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

Human Research Program
Exploration Medical Capability Element

February 7, 2022

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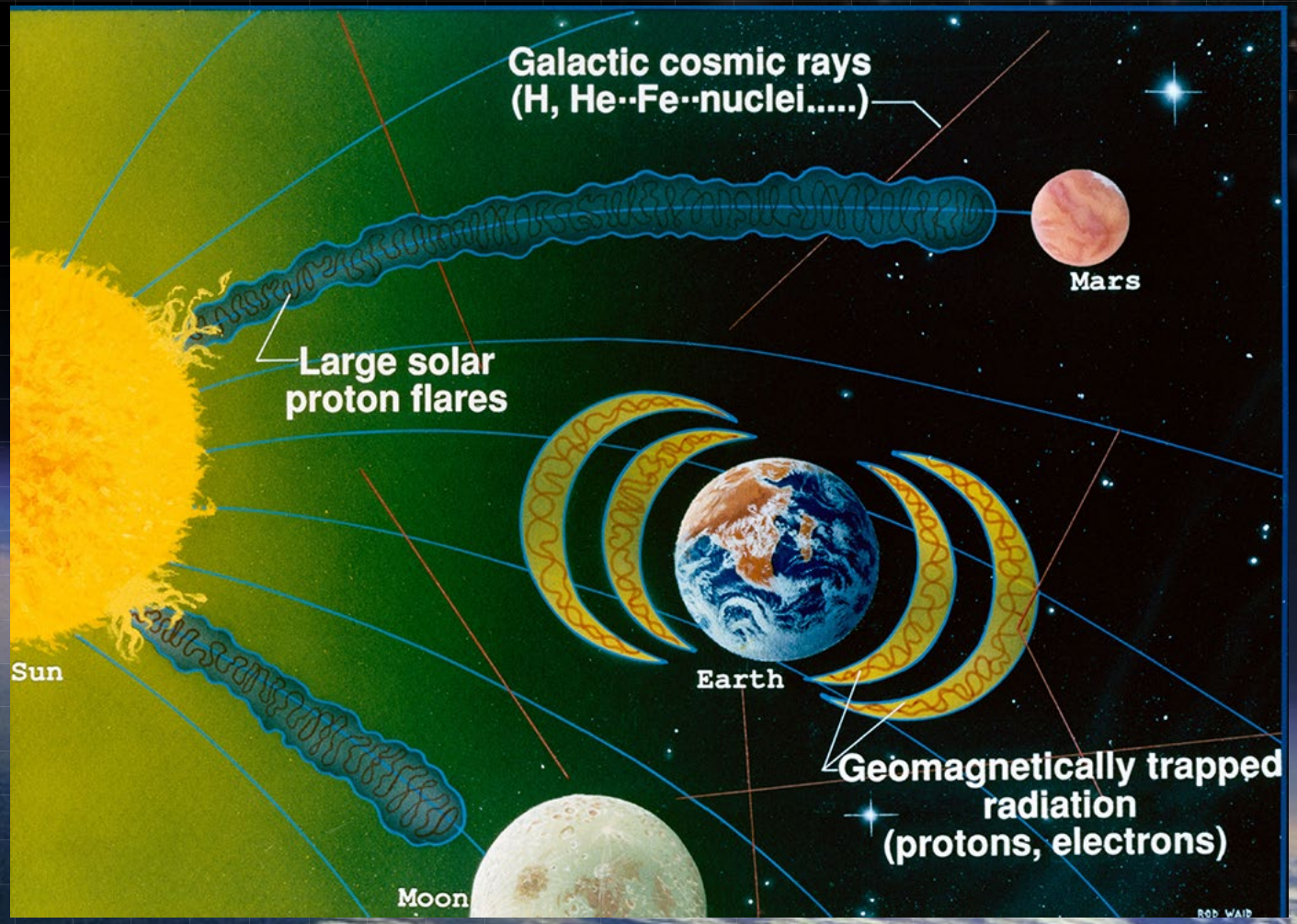
"Expanding the Boundaries of Space Medicine and Technology"

Presentation Outline

- Background & Research Objectives
- Materials and Methods
- Results
- Discussions
- Conclusion
- Limitations and Forward Work

The Problem



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- Currently, the magnetosphere shields Earth from solar particle events (SPEs) and radiation caused by the sun and galactic cosmic rays (GCRs) produced by supernova fragments.
- Ionizing radiation, like GCR, can move through substances and alter them as it passes through.
- If the atoms within space - e.g., spacecraft, crew member, or pharmaceuticals - are ionized upon collision with GCR particles, they may be irreversibly altered.

Study Background

- **Uncertainty remains regarding space radiation impacts on drug stability and shelf life. Radiation exposure to consumables is expected to increase with long duration exploration missions.**

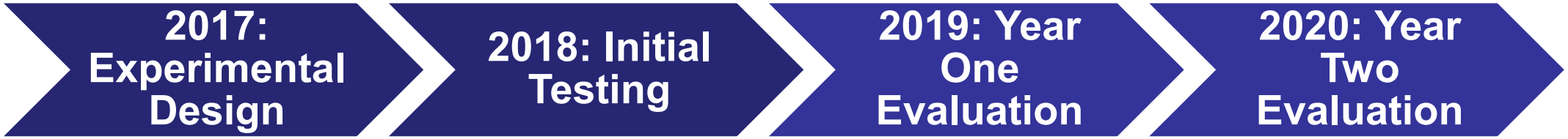
- **Space environmental analog and ground-based targeted radiation research could reveal valuable insight into drug safety and effectiveness.**

  ✪ Capability Shift: In 2018, the NASA Space Radiation Laboratory (NSRL) at Brookhaven National Laboratory (BNL) was commissioned to simulate the shielded radiation environment encountered by an astronaut within a typical exploration vehicle using mixed-species beam exposures.

Research Objectives

- Evaluate if ground-based rapid-switching radiation beam exposures can effectively reproduce previously observed effects of spaceflight on drug stability and shelf life.
- Evaluate the utility of simulated GCR single beam exposures as an effective ground-based analog for predicting GCR impacts on drug stability and shelf life during spaceflight.

High Level Plan:



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 Identifier	Drug
A	*Acetaminophen 500 mg Tablets (APAP)
B	+Amoxicillin 500 mg Capsules (AMOX)
C	*Ibuprofen 400mg Tablets (IBU)
E	+Promethazine 25mg Tablets (PMZ)

*Repackaged; +Manufacturer Packaging

  - 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 & Methods: Irradiation Logistics

Irradiation:

- The *first* experiment at NSRL to utilize the Mixed-Species Simulator
- Exposure Dose: Two mixed-beam radiation doses supported by rapid-switching beam technology
  - 0.5Gy
  - 1.0Gy
- GCR-like beam profile:
  - ^{1}H, ^{4}He, ^{12}C, ^{16}O, ^{28}Si, ^{48}Ti, and ^{56}Fe
- Dosimeters enclosed in clear gelatin capsules and attached to front and / or back, of each drug product package, to provide estimation of irradiation dose received.

Irradiation Dose Measurement TLD Placement

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

Materials and Methods: Chemical Analyses*

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

- **API chemical content analysis using USP methods (UPLC H-Class System with PDA Detector)**
  - Trial runs to validate USP method suitability
  - Assay methods validated using commercial reference standards
- **Presence of formulation impurities or degradation products verification**
  - Assessment of chromatographic peak percentages
  - Generation of drug formulation component chromatogram overlays
- **Dissolution testing to determine API release characteristics**
  - UV / Vis Spectrophotometer to assist with dissolution assessments

Method development and analysis completed by third-party vendor

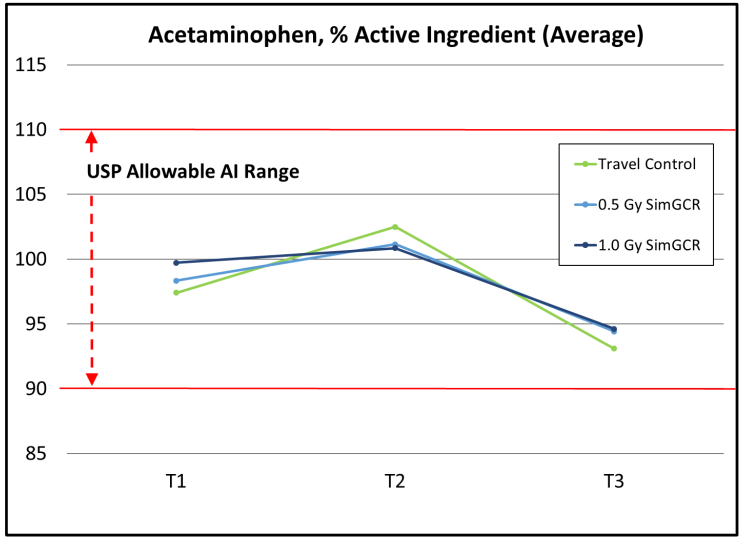
Materials and Methods: Summary

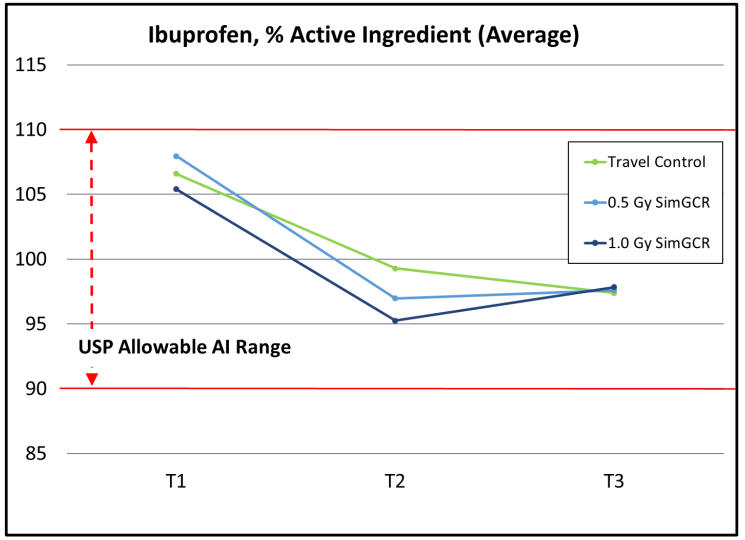
Actual Execution: 2017: Experimental Design → 2018: Initial Testing → 2019: Year One Evaluation → 2020: COVID Delays → 2021: Year Three Evaluation

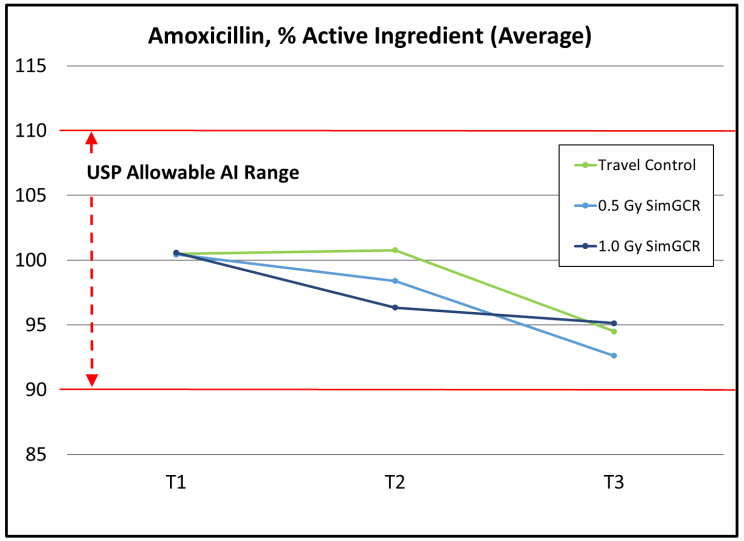
JSC CONTROL	Procured and repackaged (if necessary)	Shipped to Lab Vendor			Testing: Initial (T1), Year 1 (T2), Year 3 (T3)	Intermediate Storage: Environmental Chambers
TRAVEL CONTROL	Procured and repackaged (if necessary)	Shipped to NSRL	No treatment	Shipped to Lab Vendor	Testing: Initial (T1), Year 1 (T2), Year 3 (T3)	Intermediate Storage: Environmental Chambers
Irradiated Group 1	Procured and repackaged (if necessary)	Shipped to NSRL	Single dose of **0.5 Gy**	Shipped to Lab Vendor	Testing: Initial (T1), Year 1 (T2), Year 3 (T3)	Intermediate Storage: Environmental Chambers
Irradiated Group 2	Procured and repackaged (if necessary)	Shipped to NSRL	Single dose of **1.0 Gy**	Shipped to Lab Vendor	Testing: Initial (T1), Year 1 (T2), Year 3 (T3)	Intermediate Storage: Environmental Chambers

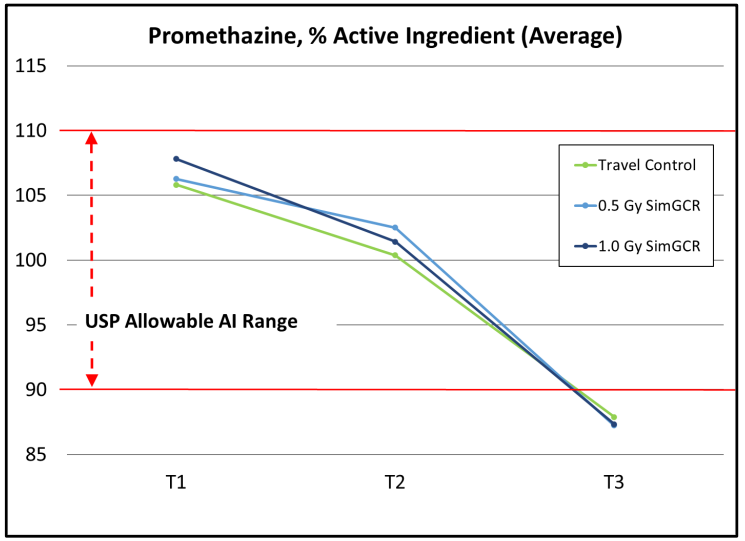
Results: API Content

- **All APAP and IBU samples met USP potency requirements:**
  - **APAP** control / irradiated API content:
  - 93 – 104%
  - **IBU** control and irradiated API content:
  - 95 – 109%
- **Most AMOX samples met USP potency requirements:**
  - T1 - T3 control API content: 94 – 102%
  - T1 – T3* irradiated API content: 90* – 102%, one replicate with API = 89.97
- **T3 PMZ samples failed to meet the USP potency requirements:**
  - T1–T2 control / irradiated API content:
  - 99 – 109%
  - T3 control / irradiated API content: 87 – 89%









Results: Dissolution and Impurities

➢Dissolution (API Release):

❖Some samples revealed changes in release between the two time-points

- No demonstrated change in APAP or IBU
- Apparent change consistent throughout all study conditions in PMZ
- Variable apparent change in AMOX with the greatest change in Irradiation Group II
- No third time-point dissolution analyses due to insufficient drug sample.

➢Impurities:

❖Chromatogram assessments for all study drugs, at all 3 timepoints revealed **no new or foreign peaks** in any of the irradiated drug samples.

Discussion

- **Evidence suggests the simulated GCR exposure did not precipitate non-characteristic degradation, following three years post-radiation exposure.**
  - ❖Although all 4 medications expired prior to T3:
    - All control and irradiated APAP and IBU met USP potency requirements
    - All control and 3 of 4 irradiated T3 samples of AMOX met USP potency requirements
  - ❖"Lag-time" degradation behavior consistent with some solid dosage forms observed in acetaminophen (APAP).
    - Little or no degradation during the initial phase of the degradation pathway (lag-time degradation behavior); followed by degrading at a rapid rate (Conners et al, 1986; Lakka, NS and Kuppan, C, 2019)

Concurrence with Stability Literature

APAP and IBU have robust drug stability profiles associated with chemical and formulation characteristics.

- Phenol ring makes APAP chemically stable and hard to degrade (Xu et al. 2018)
- FDA SLEP confirmed APAP potency 24 months beyond labeled expiration date (Lyons et al. 2006)
- APAP was one of eight medications confirmed as potent (99.7%) 28-40 years beyond expiration (Cantrel et al. 2012)
- No differences in dissolution, hardness and API potency were observed for acetaminophen tablets exposed to x-ray irradiation at 0.34 mGy, 0.1, 0.5, 300 Gy doses (Uehara et al. 2020)
- The Amneal Pharmaceuticals brand of IBU 400 mg tablets used in this BNL study is film coated.
  - Tablet film coating can protect product APIs from light, oxidation, and moisture leading to increased product stability (Seo et al. 2020)

Concurrence with Stability Literature

AMOX remains potent for more than a year post labeled expiration (19.5 months in this study).

- No loss of potency following 10.0 Mrad dose of gamma irradiation (Kabir et al. 2006)
- FDA SLEP confirmed AMOX potency 21-23 months beyond labeled expiration date (Lyons et al. 2006)

Concurrence with Stability Literature

Degradation of PMZ samples suggests a chemical or structural predisposition to degradation.

- Phenothiazines include vulnerable planar heterocyclic ring system (Smarandache et al. 2015)
- PMZ is a chiral compound, highly sensitive to oxidative, hydrolytic, and photolytic degradation (Saad et al. 2016; Takale et al. 2021)
  - Over 40 years of demonstrated oxidation of selected phenothiazines (e.g. PMZ) during analytical sample preparation (Campbel et al. 2018; Kojlo et al. 2001; Karpinska et al. 1996; Pankratov et al. 1993)

Concurrence with Drug Radiation Studies

The potency observations of this study concur with previous JSC spaceflight and beam irradiation drug stability studies:

- Sustained potency for APAP, IBU
  - (BCM Irradiation Study, L. Putcha et al. 2006), (NSRL Simulation Radiation Study, L. Putcha et al. 2006), (Wotring, 2016), (Du et al. 2011), (Cory et al., ExMC Report, Reference ID: 0923-000193, 2016)
- Declining potency for AMOX with radiation and time
  - (Du et al. 2011)
- Potency below USP thresholds for PMZ
  - (BCM Irradiation Study, L. Putcha et al. 2006), (NSRL Simulation Radiation Study, L. Putcha et al. 2006), (Du et al. 2011)

Inconclusive State

This study does not provide adequate evidence to support that the simulated GCR radiation had any effect on stability of the active ingredients, dissolution, or impurities of the 4 study drugs. The simulated GCR did not introduce any degradation effects in the 4 study drugs that were not evidenced in prior radiation or stability experiments. Because of the lack of comparable data from the actual space environment, it cannot be determined if there are no radiation effects on drug stability *or* if the analog is not reflective of space radiation.

Consequently, it is still unknown if space radiation will cause degradation in pharmaceutical products in a space mission beyond low Earth orbit.

Study Limitations

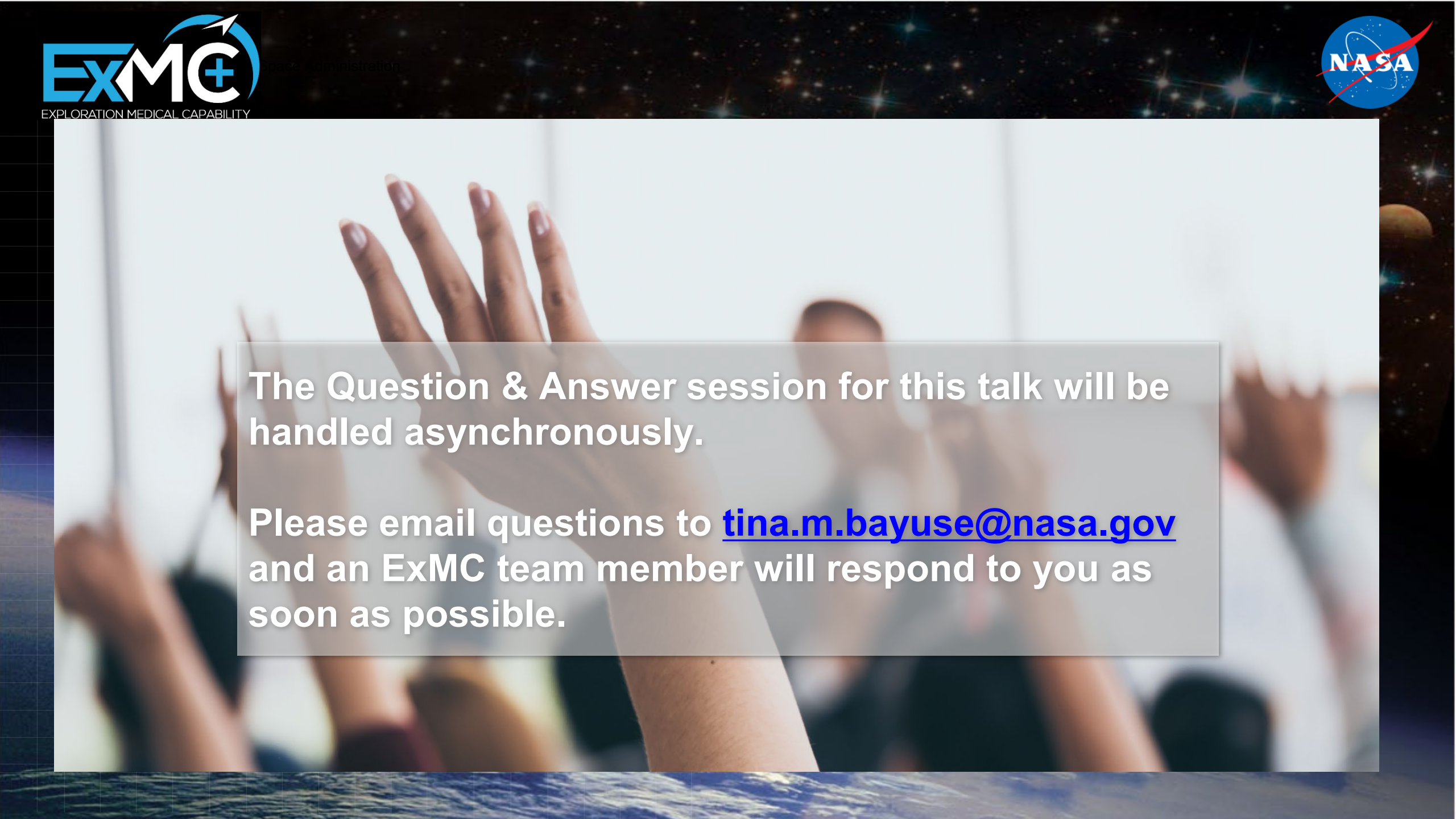
- The GCR profile may not have accurately represented the spectrum (or harshness) of radiation conditions that will be encountered during the mission.
- The experimental radiation was applied at a single time point (acute exposure of high dose) while space mission radiation will be chronic in nature (low dose over sustained period).
- The study drugs, a small subset of over 190 drugs used in space, is not reflective of the drugs most susceptible to radiation degradation.

Forward Work

- Follow-up studies to this pilot study are warranted.
  - 33-GCR, believed to be a higher fidelity analogue of space radiation, is now available at NSRL. The mixed-species beam composition has been shown to have impact on results in cellular studies.
  - Repeat study with additional replicates to verify reproducibility and capture confounding variations within starting drug lot and lab variability.
  - Test a larger and more chemically diverse pool of study drugs.
    - Liquid formulations are generally more sensitive to degradation.
    - Identify drugs sensitive to radiation specifically for next study.
  - Add a pharmacokinetics evaluation to verify drug efficacy in vivo.

Acknowledgements

- **Human Research Program and Exploration Medical Capabilities Element Management**
- **Analytical Vendor: University of Maryland Baltimore, School of Pharmacy, Applied Pharmaceutics Lab**
  - HRP Grant: TXS0143536
  - Analytical Team: Stephan Hoag, PhD - Director; Ahmed Ibrahim, PhD; Fang Wang, PhD; Gary Hollenbeck, PhD; Shailaja Somaraju, PhD
- **Human Health and Performance Directorate Management**
- **Biomedical Research and Environmental Sciences Division Management**
- **NASA-JSC Biomedical Research and Environmental Sciences Division**
- **NASA-JSC Space Radiation Analysis Group**
  - Team: Honglu Wu, PhD, Ramona Gaza, PhD
- **NASA Space Radiation Laboratory scientists, Brookhaven National Laboratory**
  - Team: Peter Guida, PhD; Tony Slaba, PhD
- **JSC Clinical Pharmacy Team**
- **NASA Shipping and Receiving**
- **ExMC Clinical & Science Team Lead**
- **KBR Human Health and Performance Contracts**
  - Logistics Team
  - Task Order Management Teams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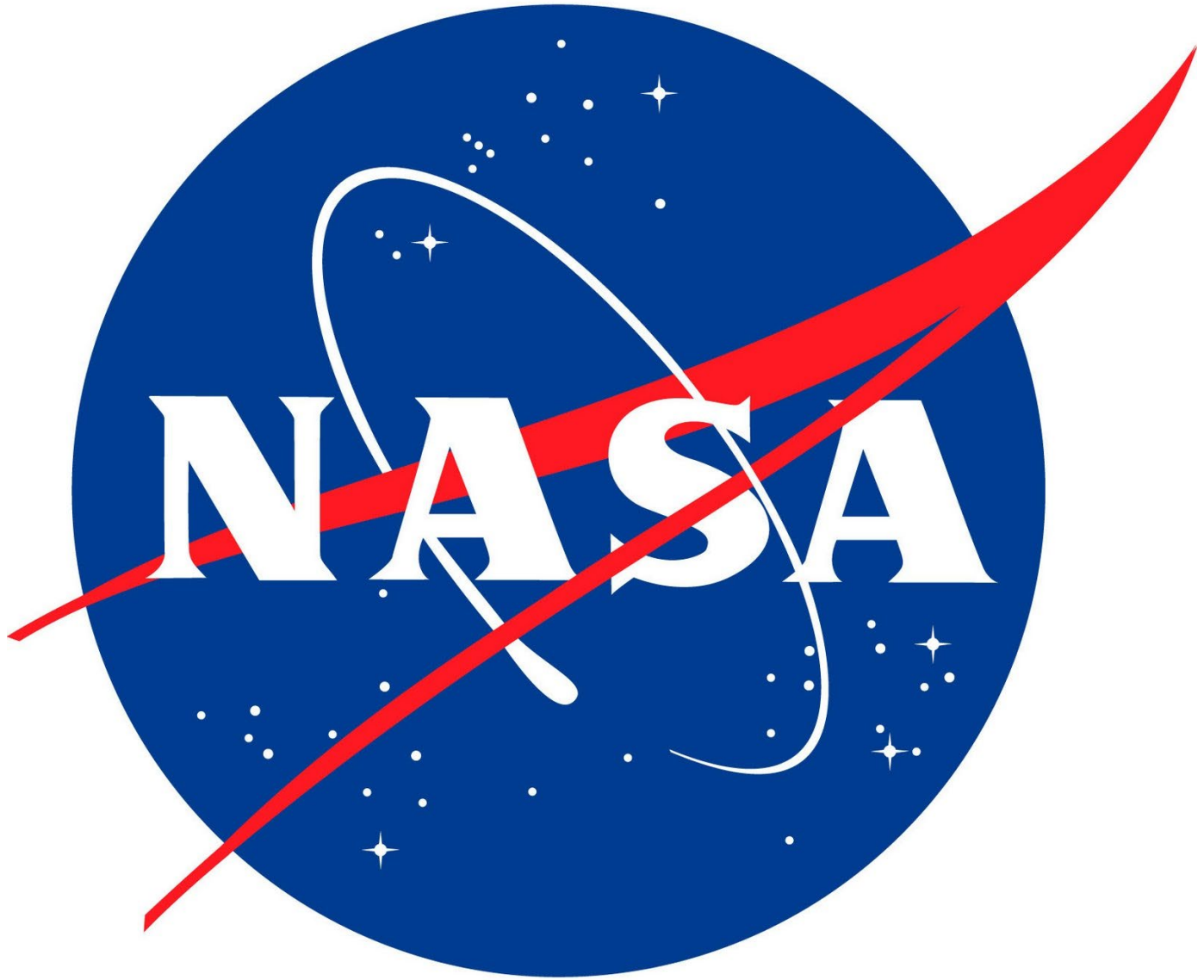
The Question & Answer session for this talk will be handled asynchronously.
Please email questions to tina.m.bayuse@nasa.gov and an ExMC team member will respond to you as soon as possible.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Irradiation Dose

➢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.

Table B: 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.

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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).

Results: API Content

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and control acetaminophen and ibuprofen drug samples analyzed at <u>all</u> three time-points met the USP acceptance criteria for potency

SAMPLE	Product Name	STUDY ARM	% LABELED API 2018 (T1)	% LABELED API 2019 (T2)	% CHANGE IN API (T2-T1/T1)	% LABELED API 2021 (T3)	RSD (%) N = 3 replicates / sample	% CHANGE IN API (T3-T1/T1)	USP %API REQUIREMENT (90-110%)
A1a	Acetaminophen 500 mg Tablets	Non-irradiated JSC Control	95.3	103.22	↑8.31	94.72	± 0.54	↓0.609	(T1, T2, T3) Pass
A1b	Acetaminophen 500 mg Tablets	Non-irradiated JSC Control	100.4	101.85	↑1.44	96.17	± 0.47	↓4.21	(T1, T2, T3) Pass
A2a	Acetaminophen 500 mg Tablets	Non-irradiated Travel Control	97.08	102.18	↑5.25	92.97	± 0.46	↓4.23	(T1, T2, T3) Pass
A2b	Acetaminophen 500 mg Tablets	Non-irradiated Travel Control	97.73	102.81	↑5.2	93.24	± 0.40	↓4.59	(T1, T2, T3) Pass
A3a	Acetaminophen 500 mg Tablets	Irradiation Group I (Mixed-beam 0.5Gy	100.18	102.45	↑2.27	94.36	± 0.71	↓5.81	(T1, T2, T3) Pass
A3b	Acetaminophen 500 mg Tablets	Irradiation Group I (Mixed-beam 0.5Gy)	96.51	99.86	↑3.47	94.49	± 0.78	↓2.09	(T1, T2, T3) Pass
A4a	Acetaminophen 500 mg Tablets	Irradiation Group II (Mixed-beam 1.0Gy)	95.76	102.4	↑6.93	94.94	± 0.35	↓0.856	(T1, T2, T3) Pass
A4b	Acetaminophen 500 mg Tablets	Irradiation Group II (Mixed-beam 1.0Gy)	103.67	99.32	↓4.2	94.28	± 0.37	↓9.06	(T1, T2, T3) Pass

SAMPLE	Product Name	STUDY ARM	% LABELED API 2018 (T1)	% LABELED API 2019 (T2)	% CHANGE IN API (T1-T2 /T1)	% LABELED API 2021 (T3)	RSD (%) N = 3 replicates /sample	% CHANGE IN API (T3-T1 /T1)	USP % API REQUIREMENT (90-110%)
C1a	Ibuprofen 400 mg Tablets	Non-irradiated Control Group	103.85	98.24	↓5.4	97.01	±0.59	↓6.59	(T1, T2, T3) Pass
C1b	Ibuprofen 400 mg Tablets	Non-irradiated Control Group	106.6	102.94	↓3.43	96.81	±0.67	↓9.18	(T1, T2, T3) Pass
C2a	Ibuprofen 400 mg Tablets	Non-irradiated Traveling Control	109.32	97.21	↓11.08	97.22	±1.17	↓11.07	(T1, T2, T3) Pass
C2b	Ibuprofen 400 mg Tablets	Non-irradiated Traveling Control	103.84	101.37	↓2.38	97.55	±0.86	↓6.06	(T1, T2, T3) Pass
C3a	Ibuprofen 400 mg Tablets	Irradiation Group I (Mixed-beam 0.5Gy)	106.6	96.98	↓9.02	97.67	±0.46	↓8.38	(T1, T2, T3) Pass
C3b	Ibuprofen 400 mg Tablets	Irradiation Group I (Mixed-beam 0.5Gy)	109.31	96.96	↓11.3	97.54	±0.33	↓10.77	(T1, T2, T3) Pass
C4a	Ibuprofen 400 mg Tablets	Irradiation Group II (Mixed-beam 1.0Gy)	104.38	95.15	↓8.84	97.85	±0.22	↓6.26	(T1, T2, T3) Pass
C4b	Ibuprofen 400 mg Tablets	Irradiation Group II (Mixed-beam 1.0Gy)	106.43	95.37	↓10.39	97.84	±0.05	↓8.07	(T1, T2, T3) Pass

"Significant Change" is 5% or more change in assay from its initial API content, or failure to meet the USP acceptance criteria for potency. Annex 10, WHO Technical Report Series 1010, 2018

Results: API Content

EXPLORATION MEDICAL CAPABILITY

acceptance criteria for potency at T3

SAMPLE	Product Name	STUDY ARM	% LABELED API 2018 (T1)	% LABELED API 2019 (T2)	% CHANGE IN API (T2-T1/T1)	% LABELED API 2021 (T3)	RSD (%) N = 3 replicates / sample	% CHANGE IN API (T3-T1/T1)	USP % API REQUIREMENT (90-120%)
B1a	Amoxicillin 500 mg Capsules	Non-irradiated JSC Control	100.16	102.08	↑1.92	96.42	± 0.36	↓3.73	(T1, T2, T3) Pass
B1b	Amoxicillin 500 mg Capsules	Non-irradiated JSC Control	97.44	98.58	↑1.17	93.83	± 0.33	↓3.70	(T1, T2, T3) Pass
B2a	Amoxicillin 500 mg Capsules	Non-irradiated Travel Control	100.96	101.51	↑0.54	94.64	± 0.55	↓6.26	(T1, T2, T3) Pass
B2b	Amoxicillin 500 mg Capsules	Non-irradiated Travel Control	100.04	100.02	↓0.02	94.35	± 0.29	↓5.69	(T1, T2, T3) Pass
B3a	Amoxicillin 500 mg Capsules	Irradiation Group I (Mixed-beam 0.5Gy	101.57	99.68	↓1.86	89.97	± 0.14	↓11.42	(T1, T2) Pass (T3) Fail
B3b	Amoxicillin 500 mg Capsules	Irradiation Group I (Mixed-beam 0.5Gy)	99.31	97.11	↓2.22	95.26	± 0.63	↓4.08	(T1, T2, T3) Pass
B4a	Amoxicillin 500 mg Capsules	Irradiation Group II (Mixed-beam 1.0Gy)	98.74	98.97	↑0.23	95.23	± 0.37	↓3.55	(T1, T2, T3) Pass
B4b	Amoxicillin 500 mg Capsules	Irradiation Group II (Mixed-beam 1.0Gy)	102.42	93.72	↓8.49	95.03	± 0.08	↓7.22	(T1, T2, T3) Pass

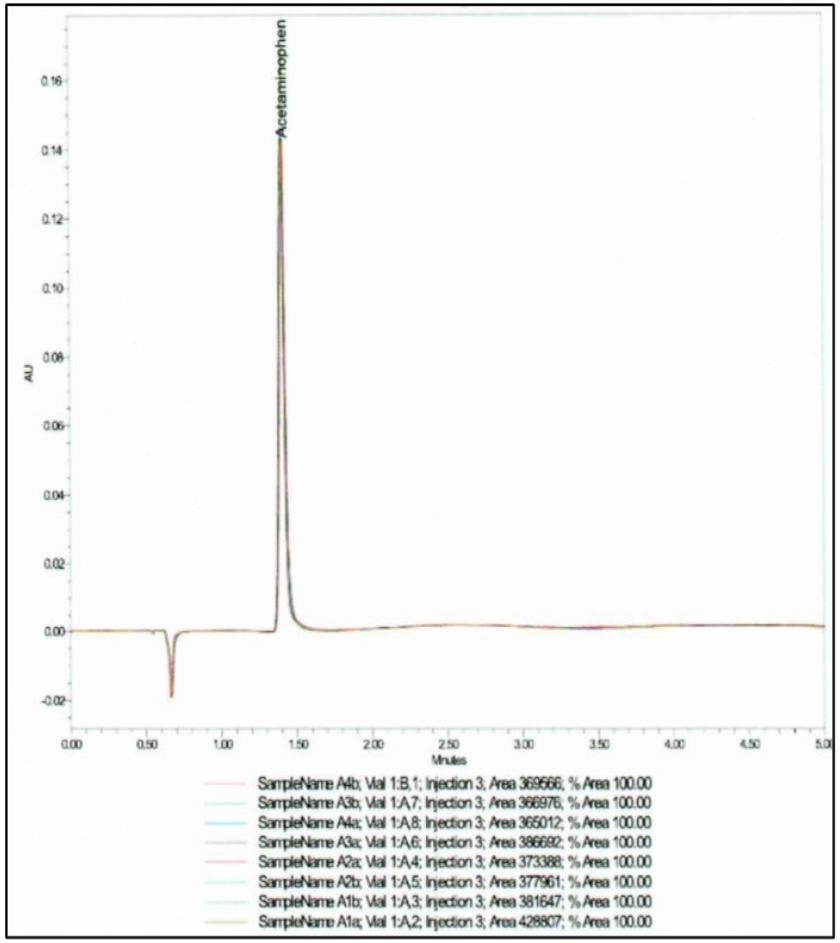
SAMPLE	Product Name	STUDY ARM	% LABELED API 2018 (T1)	% LABELED API 2019 (T2)	% CHANGE IN API (T1-T2 /T1)	% LABELED API 2021 (T3)	RSD (%) N = 3 replicates /sample	% CHANGE IN API (T3-T1 /T1)	USP % API REQUIREMENT (95-110%)
E1a	Promethazine 25 mg Tablets	Non-irradiated JSC Control	99.17	100.2	↑1.04	88.00	±1.15	↓11.26	(T1, T2) Pass (T3) Fail
E1b	Promethazine 25 mg Tablets	Non-irradiated JSC Control	104.66	101.39	↓3.12	88.86	±0.33	↓15.10	(T1, T2) Pass (T3) Fail
E2a	Promethazine 25 mg Tablets	Non-irradiated Traveling Control	107.32	100.09	↓6.73	88.13	±0.64	↓17.88	(T1, T2) Pass (T3) Fail
E2b	Promethazine 25 mg Tablets	Non-irradiated Traveling Control	104.33	100.68	↓3.49	87.67	±0.29	↓15.97	(T1, T2) Pass (T3) Fail
E3a	Promethazine 25 mg Tablets	Irradiation Group I (Mixed-beam 0.5Gy	103	104.02	↑0.99	87.23	±0.24	↓15.31	(T1, T2) Pass (T3) Fail
E3b	Promethazine 25 mg Tablets	Irradiation Group I (Mixed-beam 0.5Gy	109.53	101	↓7.79	87.26	±0.55	↓20.33	(T1, T2) Pass (T3) Fail
E4a	Promethazine 25 mg Tablets	Irradiation Group II (Mixed-beam 1.0Gy	108.33	102.3	↓5.57	87.37	±0.43	↓19.35	(T1, T2) Pass (T3) Fail
E4b	Promethazine 25 mg Tablets	Irradiation Group II (Mixed-beam 1.0Gy	107.3	100.53	↓6.31	87.29	±0.90	↓18.65	(T1, T2) Pass (T3) Fail

Cell Shading Color legend: Blue: Difference between the T1 or T2 and T3 API values fall within RSD = basically no change; Yellow: > 5% change between T1 and T3; Light Red: Failed USP API potency acceptance criteria,

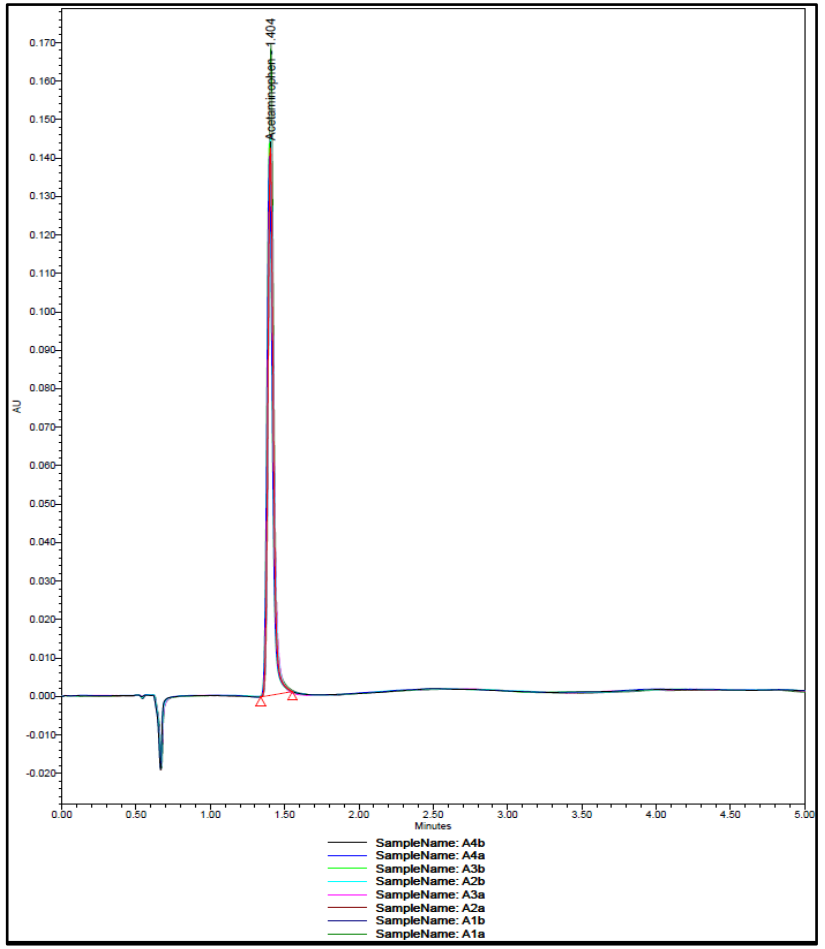
Assay Chromatograms: Acetaminophen

- Chromatogram assessments conducted for each timepoint, using USP chromatogram overlay assay methods, revealed no new or foreign peaks in any of the irradiated drug samples

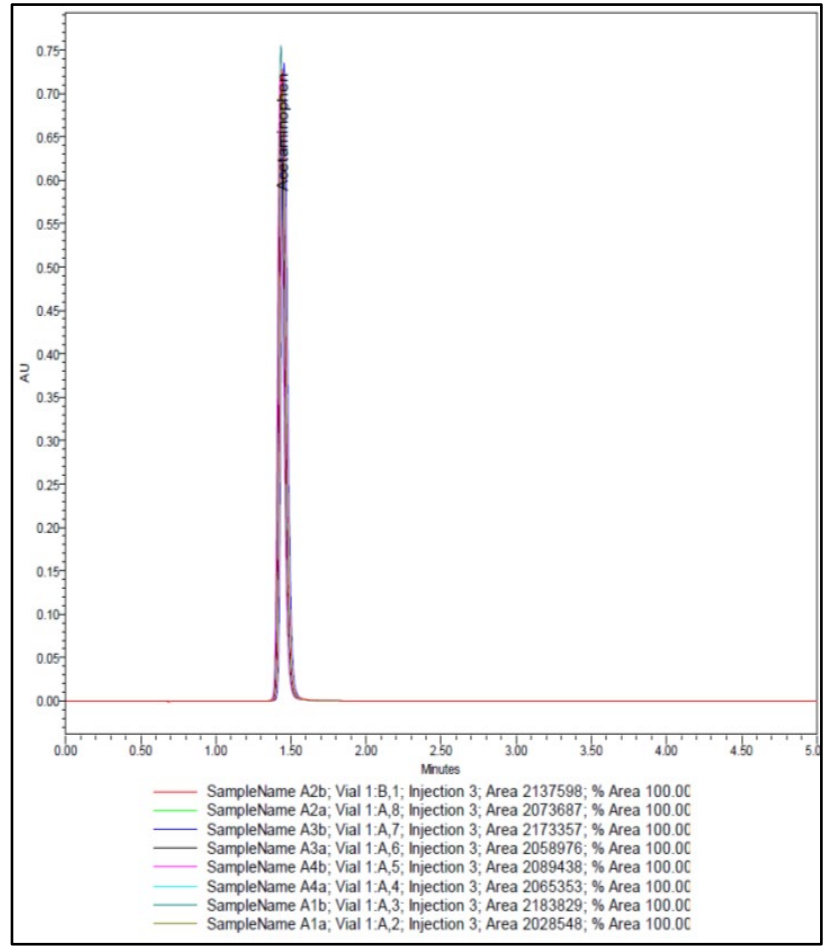
2018



2019

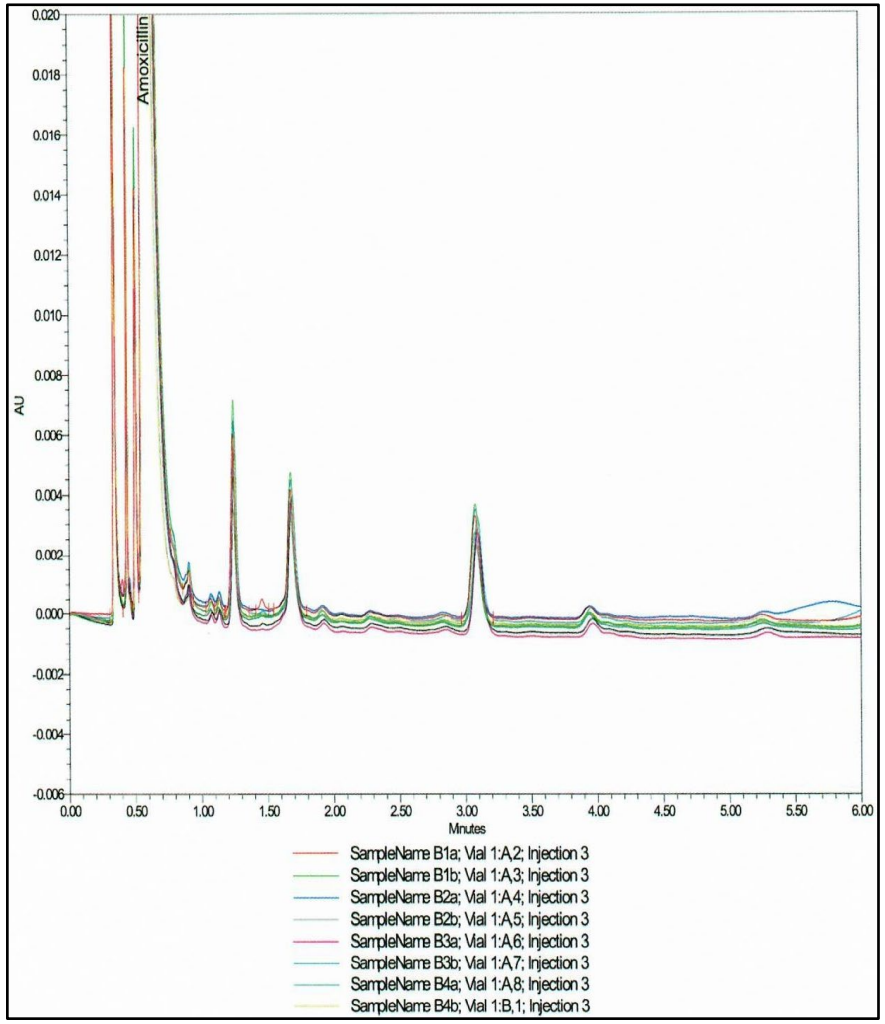


2021



Assay Chromatograms: Amoxicillin

2018



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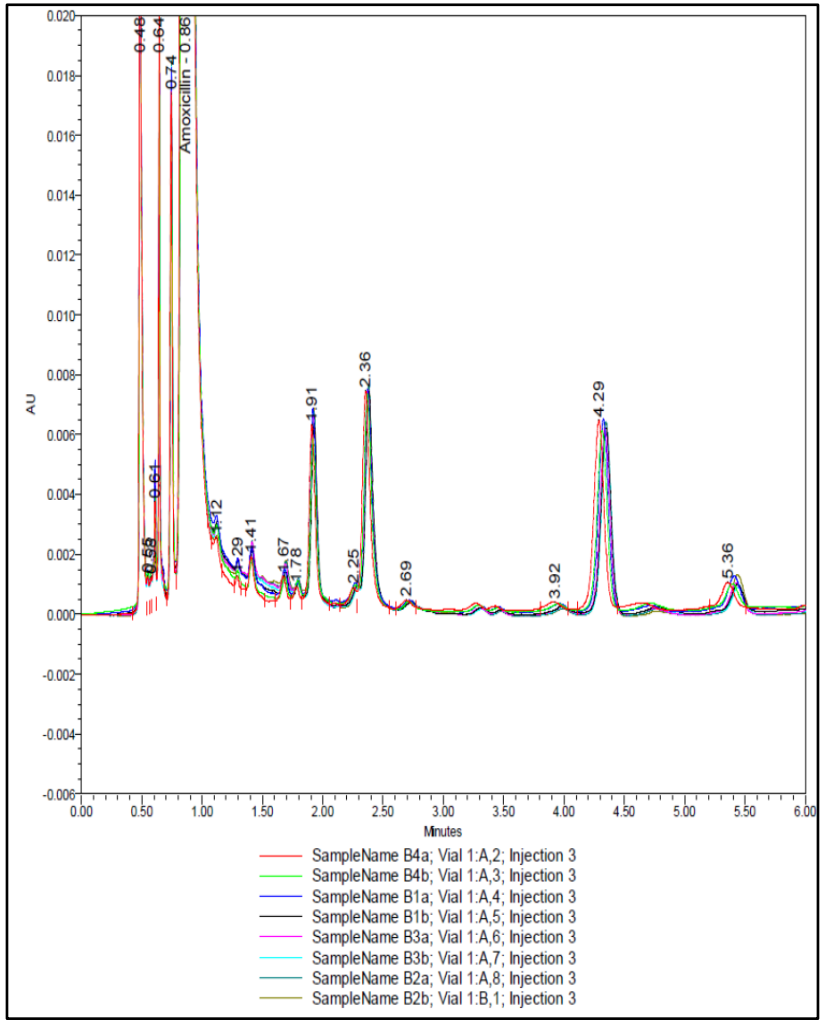

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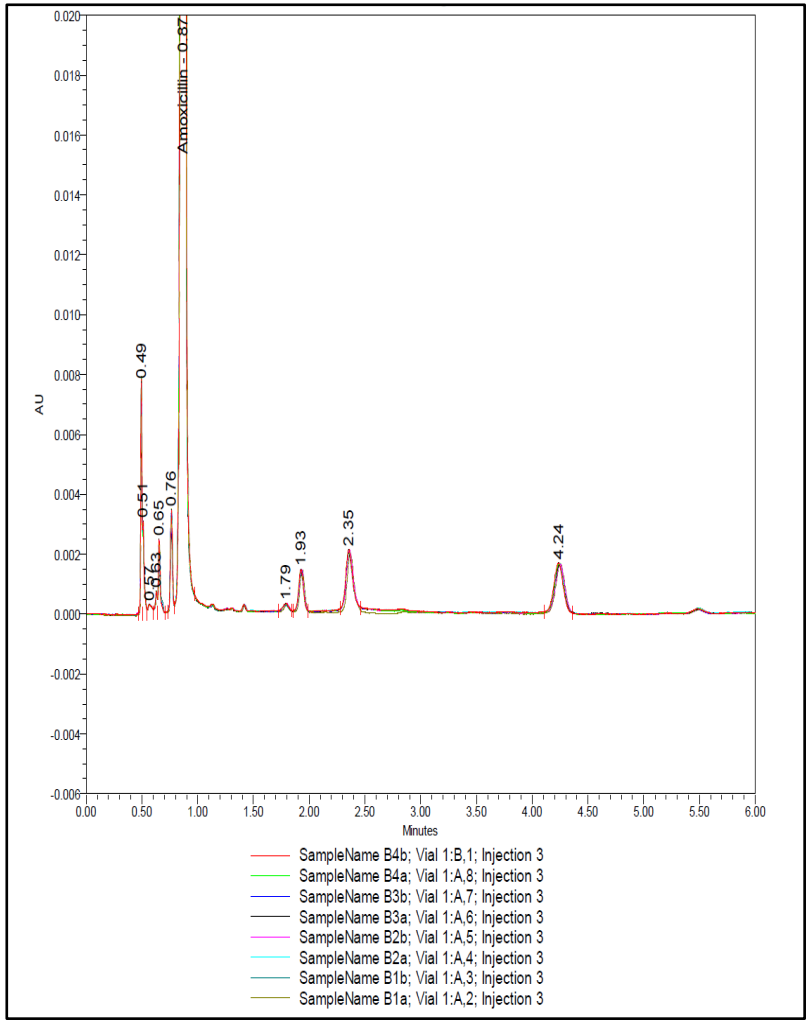
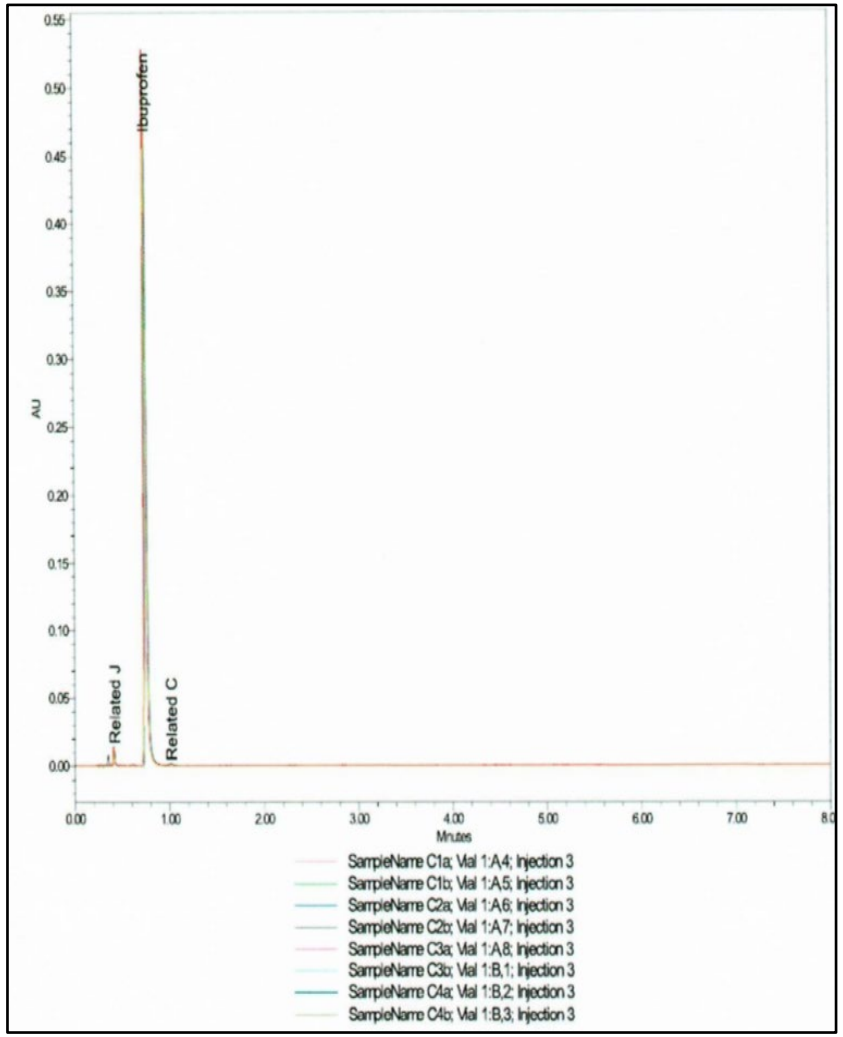
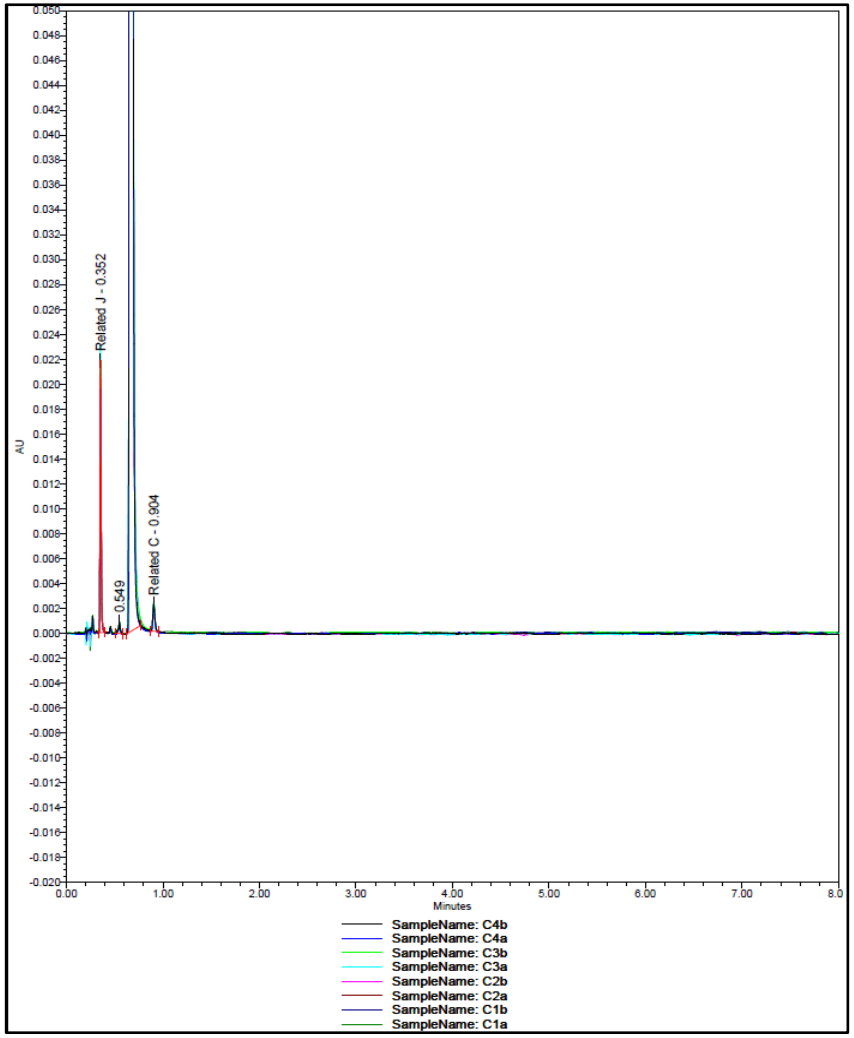


Assay Chromatograms: Ibuprofen

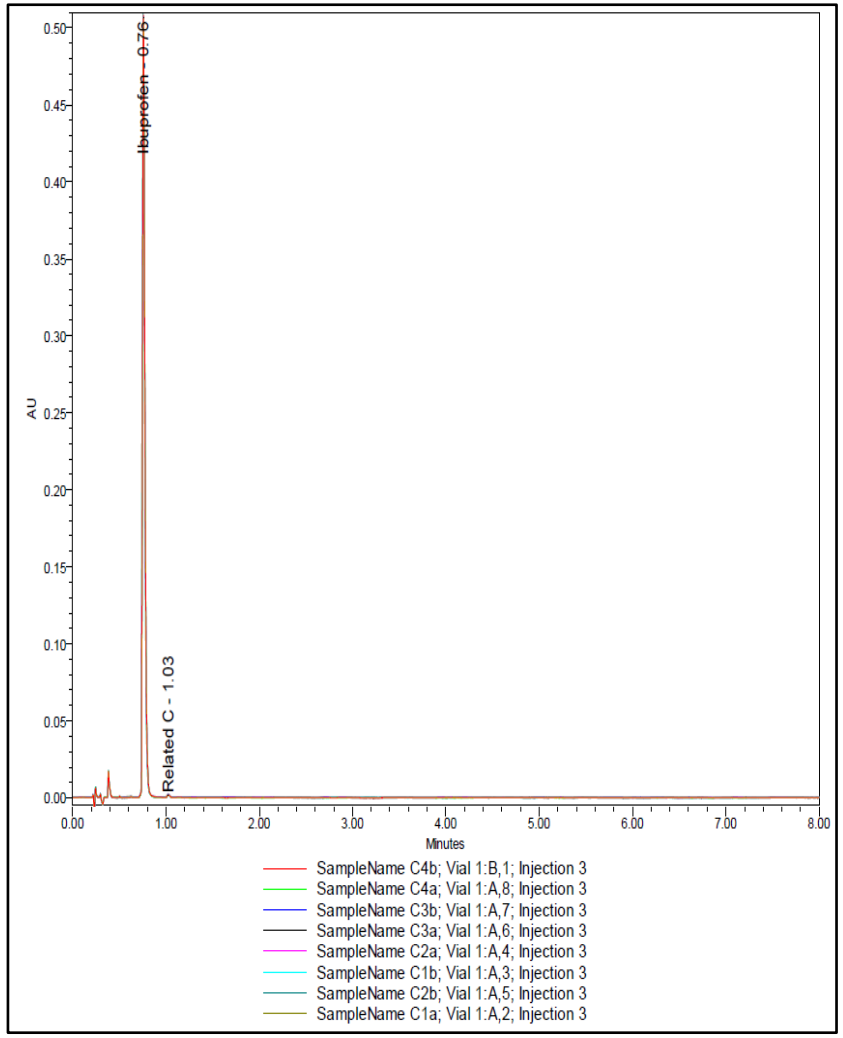
2018



2019

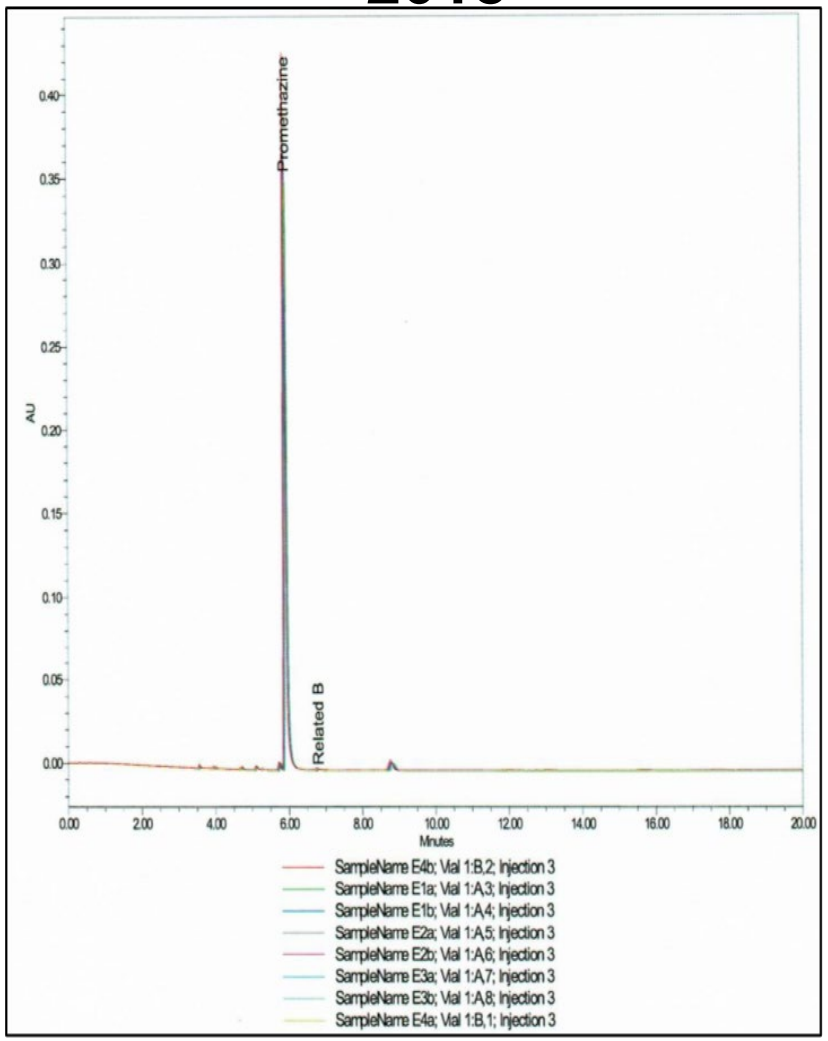


2021

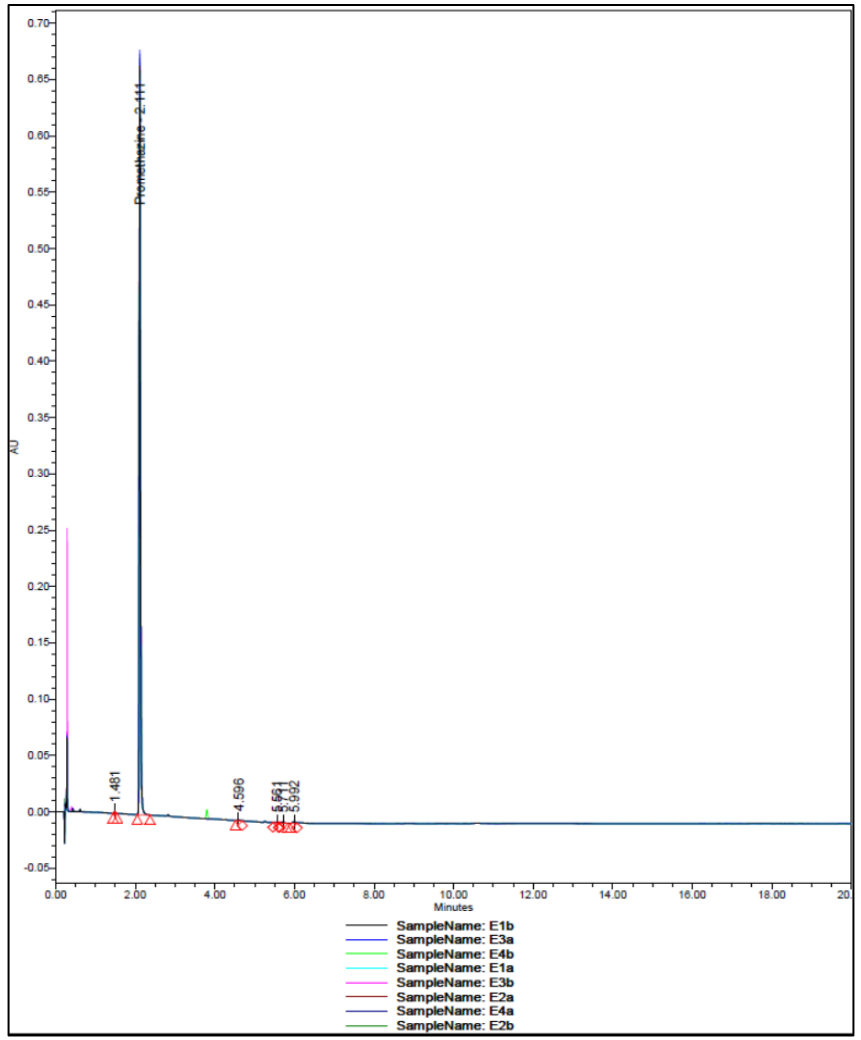


Assay Chromatograms: Promethazine

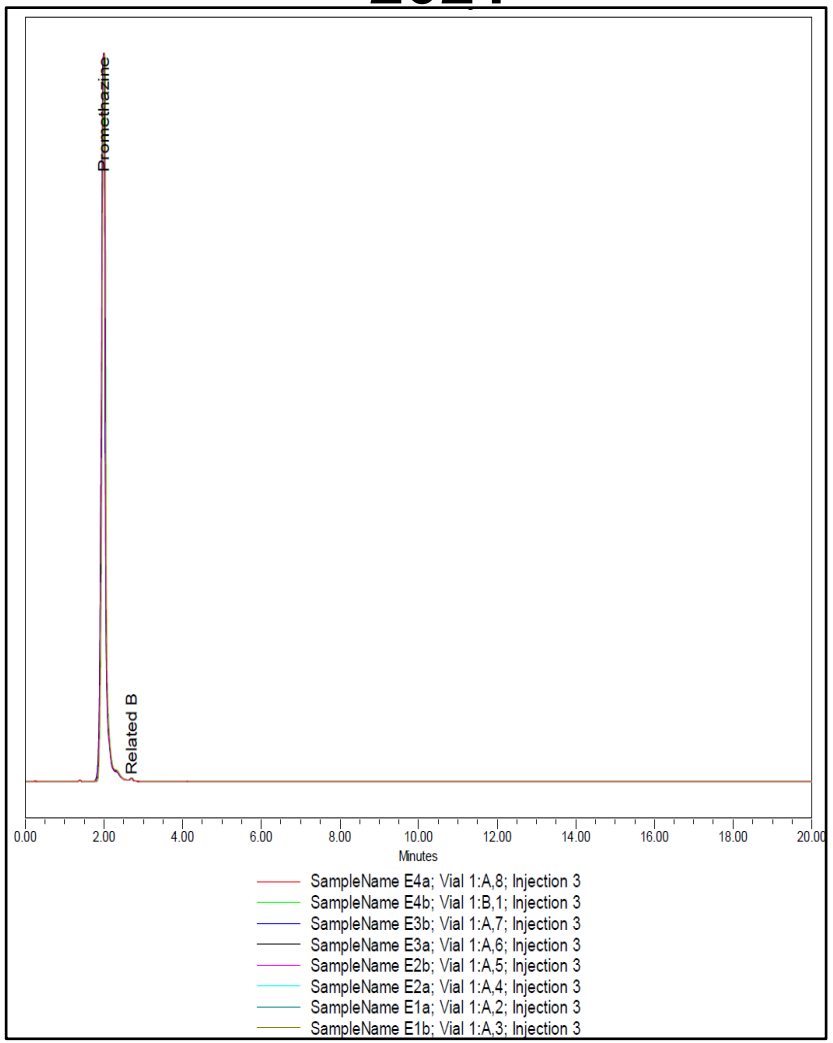
2018



2019



2021



Results: API Release (Dissolution) Recap

- **All samples met the USP requirement for Dissolution.**
  - Some samples revealed "significant changes" in release between the two time-points
  - No third time-point dissolution analyses due to Insufficient drug sample

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

Results: API Release (Dissolution) Recap

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

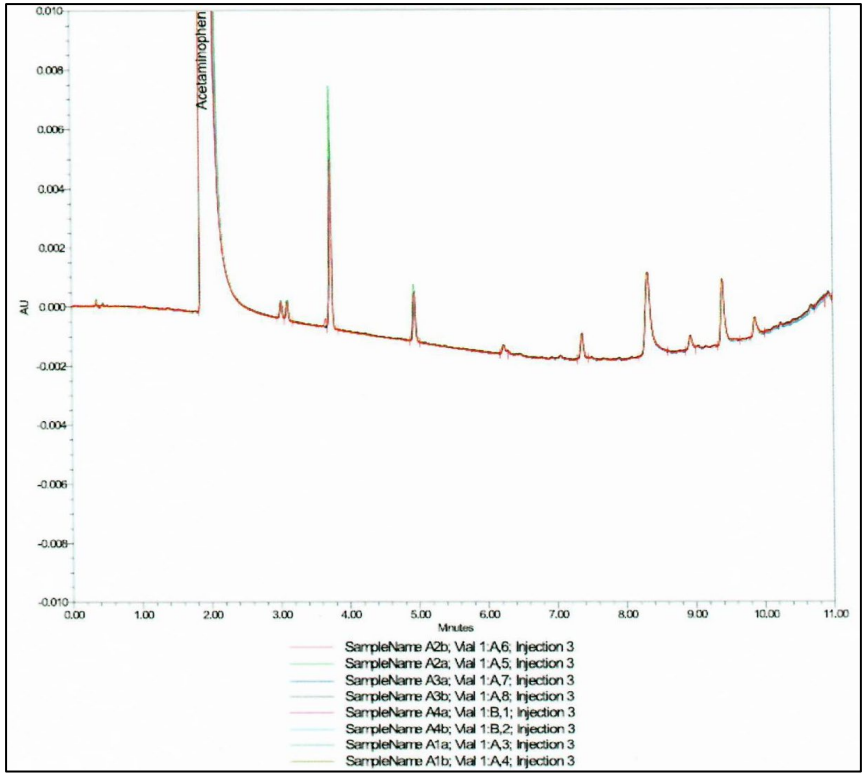
Promethazine:

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

Degradation Products / Impurities: Acetaminophen

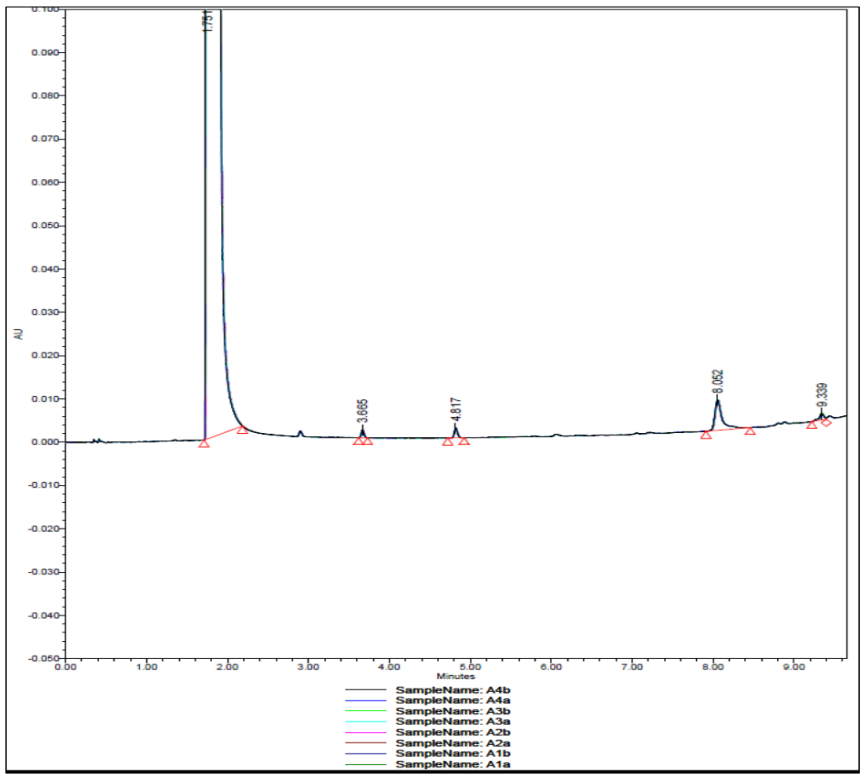
- Impurities peak percent calculations, and overlay chromatograms using USP impurities methods, revealed **no new or foreign peaks** in any of the irradiated drug samples

2018



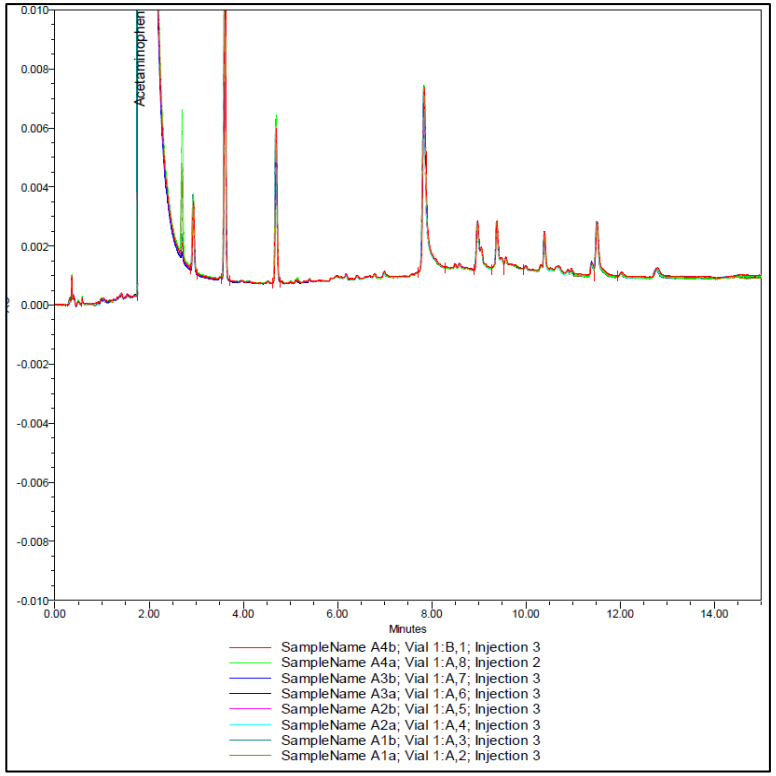
Degradation Peak#	Retention time	A1a	A1b	A2a	A2b	A3a	A3b	A4a	A4b	Standard Deviation
1	P-Aminophenol	ND	ND	ND	ND	ND	ND	ND	ND	--
2	3.738	0.11	0.12	0.15	0.11	0.11	0.12	0.1	0.130	0.016
3	4.946	0.03	0.03	0.04	0.03	0.03	0.03	0.03	0.04	0.005
4	7.369	0.02	0.02	0.02	0.02	0.02	0.03	0.02	0.03	0.005
5	8.32	0.15	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

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	0.03	0.02	0.02	0.02	0.02	0.0045
4	6.241	ND	ND	ND	ND	ND	0.01	ND	0.01	0.00
5	8.052	0.163	0.16	0.17	0.163	0.17	0.16	0.16	0.16	0.0052
6	9.34	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.0015

2021

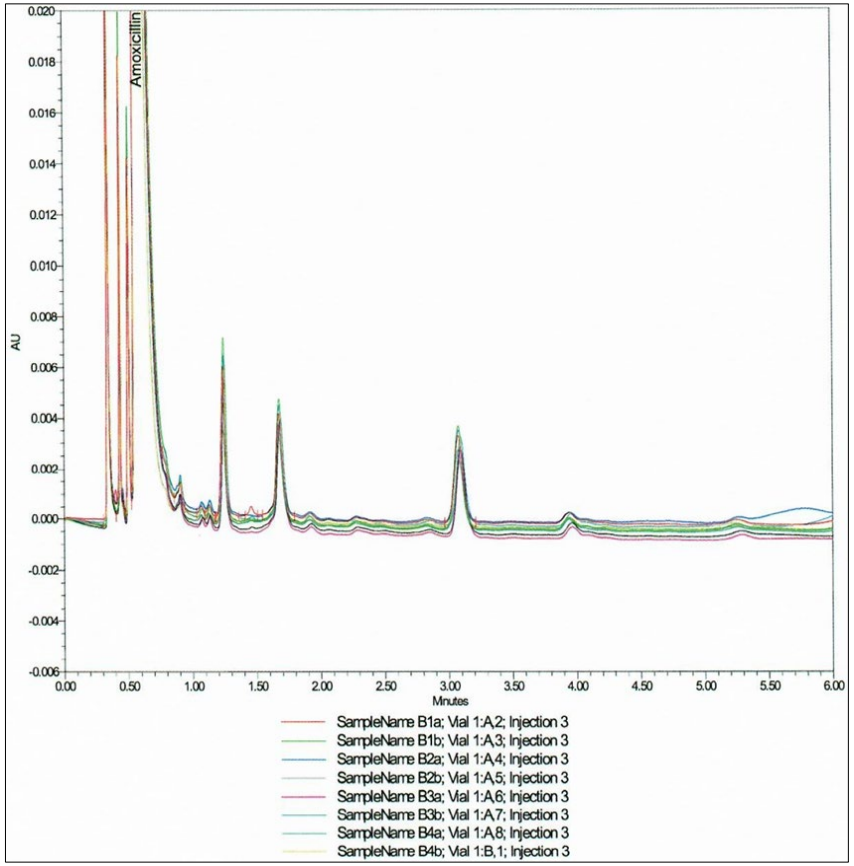


Degradation Peak#	Retention time	A1a	A1b	A2a	A2b	A3a	A3b	A4a	A4b	STD
1	P-Aminophenol	ND	ND	ND	ND	ND	ND	ND	ND	--
2	2.69	0.03	0.04	0.03	0.03	0.03	ND	0.05	0.03	0.0077
3	2.93	0.03	0.02	0.02	0.02	0.02	ND	0.02	0.03	0.0016
4	3.60	0.10	0.10	0.10	0.10	0.10	0.09	0.1	0.10	0.0035
5	4.69	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.0012
6	7.83	0.12	0.12	0.12	0.12	0.13	0.13	0.12	0.12	0.0044
7	8.97	0.01	0.03	0.03	0.03	0.03	0.04	0.03	0.03	0.0064
8	9.38	0.03	0.03	0.02	0.03	0.03	0.03	0.03	0.03	0.0041
9	10.38	0.01	0.01	0.01	0.02	0.02	ND	0.01	0.01	0.0049
10	11.50	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.0012

Degradation Products / Impurities: Amoxicillin

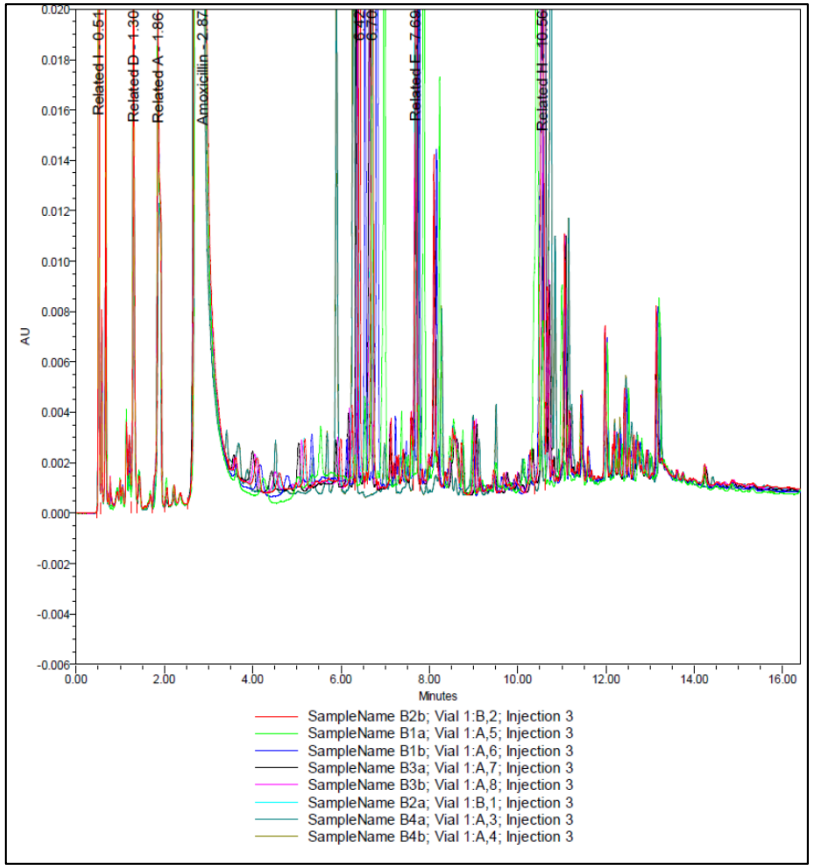
EXPLORATION MEDICAL CAPABILITY

2018



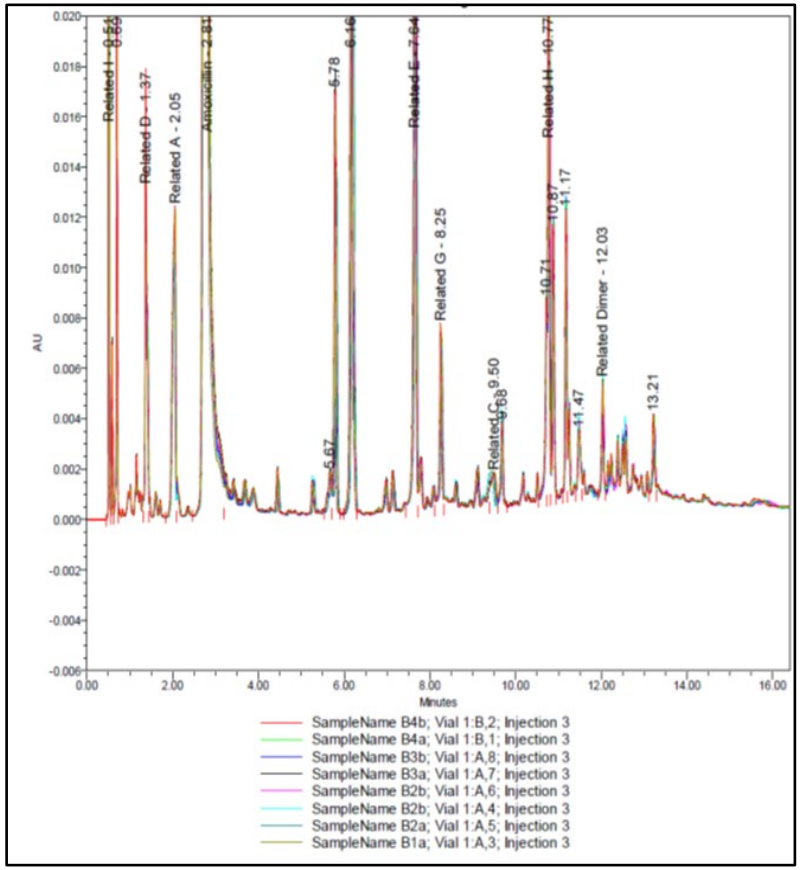
Degradation Peak#	Retention Time (Avg.)	B1a	B1b	B2a	B2b	B3a	B3b	B4a	B4b	Standard Deviation
Related I	0.52	0.5	0.48	0.49	0.49	0.46	0.47	0.42	0.45	0.32
Related D	1.32	0.22	0.23	0.22	0.23	0.26	0.24	0.34	0.26	0.040
Related A	1.95	0.44	0.45	0.44	0.45	0.49	0.47	0.61	0.48	0.056
Related B	2.26	ND	ND	ND	ND	ND	ND	ND	ND	--
Related E	7.59	0.48	0.49	0.48	0.48	0.51	0.49	0.6	0.49	0.041
Related G	8.14	0.11	0.12	0.12	0.11	0.13	0.13	0.17	0.13	0.019
Related C	9.17	0.04	0.04	0.04	0.04	0.05	0.05	0.08	0.05	0.014
Related H	10.71	0.69	0.71	0.7	0.69	0.76	0.72	0.98	0.72	0.097
Dimer	11.90	0.07	0.08	0.06	0.08	0.09	0.08	0.12	0.09	0.018

2019



Degradation Peak#	Retention Time (Avg)	B1a	B1b	B2a	B2b	B3a	B3b	B4a	B4b	Standard Deviation
Related I	0.50	0.46	0.47	0.46	0.46	0.46	0.47	0.51	0.51	0.022
Related D	1.32	0.32	0.33	0.29	0.29	0.28	0.28	ND	ND	0.020
Related A	1.95	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	7.78	0.59	0.61	0.60	0.59	0.59	0.59	0.72	0.72	0.084
Related G	8.14	ND	ND	ND	ND	ND	ND	ND	ND	-
Related C	9.3	ND	ND	ND	ND	ND	ND	ND	ND	-
Related H	10.57	0.59	0.62	0.61	0.61	0.63	0.62	0.69	0.68	0.036
Dimer	11.90	ND	ND	ND	ND	ND	ND	ND	ND	-

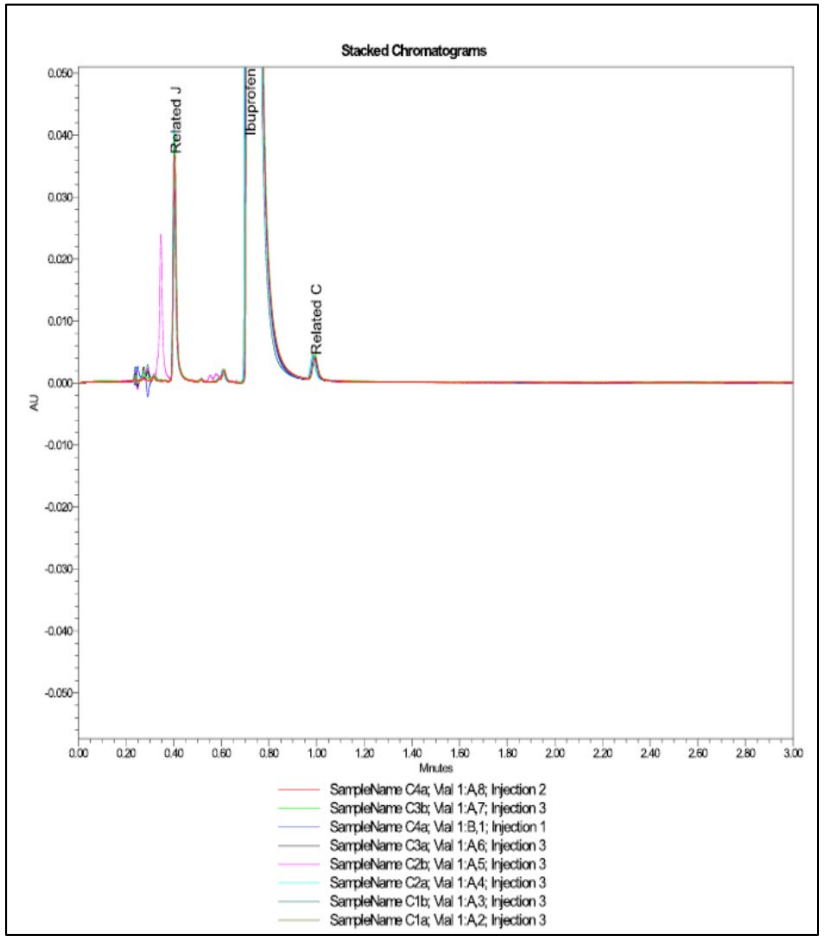
2021



Degradation Peak#	Retention Time (Avg)	B1a	B1b	B2a	B2b	B3a	B3b	B4a	B4b	Standard Deviation
Related I	0.50	0.48	0.53	0.50	0.51	0.54	0.50	0.52	0.53	0.0190
Related D	1.32	0.38	0.33	0.37	0.37	0.32	0.38	0.36	0.36	0.0202
Related A	1.95	0.48	0.46	0.47	0.44	0.47	0.48	0.50	0.50	0.0219
Related B	2.26	ND	ND	ND	ND	ND	ND	ND	ND	--
Related E	7.78	1.07	1.04	1.08	1.05	0.98	1.07	1.03	1.02	0.0336
Related G	8.14	0.19	0.18	0.19	0.19	0.17	0.20	0.20	0.20	0.0090
Related C	9.30	ND	ND	ND	ND	ND	ND	ND	ND	--
Related H	10.57	0.65	0.59	0.63	0.60	0.55	0.64	0.59	0.58	0.0340
Dimer	11.90	0.15	0.12	0.14	0.10	0.11	0.11	0.13	0.12	0.0163

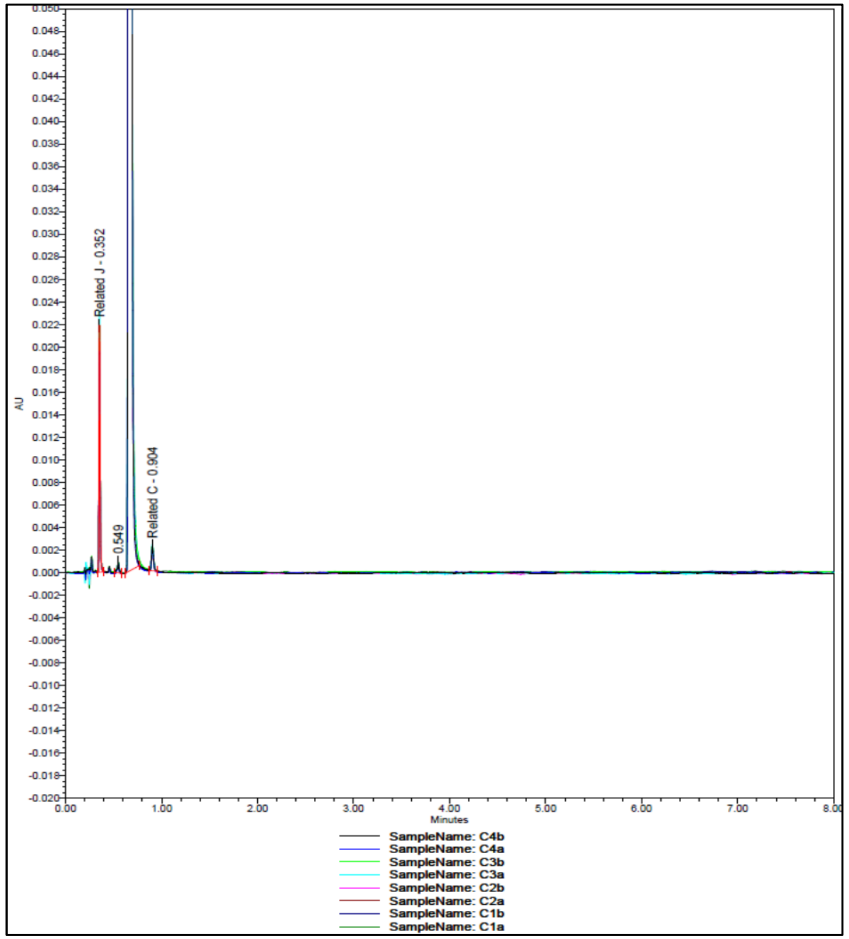
Degradation Products / Impurities: Ibuprofen

2018



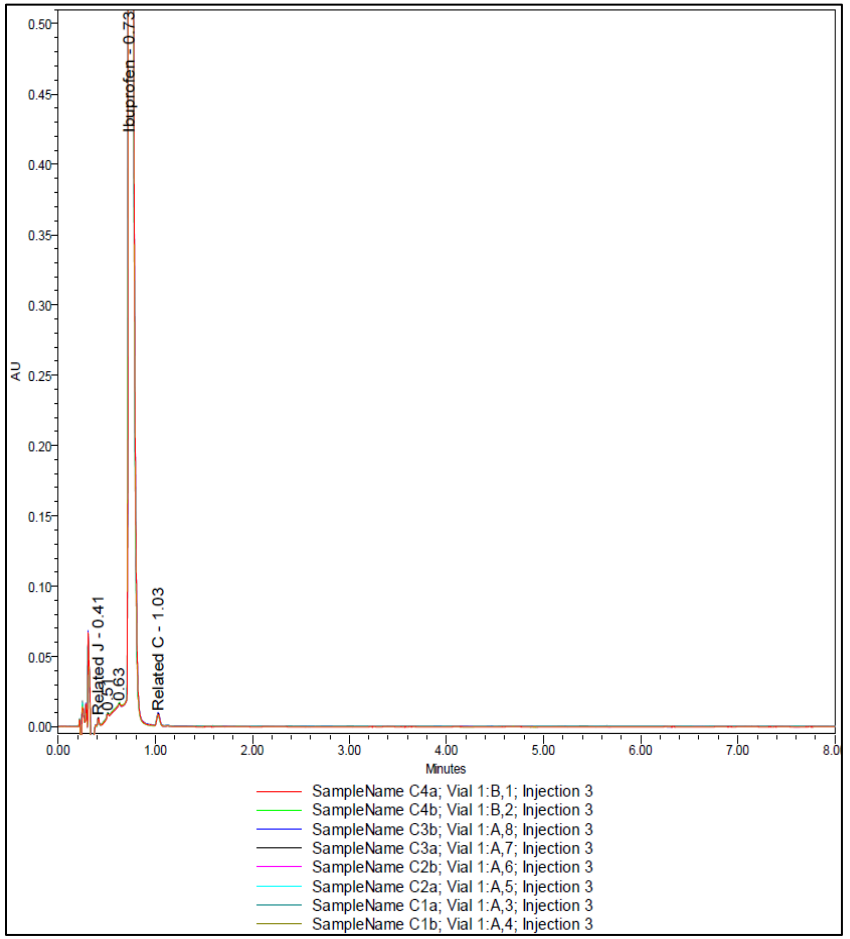
Degradation Peak#	Retention Time (min)	C1a	C1b	C2a	C2b	C3a	C3b	C4a	C4b	Standard Deviation
1	ND	ND	ND	ND	ND	0.86	ND	ND	ND	ND
Related J	0.41	1.55	1.54	1.57	1.51	1.57	1.57	1.55	1.57	0.034
3	0.622	0.17	0.13	0.16	0.12	0.15	0.23	0.14	0.17	0.279
Related C	1.011	0.22	0.27	0.25	0.27	0.26	0.27	0.26	0.25	0.021

2019



Degradation Peak#	Retention Time (min)	C1a	C1b	C2a	C2b	C3a	C3b	C4a	C4b	Standard Deviation
Related J	0.35	1.79	1.77	1.82	1.78	1.71	1.77	1.81	1.76	0.034775
3	0.55	0.12	0.115	0.125	0.12	0.11	0.11	0.12	0.12	0.0047
Related C	0.90	0.29	0.34	0.35	0.35	0.33	0.33	0.34	0.33	0.0191

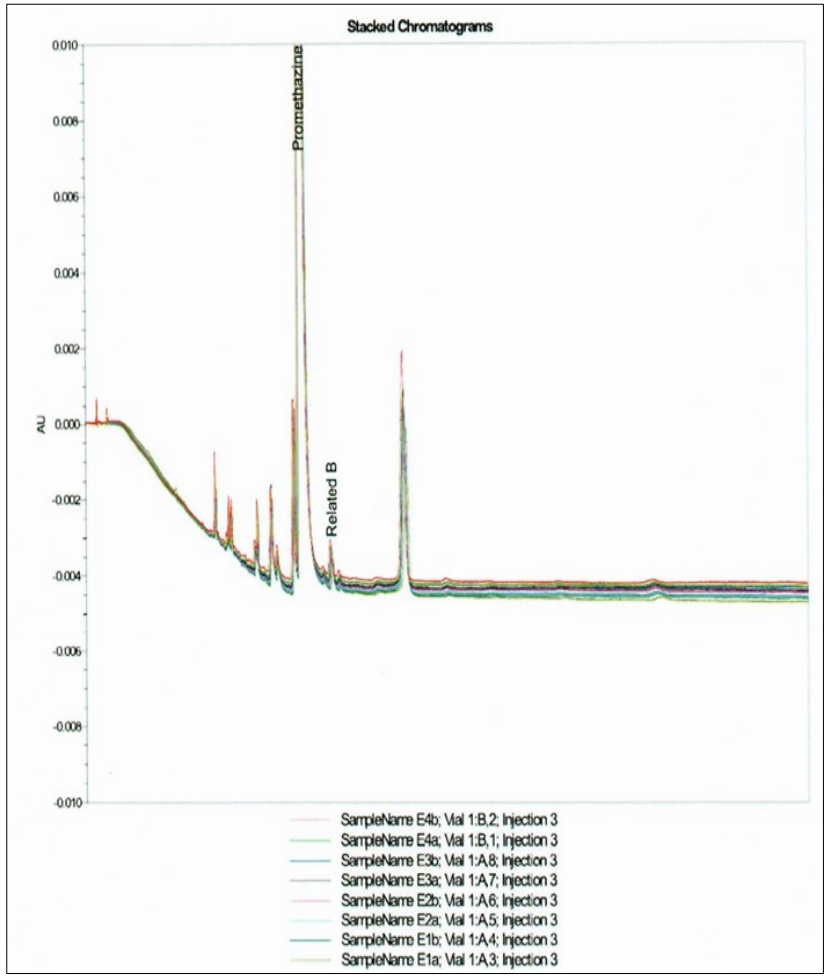
2021



Degradation Peak#	Retention Time (min)	C1a	C1b	C2a	C2b	C3a	C3b	C4a	C4b	STD
Unknown1	0.55	0.12	0.12	0.13	0.12	0.11	0.11	0.12	0.12	0.0047
Unknown2	0.51	0.47	0.45	0.42	0.47	0.51	0.46	0.39	0.49	0.0370
Unknown3	0.62	1.91	1.90	1.87	1.90	1.98	1.89	1.82	1.97	0.0510
Related J	0.35	0.12	0.12	0.12	0.12	0.13	0.13	0.11	0.12	0.0064
Related C	0.90	0.31	0.35	0.38	0.38	0.39	0.39	0.36	0.33	0.0275

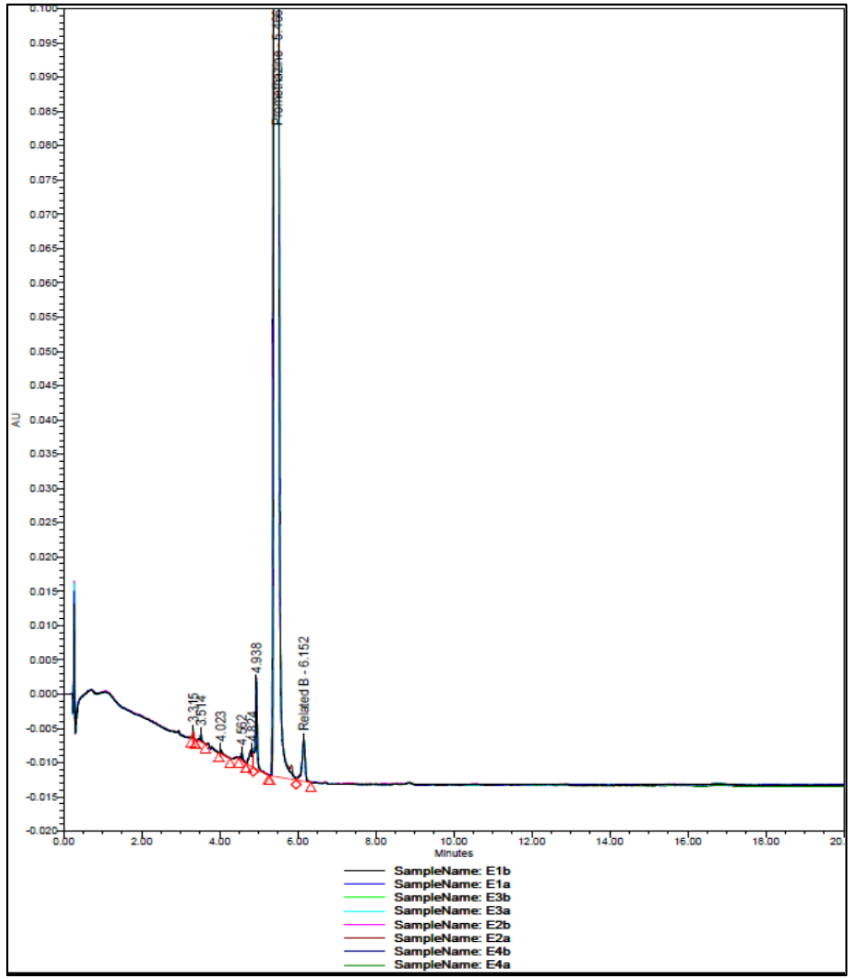
Products / Impurities: Promethazine

2019



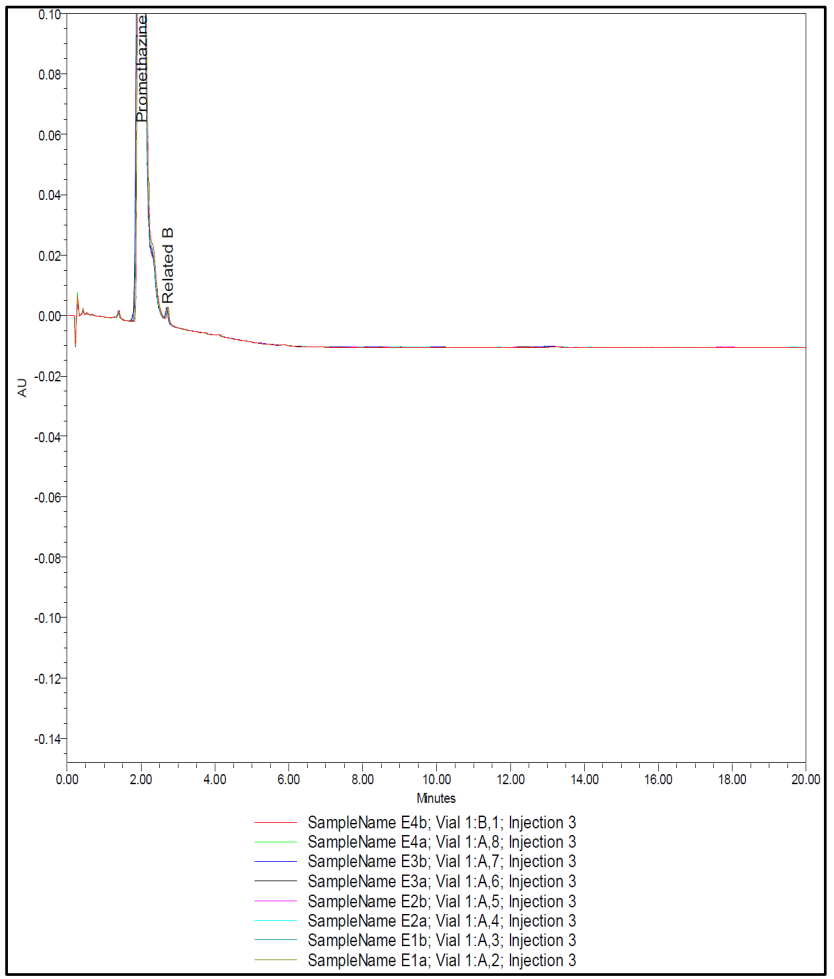
Degradation Peak#	Peak Retention Time (min)	E1a	E1b	E2a	E2b	E3a	E3b	E4a	E4b	Standard Deviation
1	1.71	0.08	0.03	ND	ND	ND	ND	ND	ND	0.035
2	3.577	0.21	0.19	0.2	0.18	0.15	0.15	0.19	0.22	0.026
3	3.651	0.05	0.05	0.06	0.05	0.03	0.06	0.07	0.05	0.012
4	3.956	0.12	0.03	0.14	0.03	0.12	0.16	0.11	0.19	0.057
5	4.026	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#	Retention Time (min)	E1a	E1b	E2a	E2b	E3a	E3b	E4a	E4b	Standard Deviation
1	3.32	0.02	0.02	0.02	0.2	0.02	0.02	0.04	0.02	0.063
2	3.52	0.03	0.03	0.03	0.3	0.03	0.03	0.1	0.03	0.095
3	4.03	0.02	0.02	0.02	0.01	0.02	0.02	0.03	0.02	0.005
4	4.57	0.03	0.03	0.02	0.025	0.02	0.02	0.16	0.02	0.048
5	4.82	0.12	0.12	0.11	0.11	0.11	0.11	0.236	0.12	0.043
6	4.95	0.33	0.32	0.33	0.33	0.33	0.33	0.566	0.32	0.085
Related B	6.14	0.45	0.45	0.45	0.45	0.45	0.45	0.48	0.45	0.01

2021



Degradation Peak#	Retention Time (min)	E1a	E1b	E2a	E2b	E3a	E3b	E4a	E4b	STD
1	1.28	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.00119
2	1.39	0.11	0.11	0.11	0.11	0.11	0.11	0.11	0.11	0
3	4.10	0.03	0.03	0.03	0.03	0.03	0.03	0.04	0.04	0.00388
4	5.59	0.01	0.02	0.01	0.02	0.02	0.01	0.02	0.01	0.00535
Related B	2.70	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.00118