September 30, 2019

Division of Dockets Management
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: University of Kentucky Drug Quality Study Citizen Petition

Dear Sir or Madam:

The undersigned, on behalf of the University of Kentucky (UK) Drug Quality Study (DQS) team, submits this Citizen Petition ("Petition") pursuant to Sections 301(21 U.S.C. § 331), 501 (21 U.S.C. § 351), 502 (21 U.S.C. § 352), 505 (21 U.S.C. § 355), 702 (21 U.S.C. § 372), 704 (21 U.S.C. § 374), and 705 (21 U.S.C. § 375) of the Federal Food, Drug and Cosmetic Act (the "FDCA"), in accordance with 21 C.F.R. 10.20 and 10.30, to request the Commissioner of Food and Drugs ("Commissioner") to take such actions set forth below.

A. Action Requested

The UK DQS team has identified anomalies with certain medications through utilizing a Process Analytical Technology (PAT) testing technique followed by the USP monograph assay and additional destructive testing methods. This Petition requests that the Commissioner take the following actions:

1) request a recall on identified lots of Acetazolamide for injection on the basis that, due to under-potency and excessive impurities in some vials, these drugs are adulterated under Section 501 of the FDCA (21 U.S.C. § 351) and misbranded under Section 502 of the FDCA (21 U.S.C. § 352);
2) conduct examinations and investigation under Section 702(a) of the FDCA (21 U.S.C. § 372(a)) regarding these products, their manufacturing processes, and the manufacturer submissions made for FDA approval under 704(a) of the FDCA (21 U.S.C. § 374(a)) and effect labeling revisions as needed;
3) provide information to the public regarding this product under Section 705(b) of the FDCA (21 U.S.C. § 375(b)); and
4) promulgate regulations requiring robust independent chemical batch-level testing and verification of the chemical content of batches of pharmaceuticals of drugs and, while these regulations are pending, issue guidance requesting such testing and verification.

Background on Petitioner

The UK DQS team formed in August of 2019. The objectives of the UK DQS team are to test UK HealthCare's incoming drugs for identity and quality in order to improve patient outcomes with reporting adulterated drugs to the Food and Drug Administration (FDA) as necessary. In March of 2020 correspondences with the FDA Office of Pharmaceutical Quality began concerning the direction of certification or accreditation for the work product. Although not officially directed to pursue a particular pathway, the FDA communicated multiple times that GXP would likely be the most appropriate direction. The UK DQS team started officially testing

products in August of 2020 and has the goal of achieving compliance with GXP regulations following an onsite audit in the coming months.

The UK DQS team also has been in regular communication with the United States Pharmacopeia (USP) regarding our ongoing study and has employed its standards and monograph literature to support our efforts.

B. Statement of Grounds

Mylan - Acetazolamide for Injection

In early August 2020, while utilizing noninvasive and nondestructive PAT scanning techniques based on Fourier transform near-infrared spectroscopy (FTNIR)(Thermo Scientific™ Antaris™ II FT-NIR Analyzer), it was observed that 11 of 30 vials from the same NDC and lot number of Mylan's Acetazolamide for Injection demonstrated significant variations with their collected spectra:

- Drug Name: Acetazolamide for Injection, USP
- Strength: 500 mg
- Form: Lyophilized powder vial for injection
- Manufacturer: Mylan Laboratories Limited, Bangalore, India
- NDC: 67457-0853-50
- Lot #: 7604764
- Expiration Date: June 30, 2021

Vials of this lot were then sequestered and the FTNIR reflectance spectra of these vials (obtained nondestructively through the vials without opening them) appear in Figure 1. The most obvious variations among the spectra appear in the range of 4500 to 5200 wavenumbers.

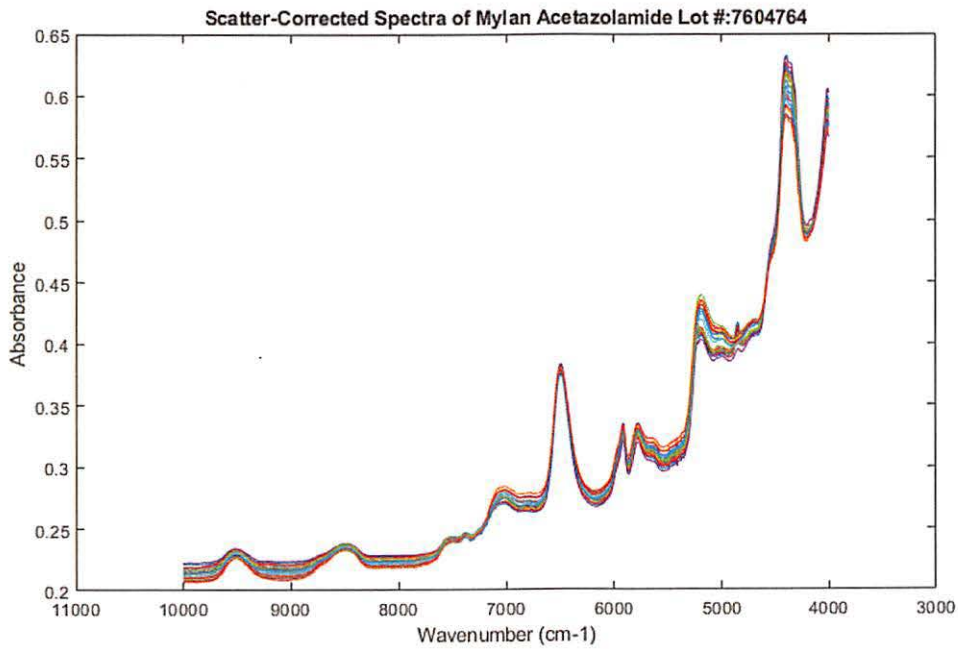

Figure 1a. Thirty FT-NIR spectra of Mylan acetazolamide (Lot #:7604764). Additional peaks are most obvious in the region from 4500-5200 cm^{-1}.

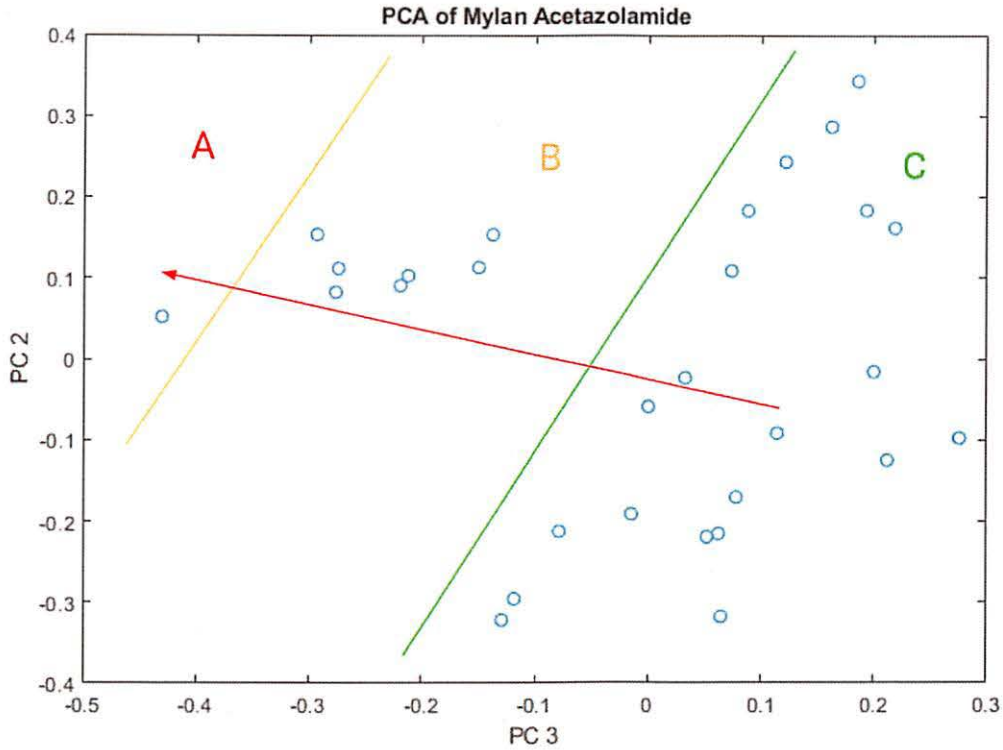

Figure 1b. Principal component plot of the spectra in Figure 1a. A is the apparently most adulterated sample based on additional peaks in the spectrum, B are samples that contain similar peaks to A but in smaller amounts, and C are the vials with normal FTNIR spectra. The manufacturing procedure appears to be operating out of a state of process control.

The variability in these spectra suggest a manufacturing procedure that is out of process control.

The FTNIR reflectance spectrum of the USP reference standard for acetazolamide (purchased directly from the US Pharmacopeia, USP Catalog No.: 1005004, USP Lot No.: R089P0, CAS No.: 59-66-5) appears in Figure 2. This USP standard was scanned noninvasively and nondestructively through an unopened amber vial. The spectral range from 4000-7200 cm^{-1} is most important for comparison between the USP standard and the Mylan drug because it avoids the region where the amber vial absorbs light.

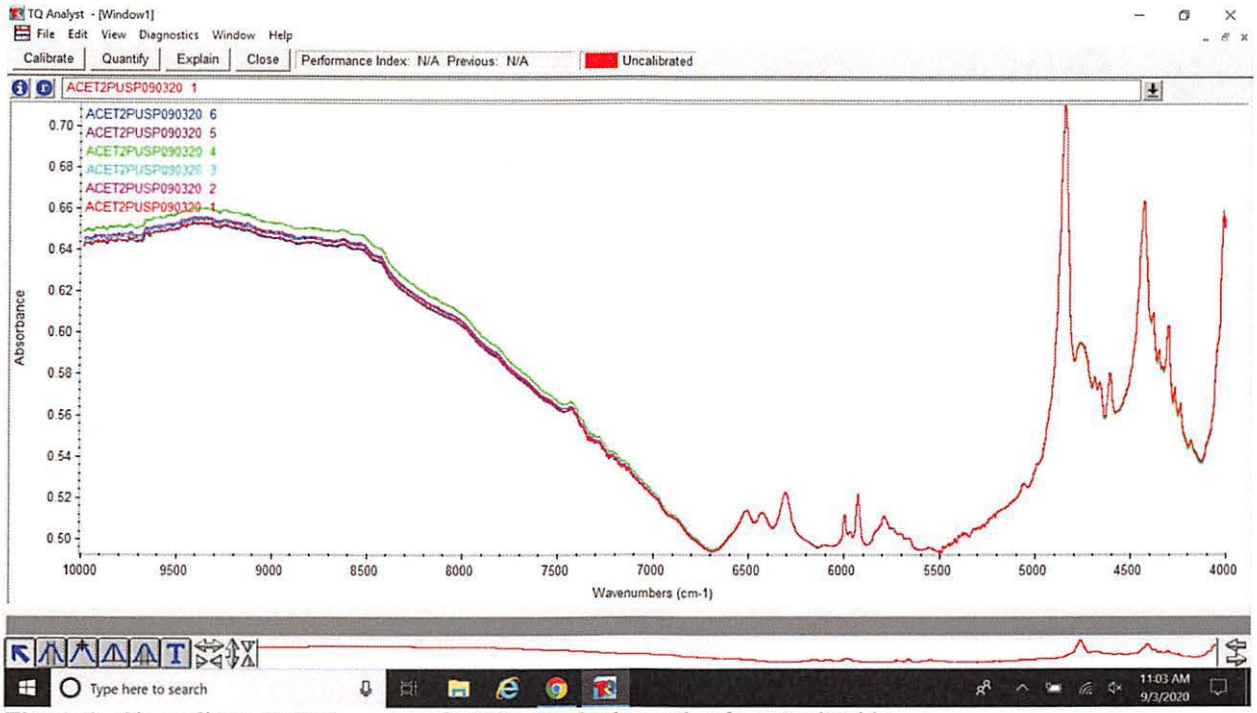

Figure 2. Six replicate FTNIR spectra of a USP standard sample of acetazolamide

There are significant spectral differences between the spectra USP standard and the Mylan acetazolamide formulation, as seen in Figure 3, with changes in peaks in the Mylan samples that cannot be easily accounted for by the spectrum of acetazolamide.

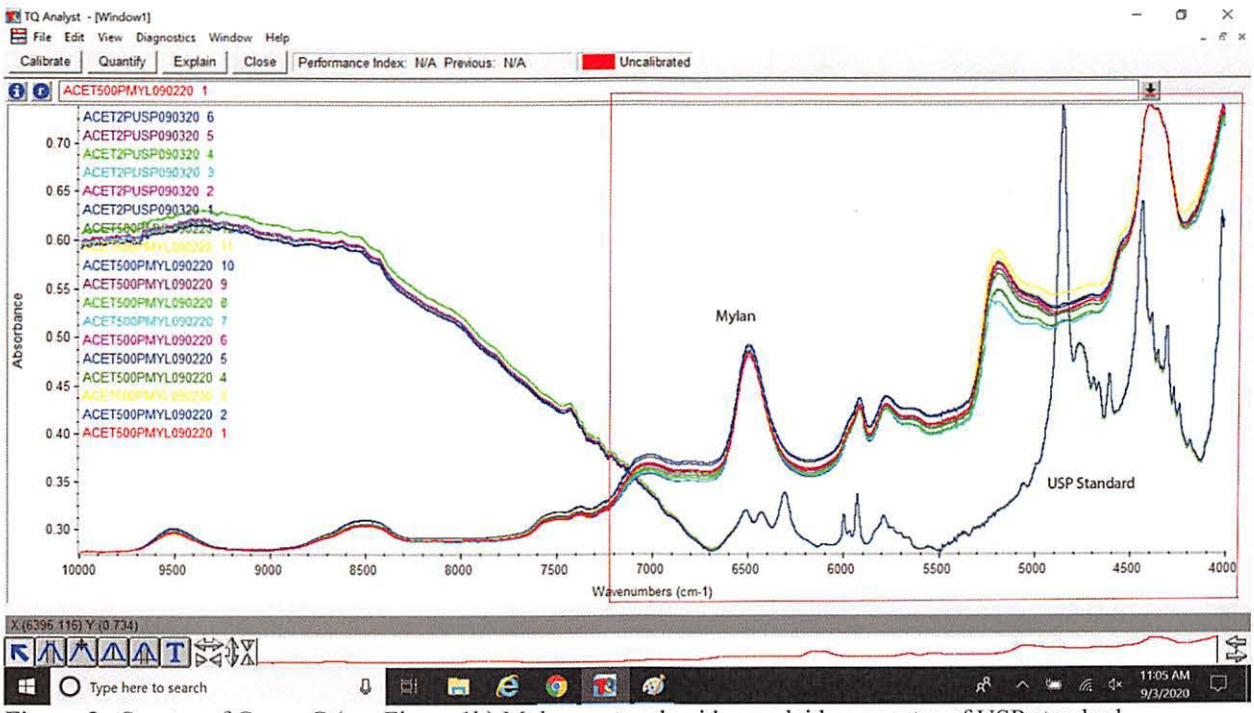

Figure 3. Spectra of Group C (see Figure 1b) Mylan acetazolamide overlaid on spectra of USP standard acetazolamide.

Grinding the USP standard of acetazolamide with a mortar and pestle for 10 minutes does not significantly alter its near-infrared spectrum (see Figure 4).

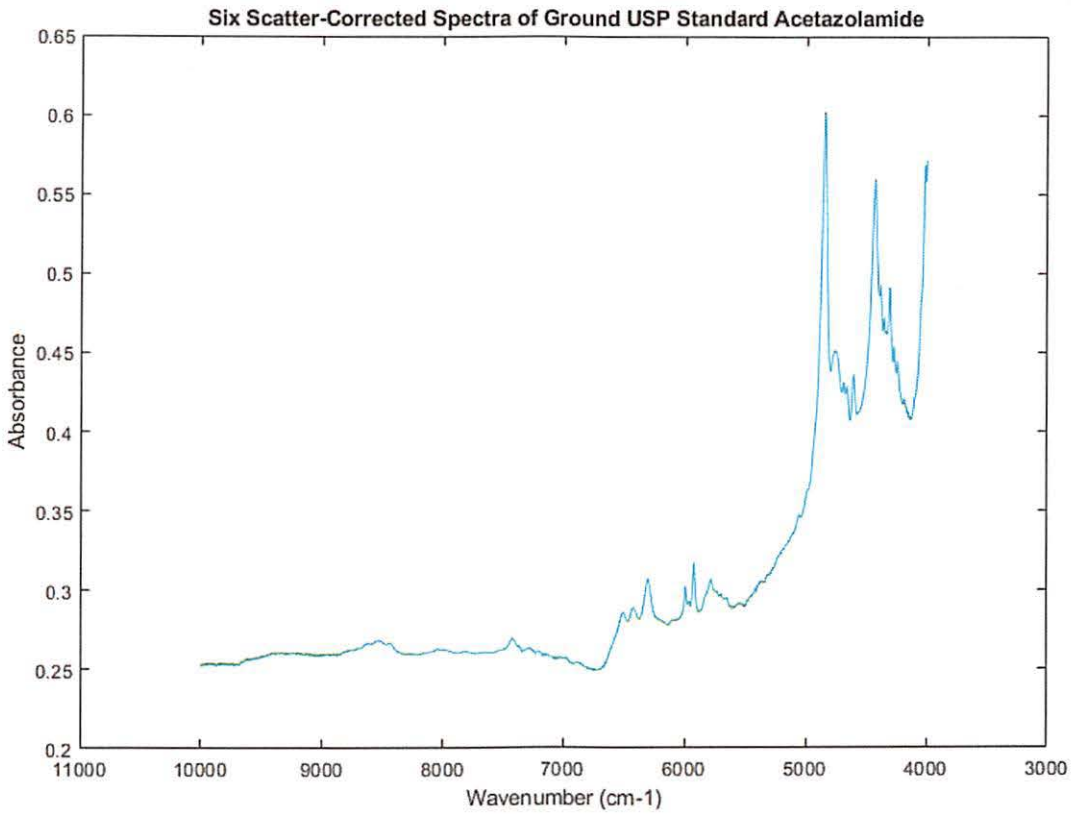

Figure 4. Six replicate spectra of ground USP standard acetazolamide after multiplicative scatter correction (no amber vial)

A single vial of Mylan product that did not demonstrate the anomalies (group C in Figure 1b) and a single vial that did demonstrate the anomalies (group A in Figure 1b) were each examined with Gas Chromatography Mass Spectroscopy (GC-MS) (see Figure 5). The GC-MS results demonstrated notable variations between the total ion chromatograms of the vial from group C and the vial from group A. Importantly, the Mylan label did not indicate any substances other than the API on its label. In the vial from group A, the two peaks that elute before the main peak (6.296 minutes and 6.346 minutes) are much larger than in the vial from group C, and additional peaks at retention times of 5.922, 6.899, and 7.605 minutes appear in the vial from group A.

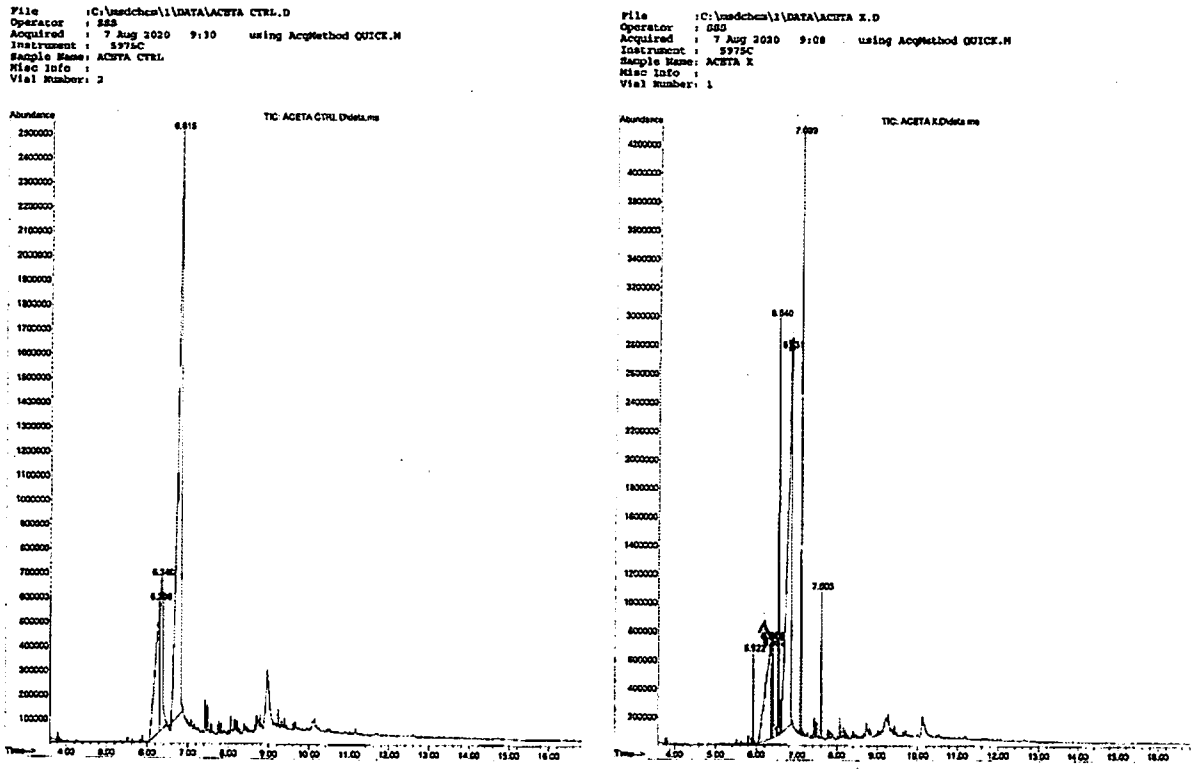

Figure 5. Total ion chromatograms from GC-MS of Mylan acetazolamide (left, labeled "control vial" from group C in Figure 1b) and Mylan acetazolamide with anomalous FTNIR pattern (right, labeled vial X, from Group A in Figure 1b)

Upon consulting the USP monograph for acetazolamide for injection, we found that there are eight known impurities that may be present in small quantities in USP grade acetazolamide for injection, and that the highest acceptance criteria allowed for all of these compounds combined is no more than 3%. Based on the differences observed in the total ion chromatograms between the vial from Group C and the vial from group A, the UK DQS team found it appropriate to pursue additional methodologies to evaluate the API content in both the group C and A/B samples from this lot of Mylan acetazolamide product.

At the time of this discovery we had only scanned 12 vials from our stock. Two with near-IR spectral anomalies (groups A and B) and 10 without (Group C). We contacted the FDA Office of Pharmaceutical Quality (OPQ) in writing on August 10, 2020 detailing our findings and sent via overnight UPS ten vials from the lot in question, with nine group C vials and one vial from Group A. We received proof of delivery to the offices of FDA OPQ, however, did not receive any communications regarding next steps. On this same day our wholesaler, Cardinal Health, was notified of our initial findings in writing. The manufacturer was contacted as well via their medical affairs telephone number.

The following day (August 11, 2020) our team identified 19 more vials from the same lot located in a remote stock location. These vials were then sequestered and scanned. Nine of the vials exhibited spectral anomalies upon FTNIR scanning (groups A and B) while ten did not (group C). None of the vials were beyond their expiration dates, and all were stored according to the

manufacturer's recommendations. On August 12, 2020 our team contacted the FDA OPQ in writing to provide this updated information with an offer to send four additional vials from groups A and B. We also notified the FDA OPQ that the UK DQS team planned to send five of the vials from groups A and B to an independent laboratory for additional analysis using the USP monograph method.

On August 20, 2020, UK DQS supplied samples to an independent third-party laboratory (AMRI Global) for testing using the USP Acetazolamide for Injection chromatographic assay. Five of the vials from groups A and B were shipped via overnight UPS in compliance with USP <659> requirements with validated packaging for shipping drugs requiring room temperature (15-25 degrees Celsius). This independent lab conducted purity assays of the five group A and B samples by High Performance Liquid Chromatography (HPLC). The USP standard was compared to the groups A and B samples utilizing an isocratic method on a C18 column.

On September 21, 2020 the independent lab reviewed their findings with the UK DQS team and it was determined that the five vials in question contained between 80% and 87% of the 500 mg label amount of API, suggesting that up to 13 to 20% were unknown excipients and impurities and these vials should officially be determined to be adulterated and unsuitable for human use.

To further substantiate the results from the independent lab, an LC-MS/MS method was developed by the UK DQS team and optimized for detection of acetazolamide using two qualifier/quantifier ion pairs including 223/181 and 223/163.9 (positive ion mode). LC-MS/MS samples were prepared for replicate (5x) analysis from stock solutions of acetazolamide samples, including: the USP acetazolamide standard, a Mylan Group C Vial, and Mylan Suspect vials (from groups A and B): X1, X2, X3. The area under the curve (AUC) for the replicates of each sample were averaged and the percent acetazolamide was calculated by comparing the average AUC for each sample set to the average AUC of USP acetazolamide standard (assuming the USP standard to be 100% acetazolamide). This analysis was completed using the area under the curve (AUC) for both ion pairs (223/181 and 223/163.9) and the resulting % acetazolamide for each ion pair was then averaged to yield the average % acetazolamide summarized in Table 1. The LC-MS/MS results completed on September 28, 2020 ultimately revealed the average % acetazolamide for the Mylan group C vial and 3 suspect vials (from groups A and B) to fall between 83.3-86.5%.

Sample	C1	X1	X2	X3
Sample ID	Mylan Acetazolamide Lot: 7604764 Exp: June 30, 2021	Mylan Acetazolamide Lot: 7604764 Exp: June 30, 2021	Mylan Acetazolamide Lot: 7604764 Exp: June 30, 2021	Mylan Acetazolamide Lot: 7604764 Exp: June 30, 2021
Average % Acetazolamide	83.3%	84.8%	85.7%	86.5%

Table 1. UK DQS LC-MS/MS Analysis of Mylan Acetazolamide for Injection (lot 7604764) by comparison to USP Acetazolamide Standard (lot R089P0).

The observation that the Mylan group C vial (C1) demonstrated a similar % acetazolamide as the suspect vials (groups A and B) from the FTNIR analysis led the DQS team to evaluate two additional Mylan group C vials previously categorized by FTNIR analysis with the LC-MS/MS method on September 29, 2020 (Table 2).

Sample	MC2	MC3
Sample ID	Mylan Acetazolamide Lot: 7604764 Exp: June 30, 2021	Mylan Acetazolamide Lot: 7604764 Exp: June 30, 2021
Average % Acetazolamide	81.6%	80.0%

Table 2. Additional UK DQS LC-MS/MS Analysis of Mylan group C Acetazolamide vials for Injection (lot 7604764) by comparison to USP Acetazolamide Standard (lot R089P0).

The evaluation of the additional Mylan group C vials by LC-MS/MS analysis revealed similar results to the previous Mylan group C sample (C1) evaluated on September 28, 2020, yielding average % acetazolamide values of 81.6% and 80.0% for the MC2 and MC3 samples, respectively. Together, the LC-MS/MS analysis confirms our findings with the vials in question identified from the FTNIR scanning that were submitted to a third party for testing, but it also demonstrates concerns that the entire lot may be subpotent and adulterated with unknown impurities.

The FDA OPQ responded to August 2020 notifications on September 28, 2020, the same day that the initial LC-MS/MS analysis was completed. Direction was given to report our concerns to the FDA's MedWatch System. Per this direction we are simultaneously reporting our concerns through MedWatch on the same day as filing this Citizen's Petition.

Hikma - Acetazolamide for Injection

Shortly after sequestering the Mylan product, the only other manufactured product available at the time from our wholesaler was the Hikma Acetazolamide for Injection product. Upon receiving this inventory, we screened it with FTNIR and found anomalies in two of the ten vials that were slightly different than those observed with the Mylan vials (see Figure 6). The vial details are below:

- Drug Name: Acetazolamide for Injection, USP
- Strength: 500 mg
- Form: Lyophilized powder vial for injection
- Manufacturer: Hikma Farmacêutica (Portugal), S.A.
- NDC: 00143-9503-01
- Lot #: 2001028.1
- Expiration Date: February 2022

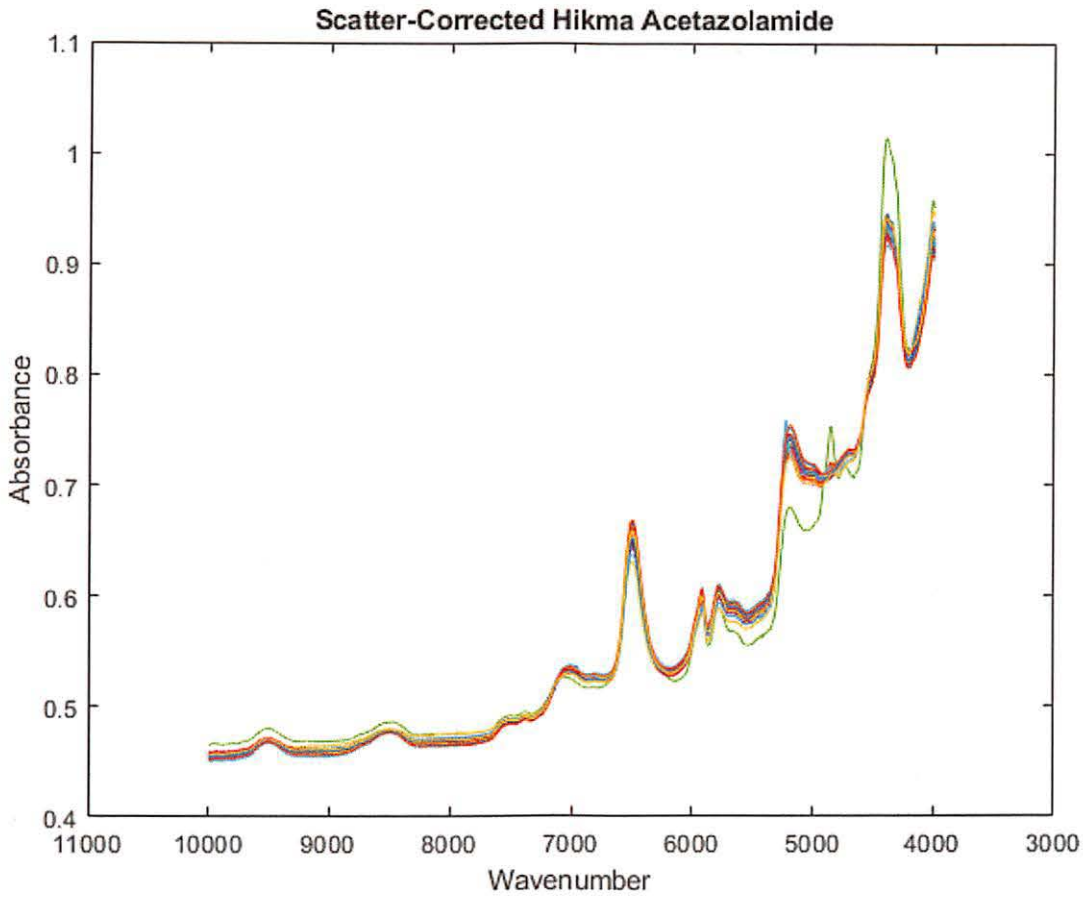

Figure 6. Spectra of vials of Hikma acetazolamide (Lot #: 2001028.1) after multiplicative scatter correction. One spectrum stands out distinctly (green line, spectrum #5).

Principal component plots (see Figure 7) help to show how different the spectra are. While the spectrum of vial 5 is a number of multidimensional standard deviations from what appears to be the normal drug material, vials 2, 11, 12, 16, 19, 23, 25, and 31 also show smaller levels of the peaks in vial 5.

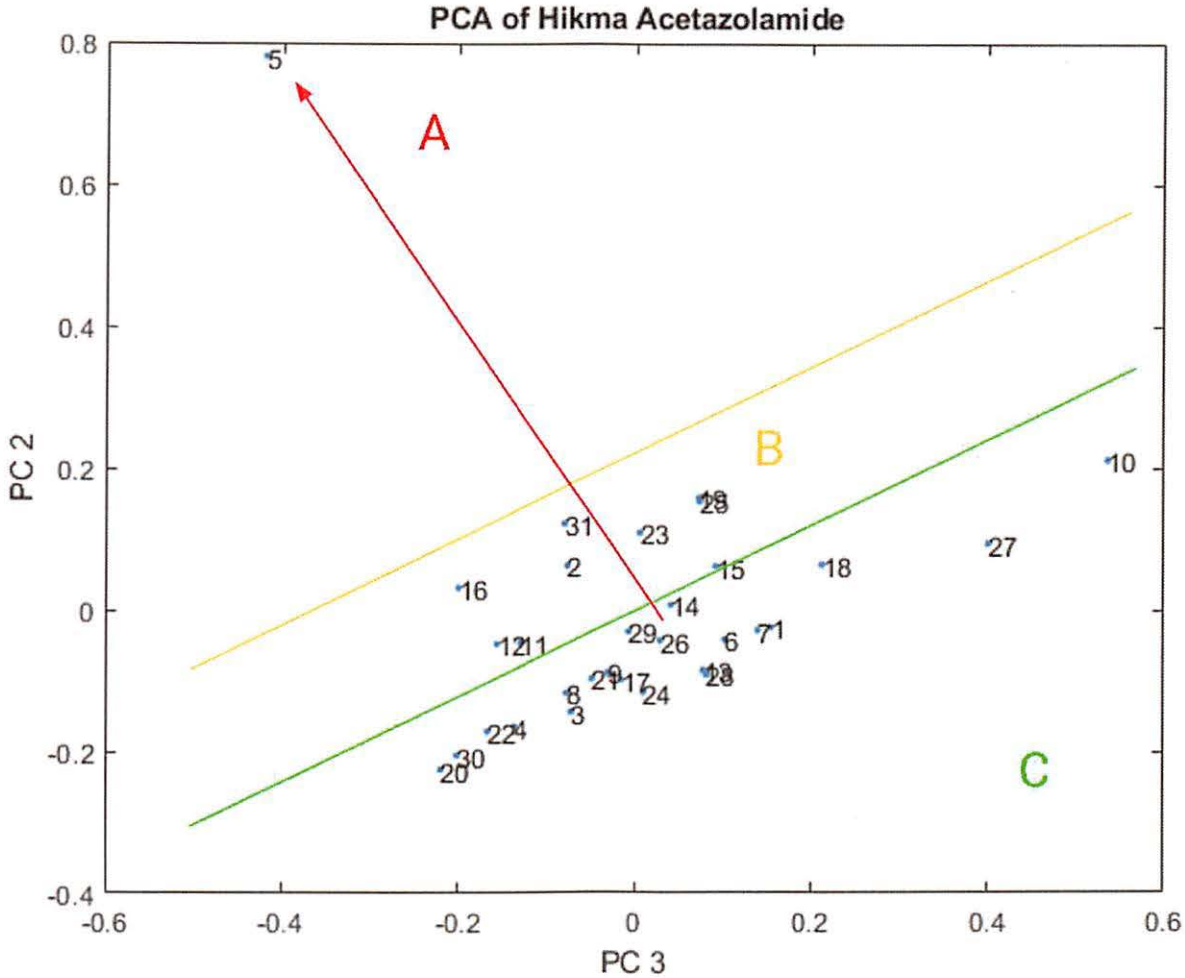

Figure 7. Principal component plot of the spectra in Figure 6. Eight other vials show the same peaks as vial 5, but at lower levels. A is the apparently most adulterated sample based on additional peaks in the spectrum, B are samples that contain similar peaks to A but in smaller amounts, and C are the vials with normal FTNIR spectra. The manufacturing procedure appears to be operating out of a state of process control.

Unlike the Mylan product that appeared as a lyophilized cake, the Hikma product resembled a crusty, flaky powder. One of the vials that didn't show any near-IR spectral anomalies (from group C in Figure 7) and one of the vials that demonstrated anomalies (from group A in Figure 7) were then scanned with GC-MS. The GC-MS results were strikingly different between Hikma vials from group C and the vial from A. Additionally, the Hikma vials from A and C were strikingly different from all of the Mylan vials (groups A, B, and C). Peaks at 6.5, 7.551 and 10.03 minutes as well as other minor peaks are increased in the Hikma group A sample in comparison to the Hikma group C sample.

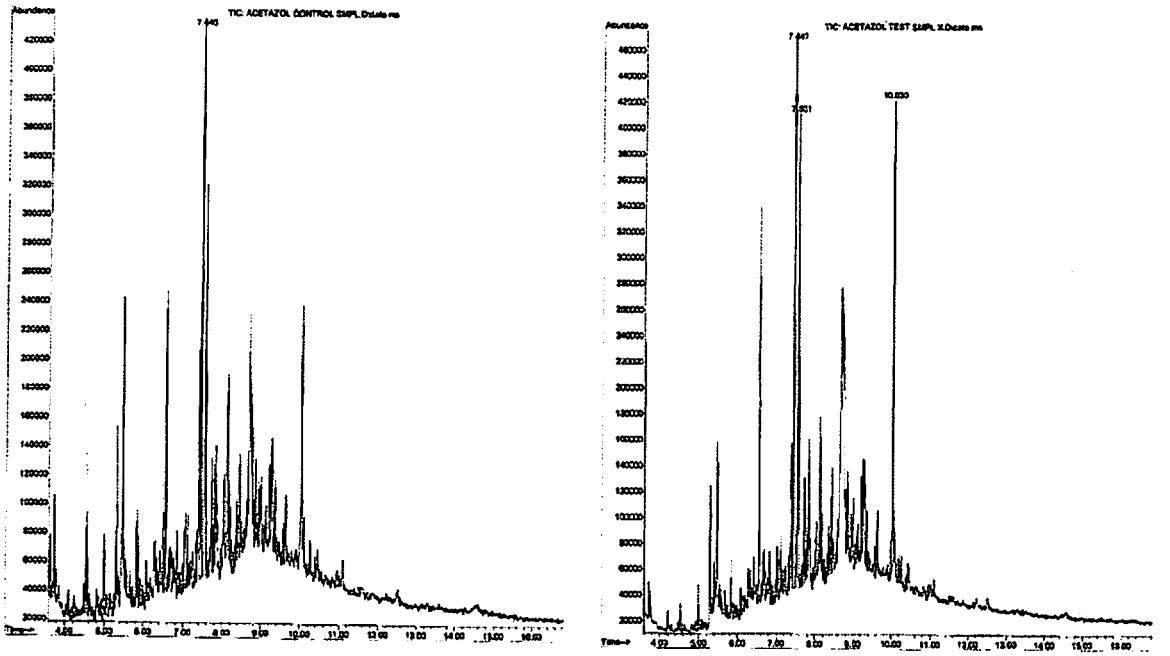

Figure 8. Total ion chromatograms from GC-MS of Hikma acetazolamide (left, labeled "control" from group C) and suspect Hikma acetazolamide (right, labeled "test" from group A). Peaks at 6.5, 7.551 and 10.03 minutes as well as other minor peaks are increased in the test sample.

On September 3, 2020 the UK DQS team contacted the FDA OPQ in writing about our concerns with the Hikma products as well. We have not received a response to this communication. This same day we notified our wholesaler in writing, as well as the manufacturer through their email address posted for such reporting. Escalating testing through independent third-party labs has not been initiated as we were waiting to see the outcome of the initial testing with the Mylan product.

On September 29, 2020 the UK DQS team performed LC-MS/MS analysis on two Hikma Acetazolamide vials that were previously evaluated by FTNIR and GC-MS, denoted vial HC (from group C in Figure 7) and HX (from group A in Figure 7) below. The same method and parameters used in the Mylan acetazolamide/USP acetazolamide LC-MS/MS analysis were applied to the Hikma acetazolamide/USP acetazolamide (USP Standard Lot R089P0) analysis. The Hikma acetazolamide vials in this study were found to contain 83.5% and 85.6% acetazolamide for the HC and HX vials, respectively. Importantly, both vials are from the same lot and neither of the samples meet the USP standards that the FDA requires. These findings warrant further investigation of the Hikma acetazolamide product.

Sample	HC	HX
Sample ID	Hikma Acetazolamide Lot: 2001028.1 Expiration: 02/2022	Hikma Acetazolamide Lot: 2001028.1 Expiration: 02/2022
Average %	83.5%	85.6%

Acetazolamide		

Table 3. UK DQS LC-MS/MS Analysis of Hikma Acetazolamide for Injection (lot 2001028.1) by comparison to USP Acetazolamide Standard (lot R089P0).

Importance of Acetazolamide for Injection

The UK DQS team understands the therapeutic needs for acetazolamide as it is currently listed on the World Health Organization's list of essential medicines. The UK DQS team also understands that a recall of any size could result in a supply disruption for patients who need this medication. Literature supports acetazolamide for injection to be utilized for the following labeled and off-labeled indications:

Adults:

- Edema
- Elevated intraocular pressure
- Metabolic alkalosis

Pediatrics:

- Edema
- Metabolic alkalosis

Given the importance of acetazolamide for injection in therapy, the definitive findings of adulteration with the Mylan lot that was examined, and the potentially concerning findings with the Hikma product, the four actions listed in section A are being petitioned.

C. Environmental Impact

Petitioner claims a categorical exclusion under 21 C.F.R. § 25.30, and believes that this Petition qualifies for a categorical exclusion from the requirement to submit an environmental assessment or environmental impact statement. To Petitioner's knowledge, no extraordinary circumstances exist.

D. Economic Impact

Pursuant to 21 C.F.R. § 10.30(b), economic impact information will be submitted by the Petitioner only upon request of the Commissioner following review of this Petition.

E. Certification

The undersigned certifies that, to the best knowledge and belief of the undersigned, this petition includes all the information and views on which the petition relies, and that it includes representative data and information known to the petitioner which are unfavorable to the petition.

Respectfully,

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