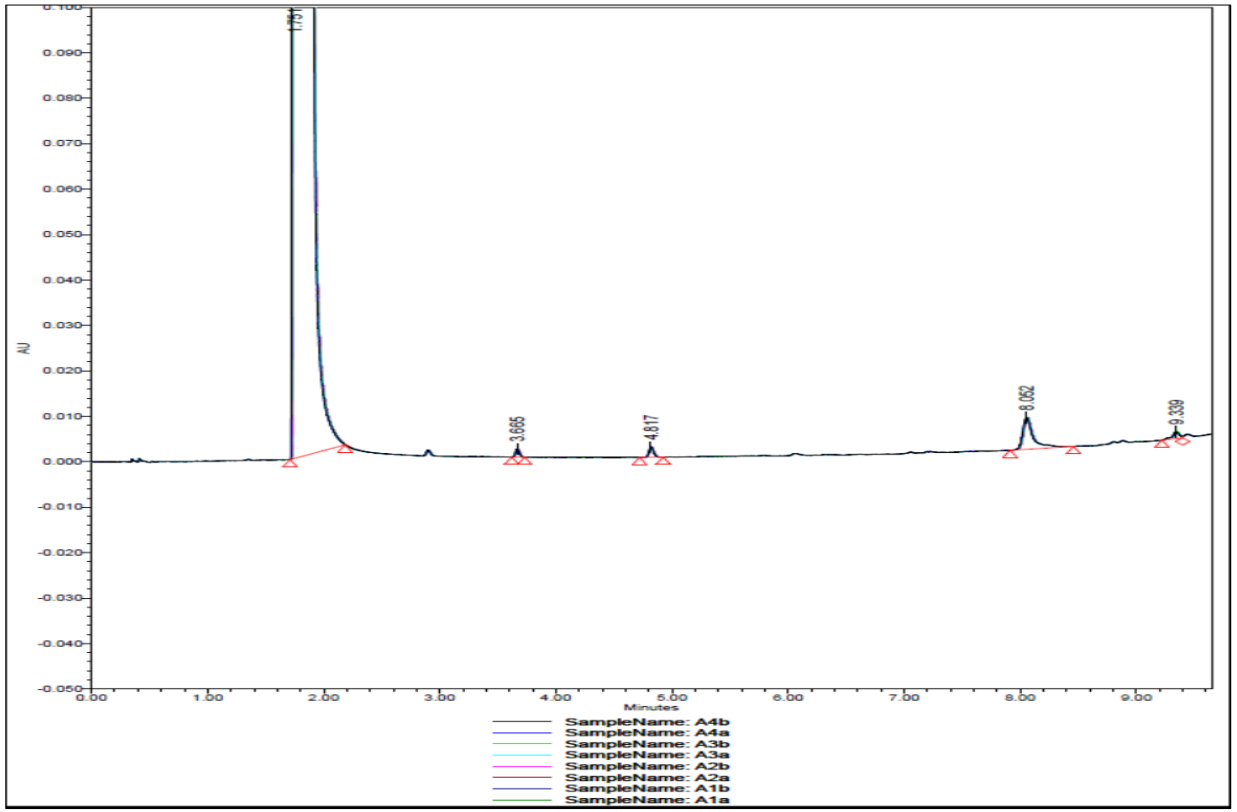
Acetaminophen: **2018**



Degradation Peak#	Retention time	A1a	A1b	A2a	A2b	A3a	A3b	A4a	A4b	Standard Deviation
1	P-Aminophenol	ND	ND	ND	ND	ND	ND	ND	ND	--
2	3.738	0.11	0.12	0.15	0.11	0.11	0.12	0.1	0.130	0.016
3	4.946	0.03	0.03	0.04	0.03	0.03	0.03	0.03	0.04	0.005
4	7.369	0.02	0.02	0.02	0.02	0.02	0.03	0.02	0.03	0.005
5	8.32	0.15	0.15	0.15	0.15	0.14	0.15	0.15	0.13	0.007
6	8.935	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.000
7	9.4	0.07	0.07	0.07	0.07	0.07	0.07	0.07	0.07	0.000
8	9.872	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.000

ND = "Not Detected"

2019

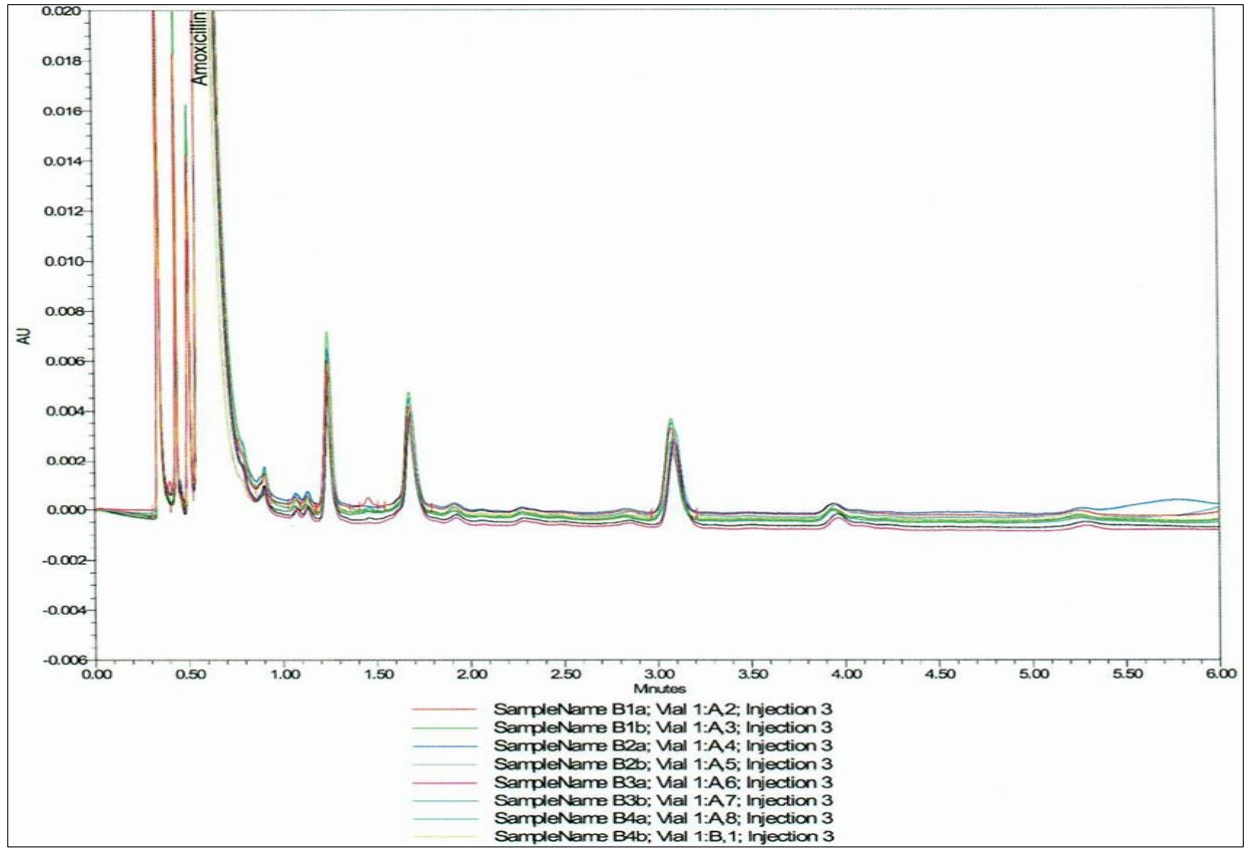


Degradation Peak#	Retention time	A1a	A1b	A2a	A2b	A3a	A3b	A4a	A4b	Standard Deviation
1	P-Aminophenol	ND	ND	ND	ND	ND	ND	ND	ND	--
2	3.665	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.00
3	4.817	0.02	0.03	0.03	0.025	0.02	0.02	0.02	0.02	0.0045
4	6.241	ND	ND	ND	ND	ND	0.01	ND	0.01	0.000
5	8.052	0.163	0.16	0.166	0.163	0.166	0.163	0.16	0.163	0.0052
6	9.339	0.02	0.02	0.02	0.02	0.023	0.023	0.02	0.02	0.0015

Preliminary Results

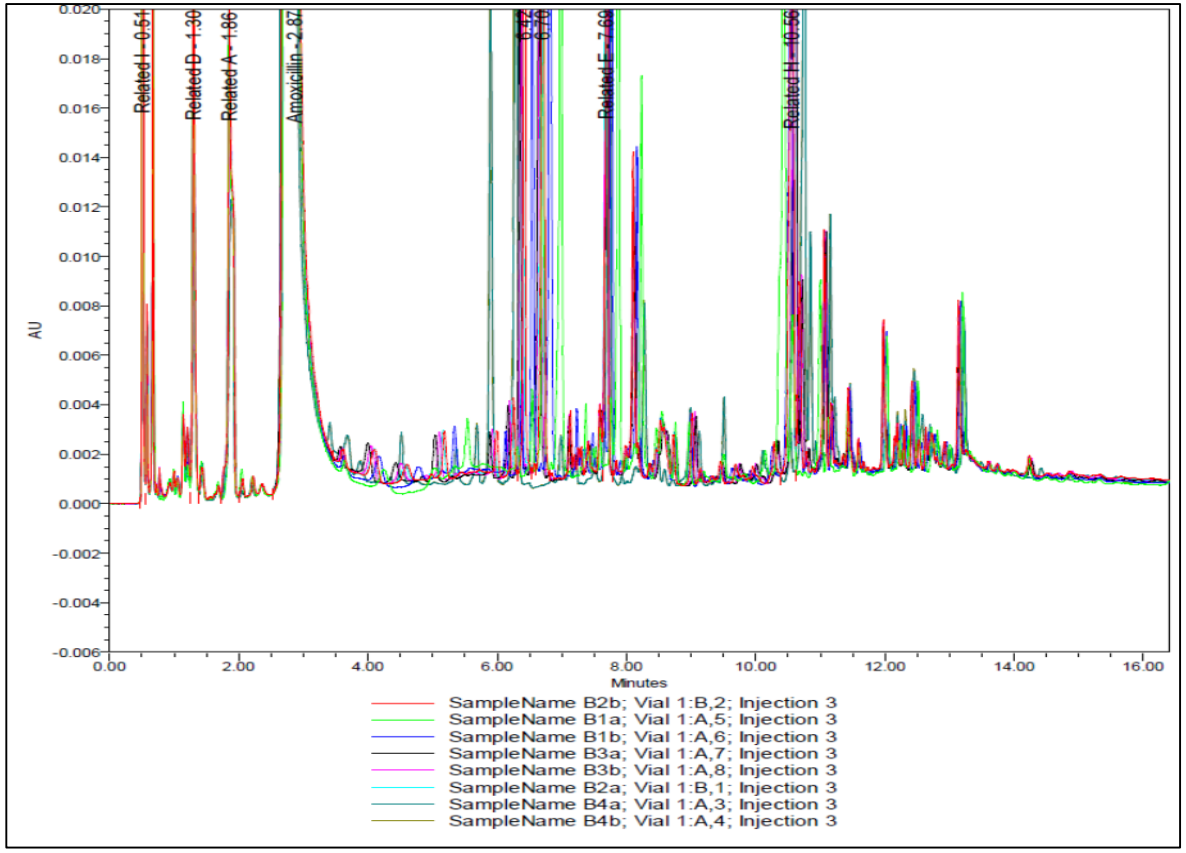
Drug Degradation Products / Impurities :

Amoxicillin: 2018



Degradation Peak#	Retention Time (Avg.)	B1a	B1b	B2a	B2b	B3a	B3b	B4a	B4b	Standard Deviation
Related I	0.52	0.5	0.48	0.49	0.49	0.46	0.47	0.42	0.45	0.32
Related D	1.322	0.22	0.23	0.22	0.23	0.26	0.24	0.34	0.26	0.040
Related A	1.945	0.44	0.45	0.44	0.45	0.49	0.47	0.61	0.48	0.056
Related B	2.26	ND	ND	ND	ND	ND	ND	ND	ND	--
Related E	7.592	0.48	0.49	0.48	0.48	0.51	0.49	0.6	0.49	0.041
Related G	8.139	0.11	0.12	0.12	0.11	0.13	0.13	0.17	0.13	0.019
Related C	9.167	0.04	0.04	0.04	0.04	0.05	0.05	0.08	0.05	0.014
Related H	10.708	0.69	0.71	0.7	0.69	0.76	0.72	0.98	0.72	0.097
Dimer	11.899	0.07	0.08	0.06	0.08	0.09	0.08	0.12	0.09	0.018

2019

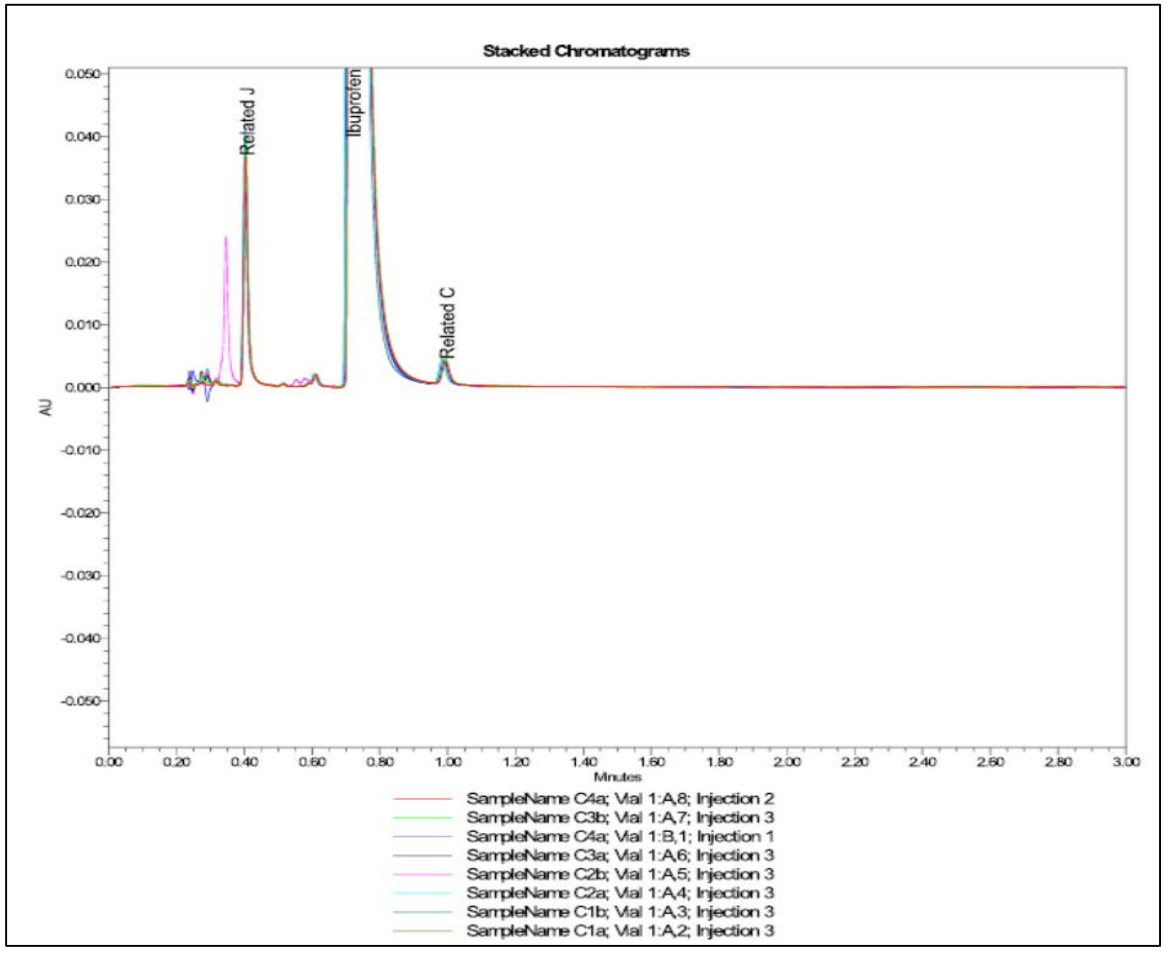


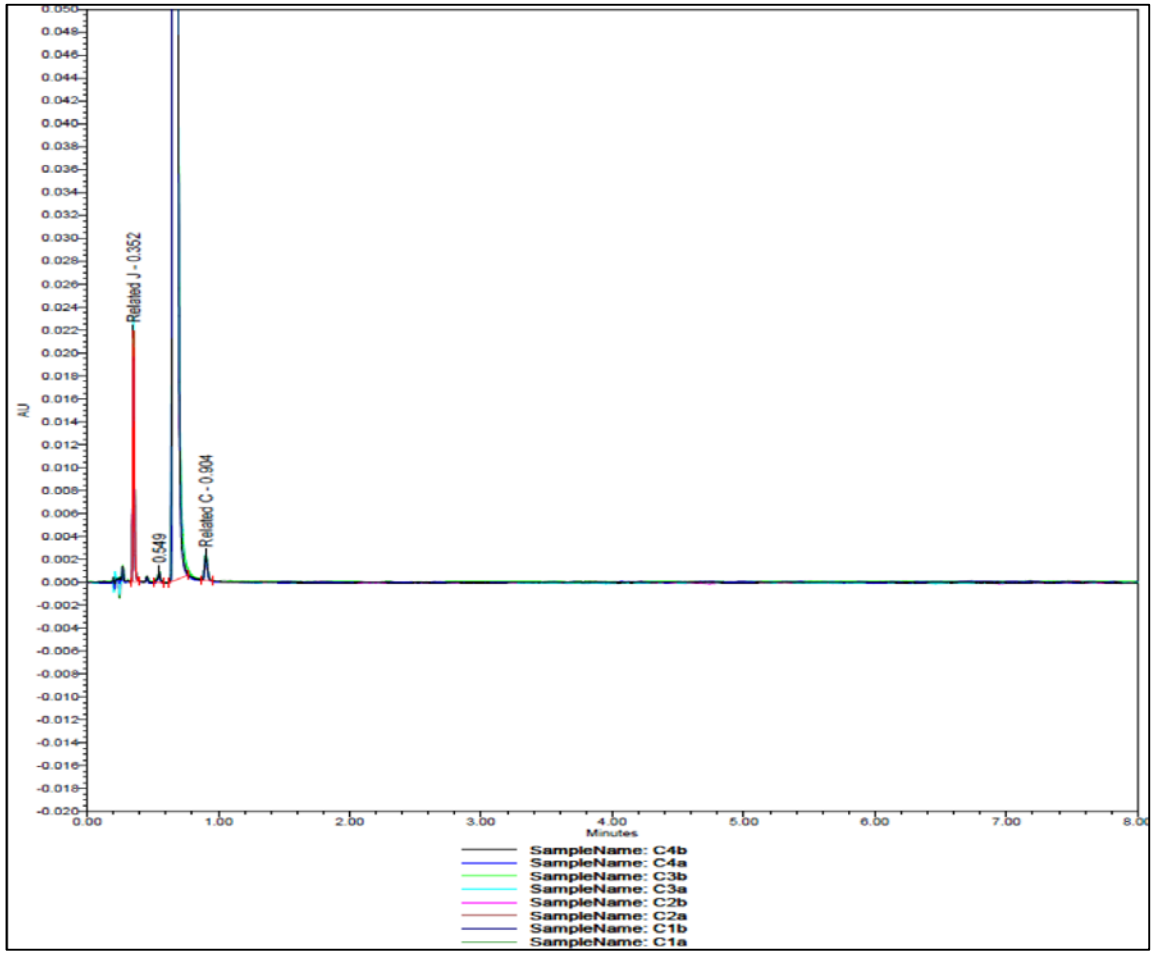
Degradation Peak#	Retention Time (Average)	B1a	B1b	B2a	B2b	B3a	B3b	B4a	B4b	Standard Deviation
Related I	0.504	0.46	0.47	0.46	0.46	0.46	0.47	0.51	0.51	0.022
Related D	1.322	0.32	0.33	0.29	0.29	0.28	0.28	ND	ND	0.020
Related A	1.945	0.42	0.43	0.42	0.42	0.41	0.43	0.38	0.43	0.016
Related B	2.26	ND	ND	ND	ND	ND	ND	ND	ND	--
Related E	7.782	0.59	0.61	0.60	0.59	0.59	0.59	0.72	0.72	0.084
Related G	8.139	ND	ND	ND	ND	ND	ND	ND	ND	-
Related C	9.3	ND	ND	ND	ND	ND	ND	ND	ND	-
Related H	10.567	0.59	0.62	0.61	0.61	0.63	0.62	0.69	0.68	0.036
Dimer	11.899	ND	ND	ND	ND	ND	ND	ND	ND	-

Preliminary Results

Drug Stability Analyses Continued: Drug Degradation Products / Impurities

Ibuprofen: **2018** **2019**





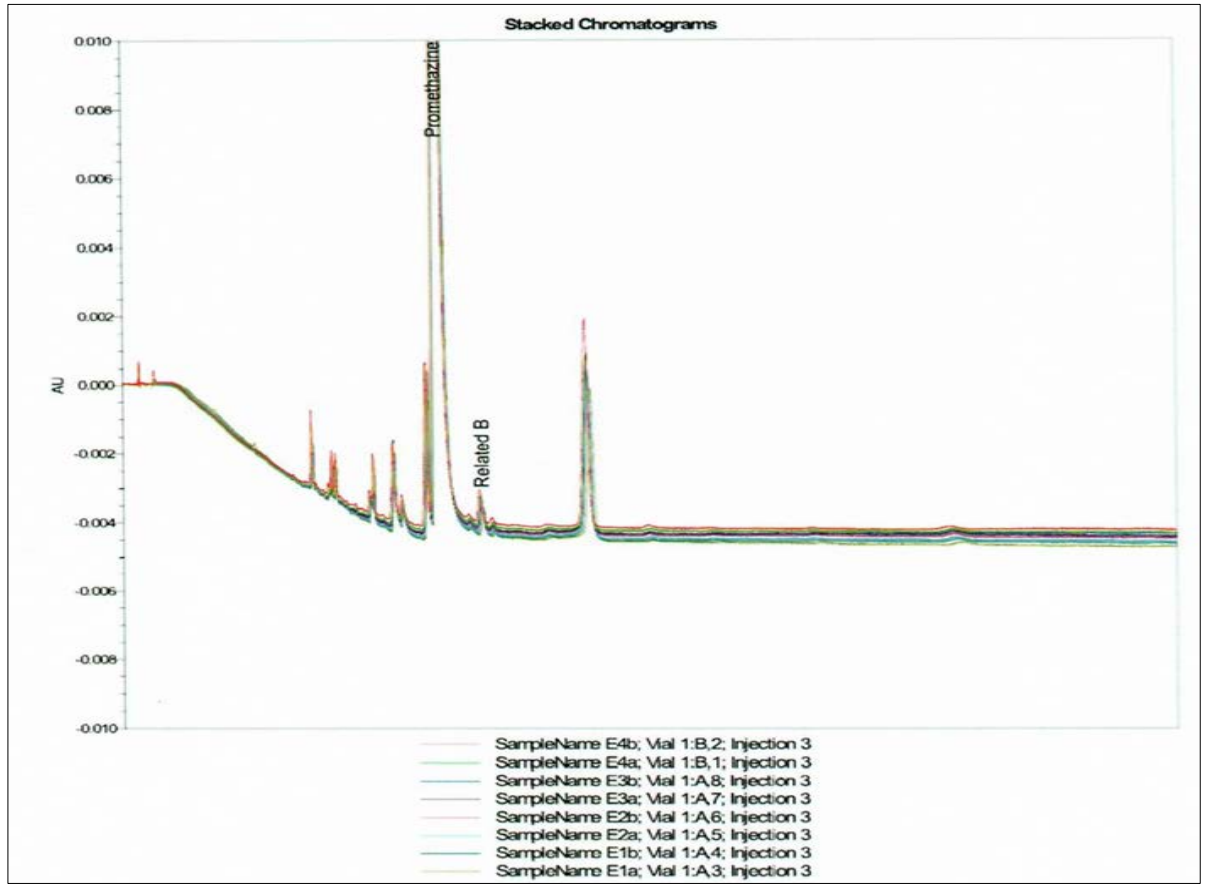
Degradation Peak#	Retention Time (min)	C1a	C1b	C2a	C2b	C3a	C3b	C4a	C4b	Standard Deviation
1	ND	ND	ND	ND	ND	0.86	ND	ND	ND	ND
Related J	0.41	1.55	1.54	1.57	1.51	1.57	1.57	1.55	1.57	0.034
3	0.622	0.17	0.13	0.16	0.12	0.15	0.23	0.14	0.17	0.279
Related C	1.011	0.22	0.27	0.25	0.27	0.26	0.27	0.26	0.25	0.021

Degradation Peak#	Retention Time (min)	C1a	C1b	C2a	C2b	C3a	C3b	C4a	C4b	Standard Deviation
Related J	0.351	1.79	1.77	1.82	1.78	1.71	1.77	1.81	1.76	0.034775
3	0.548	0.12	0.115	0.125	0.12	0.11	0.11	0.12	0.12	0.0047
Related C	0.902	0.29	0.34	0.35	0.35	0.33	0.33	0.34	0.33	0.0191

Preliminary Results

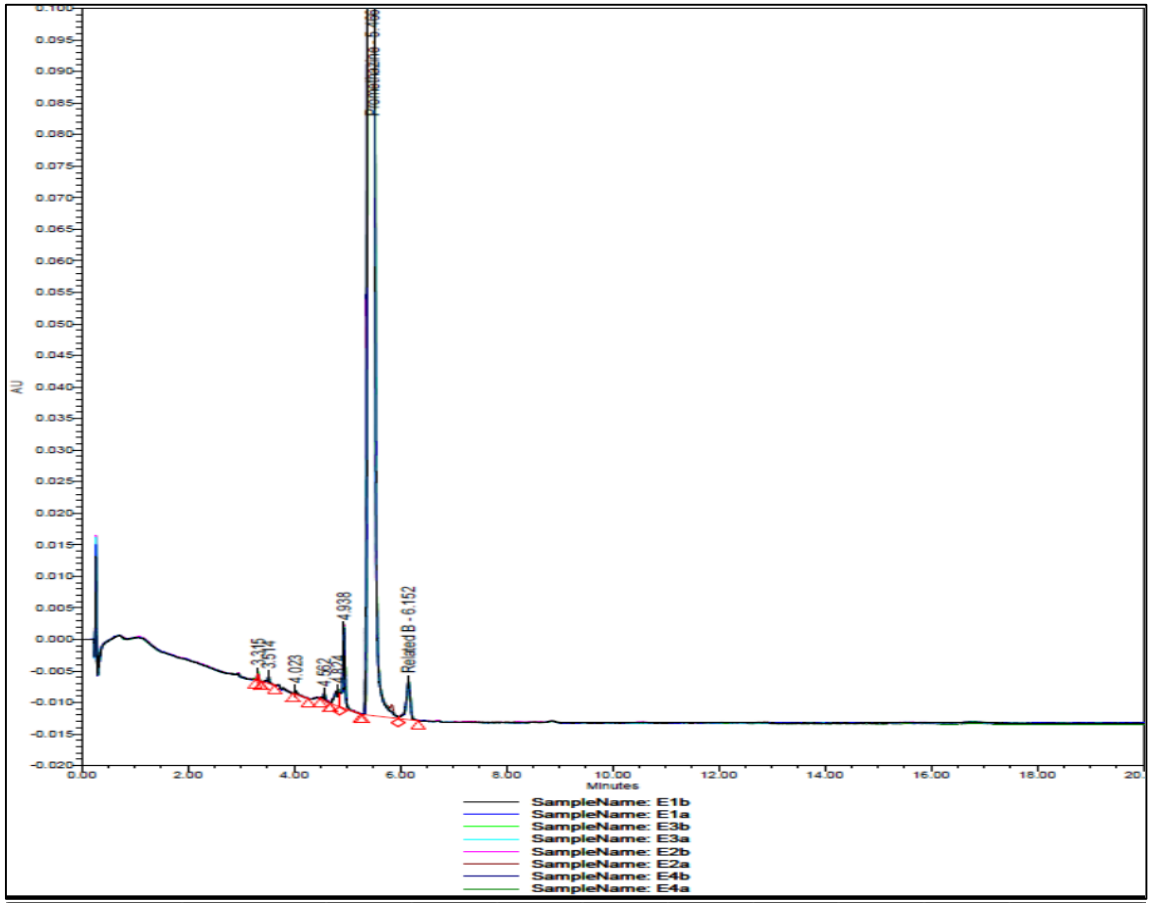
Drug Stability Analyses Continued: Drug Degradation Products / Impurities

Promethazine: 2018



Degradation Peak#	Peak Retention Time (min)	E1a	E1b	E2a	E2b	E3a	E3b	E4a	E4b	Standard Deviation
1	1.71	0.08	0.03	ND	ND	ND	ND	ND	ND	0.035
2	3.577	0.21	0.19	0.2	0.18	0.15	0.15	0.19	0.22	0.026
3	3.651	0.05	0.05	0.06	0.05	0.03	0.06	0.07	0.05	0.012
4	3.956	0.12	0.03	0.14	0.03	0.12	0.16	0.11	0.19	0.057
5	4.026	0.02	0.12	0.03	0.13	ND	0.03	0.06	0.04	0.045
6	4.734	0.04	0.04	0.04	0.04	0.06	0.05	0.05	0.06	0.009
7	5.115	0.11	0.09	0.09	0.08	0.07	0.08	0.2	0.09	0.042
8	5.274	0.1	0.1	0.1	0.1	0.1	0.09	0.11	0.03	0.025
Related B	6.77	0.21	0.21	0.2	0.21	0.2	0.21	0.21	0.22	0.006
11	8.791	0.18	0.2	0.2	0.19	0.18	0.17	0.21	0.23	0.019
12	10.003	0.02	0.02	ND	0.03	0.03	ND	ND	ND	0.006

2019



Degradation Peak#	Peak Retention Time (min)	E1a	E1b	E2a	E2b	E3a	E3b	E4a	E4b	Standard Deviation
1	3.318	0.02	0.02	0.02	0.2	0.02	0.02	0.04	0.02	0.063
2	3.516	0.03	0.03	0.03	0.3	0.03	0.03	0.1	0.03	0.095
3	4.029	0.02	0.02	0.02	0.01	0.02	0.02	0.03	0.02	0.005
4	4.571	0.03	0.03	0.02	0.025	0.02	0.02	0.16	0.02	0.048
5	4.818	0.12	0.12	0.11	0.11	0.11	0.11	0.236	0.12	0.043
6	4.945	0.33	0.32	0.33	0.33	0.33	0.33	0.566	0.32	0.085
Related B	6.142	0.45	0.45	0.45	0.45	0.45	0.45	0.48	0.45	0.01

Preliminary Conclusions

- Results revealed that the simulated GCR exposure did not facilitate non-characteristic degradation two years post radiation exposure.
  - Two study drugs (Amoxicillin, Ibuprofen) approached labeled expiration dates, **none** had expired prior to t_2 stability testing (09/16/19).
  - “Lag-time” degradation is characteristic of some solid dosage forms.
- Uncertainties regarding the extent and rate of drug degradation for the tested medications may be further clarified by t_3 testing.
- The observed results from t_1 and t_2 drug stability analyses, concur with those from previous JSC stability studies:
  - Differences in API potency between spaceflight and ground-controlled drug samples(Du et al, 2011)
  - Differences in API potency between irradiated and non-irradiated control drug samples simulated single-beam radiation ground-analog studies (Putcha et al, 2006).

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- NASA Shipping and Receiving
- ExMC Clinical & Science Team Lead
- KBR Human Health and Performance Contracts
  - Logistics Team
  - Task Order Management Teams

Backup Slides

Introduction

- **Pharmaceutical "Drug" Stability:** The chemical and physical integrity of a drug dosage unit, or finished pharmaceutical product (FPP).
  - Drug stability testing evaluates how drug quality varies as a function of time and storage conditions (e.g., temperature, humidity, radiation)
  - FDA Monographs for all approved drugs are in the United States Pharmacopeia (USP); which includes acceptance criteria for the API (ICH Q1A R2, "Stability Testing of New Drug Substances")
    - Failure to meet the acceptance criteria for **potency, presence of degradation products, and dissolution** is considered a "significant change" for an FPP
  - Chromatographic methods provide quantitative and qualitative analysis of drug substances
    - The most common chromatographic method for stability studies uses HPLC with UV detection
  - A dissolution or API release test measures the extent and rate of solution formation from a solid (e.g. tablet, capsule) or semi-solid (e.g. cream, ointment) FPP
    - Changes in API release from a FPP can influence bioavailability and therapeutic effectiveness

Introduction

- **Photostability** refers to how a drug compound responds to radiation exposure…..(Glass et al., 2004)
  - Exposure to high-intensity electromagnetic radiation may cause significant **loss of the API**, and initiate formation of **degradation** products (M Jamrógiewicz, 2016)
  - Drug photodecomposition can lead to:
    - Loss of API **potency** which could lead to a **reduction in therapeutic activity**
    - Degradation product contamination leading to **adverse drug experiences** (van Henegouwen, 1997; Moan, 1996; Kullavanijaya and Lim, 2005)

Materials and Methods

Study Design: Four Experimental Arms

1. Non-irradiated JSC Control Group
2. Non-irradiated Traveling Control Group
3. Irradiation Group I (Mixed-beam 0.5Gy Total Dose)
4. Irradiation Group II (Mixed-beam 1.0Gy Total Dose)

Environmental Monitoring

- **Temperature / RH:**
  - Shipment / Storage: USP <659> "Packaging and Storage Requirements" defined conditions for "controlled room temperature" (15 - 30˚ C, 30 - 65% RH)
    - Courier tracking: Sensitech Temp Tale®4 temperature tracker
    - Project tracking: HOBO U12-012 environmental tracking device
    - JSC storage: Environmental chambers (Darwin, Model KB0303-AA-DA, Sanyo, model MLR-350H
    - Analytical vendor storage: Caron Environmental Chamber, Model 7000-10
- **Radiation:**
  - Detection and Monitoring: Thermoluminescence Dosimeters (TLD-100 LiF:Mg,Ti)
    - TLDs enclosed in clear gelatin capsules (Lilly, No. 0, NDC 00002240702); and attached to front and / or back, of each drug product package

Materials and Methods

- **Dissolution** testing to determine API release characteristics
  - Hanson Vision Elite 8 dissolution apparatus
  - Ultraviolet–visible (UV / Vis) Spectrophotometer to assist with dissolution assessments
    - UV/Vis refers to absorption spectroscopy or reflectance spectroscopy in part of the ultraviolet and the full, adjacent visible spectral regions. Direct **UV/VIS** spectrophotometric determination of absorbance has been the traditional analytical method for **dissolution testing**

Preliminary Results

Environmental Control:

- Transport / Storage temperatures / RH on average remained within USP limits for “controlled room temperature” throughout the experimental timeline.
  - Temperatures: 18.9°C – 28.8°C
  - RH: 4% - 79% (transport from JSC to analytical vendor only)
    - Only brief excursions (< 24 hours) above RH upper and lower limits
- Irradiation Dose Measurements
  - Entrance dose for irradiated drugs at the 0.5 Gy dose: 422.7 ± 5.7 - 465.3 ± 6.3 mGy
    - a measured dose of 7-15% lower than the expected nominal dose (500 mGy)
  - Entrance dose for irradiated drugs at the 1.0 Gy dose: 856.8 ± 11.6 - 932.4 ± 12.7 mGy,
    - a measured dose of 7-14% lower than the expected nominal dose (1000 mGy)
  - A dose-decreasing trend between the front and back TLDs of 7 – 16% was observed for each drug group.