Involving Students in the Distributed Pharmaceutical Analysis Laboratory: A Citizen-Science Project to Evaluate Global Medicine Quality

Sarah L. Bliese, Margaret Berta, and Marya Lieberman*

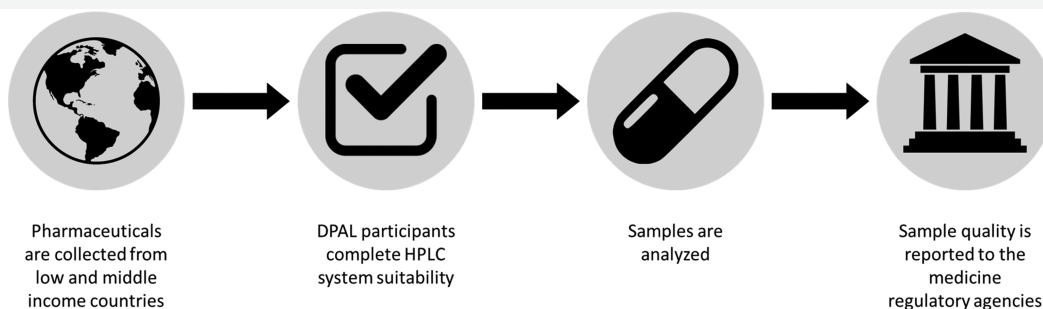Cite This: *J. Chem. Educ.* 2020, 97, 3976−3983

Read Online

| ACCESS | 📊 Metrics & More | 📰 Article Recommendations | 🔲 Supporting Information |

Pharmaceuticals are collected from low and middle income countries → DPAL participants complete HPLC system suitability → Samples are analyzed → Sample quality is reported to the medicine regulatory agencies

ABSTRACT: The distributed pharmaceutical analysis laboratory (DPAL) is a collaboration between 30 academic institutions around the world, whose goal is to determine the quality of medicines collected from partner organizations in low- and middle-income countries (LMICs). Institutions complete system suitability for a high-performance liquid chromatography (HPLC) system using United States Pharmacopeia (USP)-traceable reference standards and are then approved to analyze batches of samples that are collected in LMICs by covert shoppers. Open Science Framework (OSF) gives DPAL participants access to resources for the program including a HPLC methodology manual, a wiki with HPLC troubleshooting information, detailed checklists and Excel templates for system suitability and sample assay, as well as steps for reporting results. Participants incorporate the DPAL program into their academic curriculum as undergraduate research or via lab activities for analytical chemistry or instrumental analysis courses. Over a thousand samples have been analyzed through DPAL in the last three years, and 168 samples with quality problems have been discovered, including falsified acetaminophen, adulterated amoxicillin-clavulanate and doxycycline, and substandard losartan. These quality problems are reported to the medicine regulatory agencies in the countries of origin and the WHO Rapid Alert System for further action. This real-world program gives students a hands-on opportunity to see the importance of analytical metrics taught in the classroom.

KEYWORDS: *Second-Year Undergraduate, Analytical Chemistry, Hands-On Learning/Manipulatives, Inquiry-Based/Discovery Learning, Applications of Chemistry, Drugs/Pharmaceuticals, Instrumental Methods, HPLC, Quantitative Analysis, Undergraduate Research*

■ INTRODUCTION

The use of real-world applications in scientific teaching can be greatly beneficial for students. Learning is enhanced when the discussion shows how the topic matter can solve problems that are familiar to students.[1,2] When their research or class topic shows up on the evening news, it powerfully illustrates to students that science does, indeed, have relevance to peoples' lives.[3−5]

Substandard and falsified pharmaceuticals are a worldwide problem, with disproportionate impact in low- and middle-income countries (LMICs). The World Health Organization (WHO) reported that 1 in 10 medical products being sold in LMICs are substandard or falsified.[6] Substandard pharmaceuticals can cause drug resistance and increased mortality and morbidity and lead to a loss of confidence in the healthcare system.[7] Lack of efficacy, harmful side effects, and even death can arise from falsified pharmaceuticals that have been adulterated with inert fillers or substitute active pharmaceutical ingredients (APIs).[8]

Most pharmacopeia assays rely on high-performance liquid chromatography (HPLC), which is a scarce resource in LMICs. An HPLC costs tens of thousands of dollars, not

including operational costs such as purified solvents, analytical grade balances and glassware, columns, and pharmaceutical standards. Additionally, a complex infrastructure such as consistent power, reliable transportation of supplies, availability of trained operators and resources for maintenance and repairs, and proof of a high level of training and documentation are required for sustainable operation. These costs are magnified by the extensive assays required by the full monograph procedure and the fact that, if 10% of the drugs in a market are substandard or falsified, 9 out of 10 drugs are NOT substandard or falsified. The cost of detecting each bad quality product must include the cost of analyzing multiple good quality products. For this reason, routine analysis of medicine quality is severely limited in many LMICs.

One way to tackle a large-scale project such as pharmaceutical postmarket surveillance is by using crowd-sourcing or citizen science. Citizen science refers to a participative way of running scientific research projects, done mostly through the Internet for data collecting, processing, and analysis.[9,10] This model allows for a monitoring system that cannot be attainable by individual or government entities alone.[11] We founded the distributed pharmaceutical analysis lab (DPAL) after realizing that we had too many samples for our lab to analyze in a meaningful time frame. By partnering with other institutions, we were able to continue collecting hundreds of samples to gather a better understanding of medicine quality through the region while also speeding analysis.

The distributed pharmaceutical analysis lab project aims to make analytical capacity at colleges and universities around the world available to carry out preliminary HPLC tests of medicines purchased in LMICs.[12] Our goal in the DPAL is to allow regulatory agencies in LMICs to focus their analytical resources on the worst quality products. While other analytical chemistry experiments have been developed to allow students to study pharmaceuticals,[13−15] the focus of DPAL is on providing as robust an operational environment as possible in an academic setting. Thus, the program emphasizes standard operating procedures, record keeping, verification of system suitability, and quality assurance/control (QA/QC) practices. By placing these in the natural context of an important real-world assay, we aim to help students see why analytical chemists care about reliability of assays and how their own careful work can contribute to finding and thwarting drug counterfeiters.

■ MATERIALS

Sample Collection and Intake Protocol

Details of sample collection and intake were described in a previous work.[12] Briefly, covert shoppers collect samples of pharmaceuticals from small medicine shops in cities and towns across Western Kenya, which are then brought to Moi Teaching and Referral Hospital (MTRH), where the sample metadata (brand, expiration date, lot number, etc.) are transcribed onto a spreadsheet prior to shipping to the University of Notre Dame (UND). Permission was obtained from the MTRH Institutional Research & Ethics Committee (protocol # 000836) for the collection and shipment of samples.[16] In 2016, 2017, 2018, and 2019, 1300, 150, 200, and 667 samples were collected, respectively.

All samples are assigned a Notre Dame identification number (NDID), which is used for sample reporting. A brief physical examination of each sample is conducted to identify packaging issues that could lead to product degradation or which indicate poor manufacturing. After sample intake, samples are stored in a 4 °C cold room until they are sent for analysis.

DPAL Participant Requirements and Costs

Academic institutions that participate in DPAL are required to have the basic instrumentation required for pharmaceutical analysis, including a properly calibrated analytical balance, a high-performance liquid chromatograph with ultraviolet, photodiode array, or mass spectrometer detector capable of collecting and analyzing data. The cost of columns, analytical standards, and HPLC solvents for many pharmaceutical assays is comparable to the costs for other undergraduate HPLC experiments, so the DPAL experiments fit into existing budgets for undergraduate analytical or instrumental analysis courses.[12] In some cases, where funds are limited, the DPAL project has been able to provide reference materials and access to monographs through a partnership with the US Pharmacopeial Convention (USP).

Open Science Framework (OSF)

After participants have expressed interest in joining the distributed pharmaceutical analysis lab, they are given access to the DPAL Open Science Framework (OSF) project.[17] By joining the DPAL OSF site, participants must agree to abide by DPAL policies regarding data security, integrity, and publishing. OSF is free to use and only requires an Open Researcher and Contributor ID (ORCID) to register.[18] All participants are given access to the main DPAL site where they can download the HPLC Methodology Manual, found in the Supporting Information. The Methodology Manual is a continuously updated document that defines the standard operating procedures for carrying out pharmaceutical assays. Also available are checklists for system suitability, Excel spread-sheets formatted for one- and two-drug products, a wiki for exchanging HPLC troubleshooting tips, and other information that participants can download and use freely.[12]

Each participant school has its own component OSF site, which contains their analytical information, data, and a wiki. The faculty advisor for the participant school can load the Methodology Manual and Excel templates to the component site and give other faculty members and students access (Supporting Information). Students can download the template files and upload their data, scan and share their notebook pages, or make wiki entries (Supporting Information).[12] OSF allows users to create a snapshot of their site with its own DOI; this registered OSF site can be used to archive the raw data and calculated results for a publication or presentation.

Legal Considerations

DPAL is not a certified pharmaceutical analysis laboratory; participants perform single-tablet API assays and do not conduct full compendial testing on pharmaceutical products. This means that the data produced cannot be used in a legal context to certify a medicine's quality. The goal of the DPAL is to report suspicious samples to medicine regulatory agencies, so they can conduct the compendial analysis. DPAL provides templates to participants to record their HPLC method, system suitability results, and sample analysis results to ensure that uniform procedures and calculations are conducted so the data can be traced back and checked for error.[12] The HPLC

University	Pick Target	Phase 1 SS	Phase 2 SS	Sample Analysis
Boston University	Acetaminophen	Completed	Completed	NA
Campbell University	Albendazole	Completed	In Progress	
Coe College	Ciprofloxacin	In Progress		
DePauw University	Ampicillin	In Progress		
Dublin Institute of Technology	Azithromycin	Completed	Completed	Analyzed 50
Ferrum College	Magnesium (via AAS)	In Progress		
Geneva College	Levofloxacin	In Progress	Completed	Analyzed 12
Grand View University	Albendazole	In Progress		
Hamline University	Artemether/Lumefantrine	In Progress		
	Ciprofloxacin	Completed	Completed	Analyzed 40
Indiana University-Bloomington	Levofloxacin and Ofloxacin	Completed	Completed	Analyzed 100
Indiana University-South Bend	Acetaminophen	Completed	Completed	NA
Maryville College	Acetaminophen	Completed	Completed	Analyzed 20
Millikin University	Acetaminophen	Completed	Completed	Analyzed 5
Murdoch University	Metformin	In Progress		
Newman University	Doxycycline	In Progress		
	Sulfamethoxazole/Trimethoprim	In Progress		
Niagara University	Ampicillin/Cloxacillin	Completed	Completed	Analyzed 21
	Metformin	Completed	Completed	Analyzed 59
Pacific Union College	Doxycycline	In Progress		
Roanoke College	Acetaminophen	Completed	Completed	In Progress
	Amoxicillin	Completed	Completed	NA
	Ciprofloxacin	Completed	Completed	NA
Roberts Wesleyan College	Ampicillin/Cloxacillin	In Progress		
St. Mary's College	Acetaminophen	Completed	Completed	Analyzed 175
	Albendazole	Completed	Completed	Analyzed 180
	Amoxicillin	Completed	Completed	Analyzed 134
	Amoxicillin/Clavulanate	Completed	Completed	Analyzed 131
	Metformin	Completed	Completed	Analyzed 138
Southern Oregon University	Sulfamethoxazole/Trimethoprim	In Progress		
SUNY Adirondack	Omeprazole	In Progress		
University of Indianapolis	Ampicillin/Cloxacillin	Completed	Completed	In Progress
	Metformin	Completed	Completed	In Progress
University of Northern Colorado	Amoxicillin	In Progress		
University of Wisconsin-Madison	Cephalexin	Completed	In Progress	Analyzed 10
	Quinine	Completed	Completed	NA
US Coast Guard Academy	Doxycycline	Completed	Completed	Analyzed 30
Virginia Wesleyan University	Cephalexin	Completed	Completed	Analyzed 6
Waynesburg University	Amoxicillin/Clavulanate	In Progress		
Westminster College	Acetaminophen	In Progress		

Figure 1. DPAL participants.

Methodology Manual explicitly states the expectations for quality and data security and addressed procedural protocols.[12] Legal considerations of pharmaceutical analysis are discussed to ensure that all participants fully understand how to correctly report and present DPAL results.

System Suitability Requirements

After choosing an analyte whose assay is based on USP methodology, the DPAL participant must demonstrate system suitability through a series of tests laid out in USP <1225> and USP <1226>. These tests determine whether the methodology and the instrument are working properly for analysis of a particular pharmaceutical. The results of the system suitability tests must be within acceptable limits defined in the Methodology Manual to be considered valid. Participants must show their results in a provided Excel template to prove that they have met the qualifications for each experiment (Supporting Information). The DPAL program requires that

participants successfully complete all the required system suitability tests and submit the results for review before samples from LMICs are sent for analysis.[12]

System suitability experiments are separated into two parts. Part One is based on samples prepared using a reference standard and includes:

1. Keeping a record of peak metrics including asymmetry and theoretical plates with sample chromatograms.

2. Establishing a control chart that includes information about the peak shape, retention time, resolution, and integrated intensity. This document is not only used as a record of activity for each day but also functions as a diagnostic reference when issues arise.

3. Instrument precision is tested by the injection of one sample six consecutive times. The relative standard deviation of the integrated intensity for each run must be less than 2%.

4. To meet the linearity requirement for system suitability, the y intercept must fall within the error of zero and the R^2 value should be greater than 0.98.

5. The accuracy and range experiment demonstrates that the method can accurately analyze various sample concentrations along the defined linear range. To evaluate the accuracy and range, four solutions are prepared: an overdosed sample, a normal sample, a deficient sample, and a blank that contains no API. Each of these solutions are run in triplicate and the measured concentrations of the samples should be within 2% of their true concentration.

6. Limit of detection (LOD) is calculated to determine the lowest quantity detectable that is significantly different from zero. The experiment is conducted via the slope-standard deviation method, with the standard deviation generated by running six samples at concentrations 2–3 times the expected LOD as estimated from the linearity plot. A chromatogram must be collected at the calculated LOD concentration to confirm detection.

Part Two of the system suitability is conducted using real dosage forms supplied by UND and includes:

1. For the spike recovery experiment, a pharmaceutical dosage form is used to make the sample solution. An aliquot of the sample solution is prepared with an additional 30% spike of API standard. The spike is determined by comparing the sample assay to the spiked sample assay. An acceptable spike recovery is between 90 and 110% of the spike.

2. Specificity is completed like spike recovery but with a complex matrix, such as one that contains degradation products of the API. An expired sample may be used or one that has been thermally or chemically degraded. The samples are run per the spike-recovery method to calculate percent recovery. An acceptable spike recovery is between 90 and 110% of the spike.

After the participant institution meets the system suitability requirements, they can analyze pharmaceutical samples from LMICs. Before each day's sample analysis, five injections of an external calibration standard are analyzed to check precision (alternatively five solutions are prepared to generate a calibration curve, which must meet the linearity requirements for system suitability), and this calibration standard is rechecked every five samples to be sure the integration stays within the 2% RSD limit. If the calibration check fails, the five preceding samples must be rerun. For each assay, the mass of the capsule or tablet and the stated API content are recorded and used for determining the total amount of active pharmaceutical ingredient in the sample. If the pill does not meet pharmacopeia specifications found in an official monograph (generally 90–110 or 120% of stated API content, depending on the monograph), the sample is reanalyzed to confirm the result. If the sample still fails to meet quality specifications, then two additional capsules or tablets are assayed. Samples that are found to be substandard are analyzed at the University of Notre Dame for additional testing, and results are reported to the country's regulatory agency and the WHO Rapid Alert program.

■ RESULTS

The DPAL project started in 2014 and expanded significantly in 2018 after presentations on the project at the BCCE meeting.[19] There are currently 29 institutions in DPAL. Some of these schools incorporate the DPAL program as an undergraduate research project or chemistry club activity, and others use it as part of instrumental analysis or analytical chemistry courses. Fifteen of the institutions have completed system suitability for at least one drug, and 11 have reported assays for samples. Figure 1 shows the participating institutions, their target pharmaceuticals, and their status within the program.

DPAL participants were surveyed about the program structure and outcomes from their participation. Eleven participants who had completed at least phase 1 of system suitability testing responded to the survey. Most of the participants (73%) were either the only analytical chemist in their department or had one other analytical colleague. Instructor support and the connections with analytical chemists at other DPAL schools were viewed as a positive feature, "DPAL makes it easier on me as a supervisor because there is a clear path to follow for every student and they have to show proficiency at each step before they can go on to the next step - not unlike working at a commercial analysis facility." "Although we are independently collecting and analyzing our own samples, we take advantage of the validated HPLC methods developed by other groups."

Over 90% of participants agreed or strongly agreed that DPAL engages students and that it is relevant to instrumental analysis topics. Features that advisors felt contributed to student engagement included the humanitarian application— as one respondent put it, "The analysis was implemented with a freshmen honors chemistry class. They could not believe that they were doing lab work that really mattered." The tie-ins to other instrumentation topics were also seen as motivating, as one respondent noted "Doxycycline capsule contents varied widely. Our students are planning to use FT-IR and RAMAN to analyze the differences associated with each of them. We will also look at the carbon and proton NMR for further analysis." Advisors noted that although the instrumental techniques were usually straightforward, students gained a deep understanding of instrumental quality control. They felt that this feature of the project built skills that are needed by industrial chemists. "It transforms mundane and boring technical work into the important context that these students would face if they worked in a pharmaceutical lab, and having that reality during the learning event makes the students much more engaged and committed to doing good work."

The DPAL projects have two main stages: system suitability, followed by sample analysis. Sample analysis was viewed as slightly easier to incorporate into the analytical lab courses, mostly because system suitability involves a larger variety of tasks and a greater number of potential problems that could arise. "···sample analysis is a simpler SOP and was easy to implement in the teaching laboratory." "System suitability requires greater dedication and time commitment along with strong record-keeping and so I think it better matches with undergraduate research." "The system suitability process took one and a half semesters to troubleshoot and perform. We moved at the speed of my one research student who is signed up for 6 h a week." Other participants worked system suitability into a lab class, "The mathematics required for determining and understanding LOD or standard deviation in conjunction with the HPLC-UV/Vis is a great way to show the importance of the instrument to an analytical class." All participants agreed that both system suitability and sample
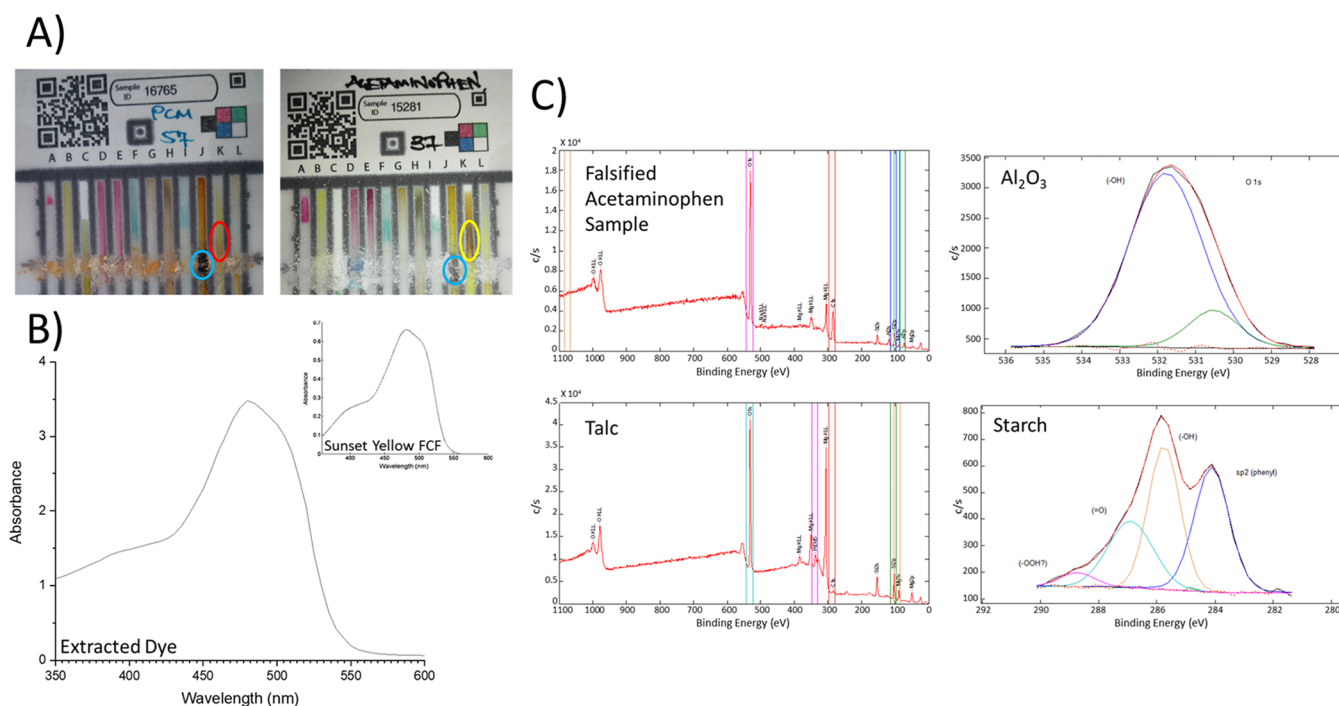
Figure 2. Falsified sample of acetaminophen. (A) Left PAD is the suspicious sample that did not turn Lane K brown (red circle), as shown in the PAD on the right (yellow circle). Both PADs detected starch (blue circles). (B) Extracted dye in chloroform from the suspicious sample with an insert of Sunset Yellow FCF used to confirm the identity. (C) Left XPS spectra show the comparison of the suspicious sample to talc, and the right show the detection of aluminum oxide and starch.

analysis were suitable for undergraduate research projects; 42 students have participated in this form of the DPAL program. Thirty-six percent of the respondents implemented at least one of the DPAL tasks in analytical or instrumental analysis courses as well, and 171 students participated in this form of the DPAL program. Some respondents felt that sample analysis was too limited as the basis for an undergraduate thesis but that the projects could be expanded by including other instrumental techniques or analysis methods, "The ability to participate in this program early has allowed students to gain a better understanding of analytical procedures. Continued participation also allowed them to think of other analysis techniques (degradation study, FT-IR or RAMAN analysis)." A total of 68 poster presentations, 38 oral presentations, and 28 senior theses or capstone reports have been completed by undergraduates throughout the program. Most of these were internal presentations, but there have been nine national or international poster presentations and three national or international oral presentations by DPAL participants.

Over 1000 samples have been analyzed through DPAL. A total of 168 samples failed HPLC assay; this level of failing samples is consistent with estimates for the prevalence of substandard and falsified (SF) pharmaceuticals in the countries where the samples were collected.[20] Failing samples included falsified acetaminophen tablets, losartan pills with unacceptable pill-to-pill variation in API content, falsified doxycycline capsules, substandard and falsified amoxicillin capsules,[21] substandard amoxicillin/clavulanic acid tablets, and degraded injectable ceftriaxone.[22] A report of the findings is sent as quickly as possible to the drug regulatory agency and partner organizations in the country where the samples were collected; products with less than 50% API content are also reported to the WHO Rapid Alert system.

Products that fail quality standards undergo additional testing at both UND and the DPAL partner school to confirm the HPLC findings and gain insight into the root cause of the failure. These root cause investigations extend the instrumental analysis methods used by students and are also a useful contribution to the reports to regulators, as they may guide possible regulatory responses.

One hundred and ten samples of acetaminophen were analyzed, with only two failing to meet quality standards. One sample was deficient in API content and the other did not contain any active ingredient. The falsified sample was found to consist of 40% starch and 60% inorganic material. Figure 2A shows the paper analytical device (PAD)[23] screening that detected the starch and noted the absence of acetaminophen. Figure 2B shows the ultraviolet (UV) spectrum that identified the dye used to color the tablet as Sunset Yellow FCF. Figure 2C shows the X-ray photoelectron (XPS) spectra that suggested the presence of talc and aluminum oxide as the inorganic components left over after extraction. This sample illustrates the pervasiveness of drug falsification—even a low-cost product like generic paracetamol is the target of counterfeiters.

Thirty-eight losartan samples were assayed. Over one-third (39.5%) of the blister packs showed pill heterogeneity issues, where one or more of the tablets within the blister pack would fail the assay but a neighboring tablet would pass the assay. This quality issue was found throughout all samples and not linked to any specific brand. An example of this heterogeneity is shown in Table 1. This type of failure represents a possible failure of good manufacturing process (GMP), so the country regulatory authorities receive a report and these brands may receive more scrutiny in future rounds of testing.

Forty-nine samples of doxycycline were analyzed, and 71.4% of them were found to be falsified products composed of 50%

Table 1. HPLC Results Demonstrating Quality Issues with Losartan Samples

Sample	API Present, %	Result
Pill Heterogeneity Issue[a]		
Pill one	70.2	Fail
Pill one retest	70.0	Fail
Pill two	75.1	Fail
Pill three	90.5	Pass
Substandard Quality Issue[b]		
Pill one	82.6	Fail
Pill one retest	86.2	Fail
Pill two	83.1	Fail
Pill three	81.7	Fail

[a]Two tablets failing analysis. [b]All three tablets failing analysis.

API and 50% talc. This product was reported immediately to the country drug regulatory agency and to the WHO Rapid Alert system. Figure 3 shows the attenuated total reflectance-Fourier-transform infrared (ATR-FTIR) spectra for a standard of doxycycline, a good quality dosage form, a falsified product, and pure talc. The strong band at just below 1000 cm^{-1} is from the Si−O stretching modes for silicate groups in the talc. The venerable technique of gravimetry was used to determine the talc percentage after extensive washing with methanol to remove doxycycline.

■ DISCUSSION

The multifaceted aspect of the distributed pharmaceutical analysis laboratory makes it an ideal project for the undergraduate analytical curriculum.[12] Completion of the

system suitability components can take 1−2 semesters, which allows them to serve as a student research project focused on HPLC troubleshooting and analytical metrics prior to conducting sample analysis. Alternatively, the completion of system suitability can be conducted in an analytical chemistry or instrumental analysis lab, with different students being responsible for different components of suitability testing. In the past, we have also had instructors or their TA's complete system suitability prior to students in the class so they can focus on sample analysis by only replicating parts of the system suitability requirements with the entire class.

The effectiveness of the DPAL program is limited by several logistic factors, largely dependent on communication.[12] Participants must complete the phase one portion of system suitability using reference-grade standards, which is reviewed by DPAL program coordinators prior to sending samples from completion of the phase two portion of system suitability. Upon completion of sample analysis, substandard samples are further tested at Notre Dame to determine composition and a final report is prepared by the DPAL participant and DPAL program coordinators for the medicine regulatory agencies to review. Using Open Science Framework has helped expedite the data sharing process for more rapid turnaround from system suitability completion to sample analysis.

■ CONCLUSION

Poor quality pharmaceuticals are a problem in many LMICs due to the cost of conducting instrumental analysis required for effective postmarket surveillance. The distributed pharmaceutical analysis laboratory engages academic institutions around the world that can conduct assays of medicine
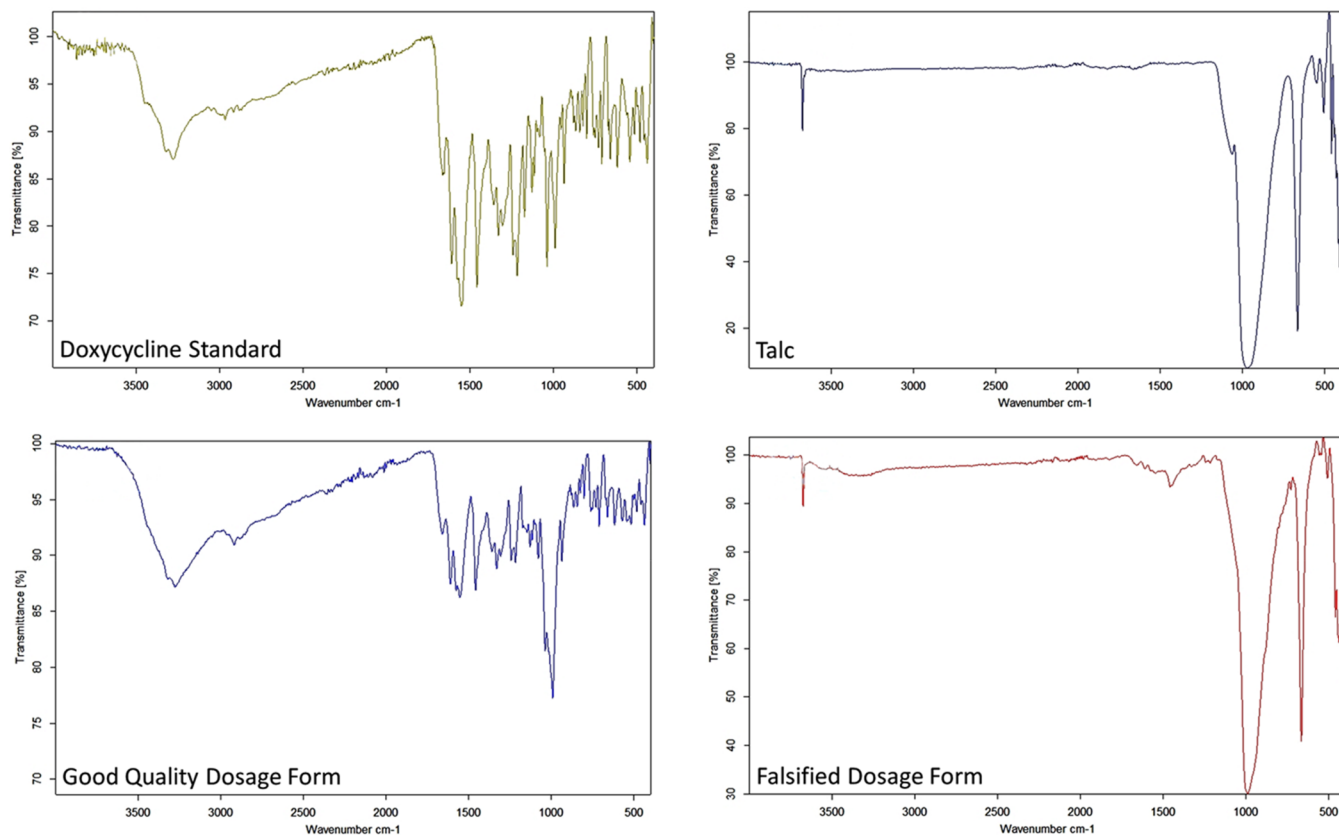

Figure 3. ATR-FTIR spectra for doxycycline dosage forms.

collected in LMICs via HPLC. The tests for system suitability and metrics for conducting sample analysis required from DPAL participants fit well into instrumental analysis and analytical chemistry lab courses and can also be carried out via undergraduate research. To ensure that the sample analysis results are accurate, DPAL participants must complete both phases of system suitability, which is reviewed by the DPAL program coordinators before analyzing samples. Open Science Framework is used for recording raw data, calculations, and summary reports between DPAL coordinators and participants. OSF houses templates, HPLC methods, and troubleshooting tips accessible by all DPAL participants. Further development of the program will focus on connecting DPAL participants to collaborators in LMICs for program growth and impact.

■ ASSOCIATED CONTENT

si Supporting Information

The Supporting Information is available at https://pubs.acs.org/doi/10.1021/acs.jchemed.0c00904.

HPLC Methodology Manual (PDF)
System suitability templates (XLSX)
Sample analysis templates (XLSX)

■ AUTHOR INFORMATION

Corresponding Author

Marya Lieberman − *Chemistry and Biochemistry Department, University of Notre Dame, Notre Dame, Indiana 46556, United States;* ⊙ orcid.org/0000-0003-3968-8044; Email: mlieberm@nd.edu

Authors

Sarah L. Bliese − *Chemistry and Biochemistry Department, University of Notre Dame, Notre Dame, Indiana 46556, United States;* ⊙ orcid.org/0000-0001-5353-4063

Margaret Berta − *Chemistry and Biochemistry Department, University of Notre Dame, Notre Dame, Indiana 46556, United States*

Complete contact information is available at:
https://pubs.acs.org/10.1021/acs.jchemed.0c00904

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

■ REFERENCES

(1) Gallagher, J. J. Teaching for Understanding and Application of Science Knowledge. *Sch. Sci. Math.* **2000**, *100* (6), 310−318.

(2) Fortus, D.; Krajcik, J.; Dershimer, R. C.; Marx, R. W.; Mamlok-Naaman, R. Design-based science and real-word problem-solving. *Internat. J. Sci. Ed.* **2005**, *27* (7), 855−879.

(3) Strand, K. J. Community-Based Research as Pedagogy. *Mich. J. Comm. Serv. Learn.* **2000**, *7*, 85−96.

(4) Piranty, S. Coronavirus fuels a surge in fake medicines. https://www.bbc.com/news/health-52201077 (accessed 2020-09-09), BBC World Service, 2020.

(5) Hirschler, B. Tens of thousands dying from $30 billion fake durgs trade, WHO says. https://www.reuters.com/article/us-pharmaceuticals-fakes/tens-of-thousands-dying-from-30-billion-fake-drugs-trade-who-says-idUSKBN1DS1XJ (accessed 2020-09-09) Health News, Reuters, 2017.

(6) World Health Organization. License: CC BY-NC-SA 3.0 IGO. *WHO Global Surveillance and Monitoring System for Substandard and Falsified Medical Products*, 2017.

(7) Newton, P. N.; Green, M.; Fernandez, F. M. Impact of poor-quality medicines in the 'developing' world. *Trends Pharmacol. Sci.* **2010**, *31*, 99−101.

(8) World Health Organization. Ref. RHT/SAV/MD/4/2015. *WHO Medical Product Alert No. 4/2015: Adverse reactions caused by falsified Diazepam in Central Africa*, 2015.

(9) Prats López, M.; Soekijad, M.; Berends, H.; Huysman, M. A Knowledge Perspective on Quality in Complex Citizen Science. *Citizen Science: Theory and Practice* **2020**, *5* (1), 15.

(10) Aristeidou, M.; Herodotou, C. Online Citizen Science: A Systematic Review of Efforts on Learning and Scientific Literacy. *Citizen Science: Theory and Practice* **2020**, *5* (1), 11.

(11) Roger, E.; Turak, E.; Tegart, P. Adopting Citizen Science as a Toll to Enhance Monitoring for an Environment Agency. *Citizen Science: Theory and Practice* **2019**, *4* (1), 35.

(12) Bliese, S. L.; Berta, M.; Myers, N. M.; Lieberman, M. Distributed Pharmaceutical Analysis Laboratory (DPAL): Citizen Scientists Tackle a Global Problem in Mobilizing chemistry expertise to solve humanitarian problems. *Mobilizing Chemistry Expertise To Solve Humanitarian Problems*, Vol. 1; American Chemical Society: Washington DC, 2017; 117−128.

(13) Fakayode, S. O. Purity Analysis of the Pharmaceuticals Naproxen and Propranolol: A Guided-Inquiry Laboratory Experiment in the Analytical Chemistry Laboratory. *J. Chem. Educ.* **2015**, 92 (1), 157−162.

(14) Zakrzewski, R.; Skowron, M.; Ciesielski, W.; Rembisz, Z. Spectrophotometric Determination of 6-Propyl-2-thiouracil in Pharmaceutical Formulations Based on Prussian Blue Complex Formation: An Undergraduate Instrumental Analysis Laboratory Experiment. *J. Chem. Educ.* **2016**, 93 (1), 182−185.

(15) Pacilio, J. E.; Tokarski, J. T.; Quiñones, R.; Iuliucci, R. J. High-Resoluion Solid-State NMR Spectroscopy: Characterization of Polymorphism in Cimetidine, a Pharmaceutical Compound. *J. Chem. Educ.* **2014**, 91 (8), 1236−1239.

(16) Karwa, R.; Tran, D. N.; Maina, M.; Njuguna, B.; Manji, I.; Wasike, P.; Tonui, E.; Kigen, G.; Pastakia, S. D. Addressing the 3A's (Availability, Accountability, Adherence) of Supply Chain Systems in Western Kenya in Mobilizing chemistry expertise to solve humanitarian problems. *Mobilizing Chemistry Expertise To Solve Humanitarian Problems*, Vol. 1; American Chemical Society: Washington DC, 2017; 129−158.

(17) OSF. Distributed Pharmaceutical Analysis Laboratory (DPAL). https://osf.io/k9ap7/ (accessed 2020-09-09).

(18) ORCID: Connecting research and researchers. https://orcid.org/ (accessed 2020-09-09).

(19) Lieberman, M. What Would You Fight For?. 25th Biennial Conference on Chemical Education, Notre Dame, IN, July 30, 2018.

(20) Ozawa, S.; Evans, D. R.; Bessias, S.; Haynie, D. G.; Yemeke, T. T.; Laing, S. K.; Herrington, J. E. Prevalence and Estimated Economic Burden of Substandard and Falsified Medicines in Low- and Middle-Income Countries: A Systematic Review and Meta-analysis. *JAMA Netw Open* **2018**, 1 (4), e181662.

(21) Myers, N. M.; Maina, M. W.; Were, P. M.; Karwa, R.; Pastakia, S. D.; Sharp, J. C.; Luther, J. L.; Cooper, A.; Bliese, S. L.; Oberhof, N.; Aldulaimi, D.; Lieberman, M. Lab on paper: assay of beta-lactam pharmaceuticals by redox titration. *Anal. Methods* **2019**, 11, 4741−4750.

(22) Bliese, S. L.; Maina, M. W.; Were, P. M.; Lieberman, M. Detection of degraded, adulterated, and falsified ceftriaxone using paper analytical devices. *Anal. Methods* **2019**, 11, 4727−4732.

(23) Weaver, A. A.; Reiser, H.; Barstis, T.; Benvenuti, M.; Ghosh, D.; Hunckler, M.; Joy, B.; Koenig, L.; Raddell, K.; Lieberman, M. Paper analytical devices for fast field screening of beta lactam antibiotics and anti-tuberculosis pharmaceuticals. *Anal. Chem.* **2013**, 85 (13), 6453−6460.