USP Technology Review: ASD QualitySpec® (Trek)

Report Date: May 2019

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Executive Summary

A technology review was carried out on the ASD QualitySpec® (Trek), a portable near infrared (NIR) spectrometer, to determine its feasibility as a first-line screening technology to identify the presence of active pharmaceutical ingredients (APIs) in select drug products (DPs). The performance evaluation involved the analysis of four coformulated tablet samples (artemether+lumefantrine, rifampicin+isoniazid+pyrazinamide+ethambutol, rifampicin+isoniazid+ethambutol, and rifampicin+isoniazid), single API tablet and capsule samples (amoxicillin), one coformulated oral suspension sample (sulfamethoxazole and trimethoprim), and one gel formulation sample (chlorhexidine digluconate). Samples were analyzed through their original packaging, in glass vials, in plastic bags, and directly against the dosage form, both "as is" and powdered. Samples of different dosage strengths were used. To mimic substandard/falsified medicines, some samples were subjected to heat exposure at 105°C for 17 hours.

Overall, Trek provides reliable NIR data for DP identification (ID), with distinct advantages over other vibrational spectroscopies such as Fourier transform infrared and Raman. The NIR penetration depth for solid dosage form medicines is better than IR or Raman, and this enables through-package analysis. The ID method involved applying a match factor ID metric following spectral preprocessing. A correlation coefficient match factor, termed a mismatch factor (MMF), ID algorithm was applied successfully using a sensitivity and selectivity threshold of no more than (NMT) 5 and no less than (NLT) 15, respectively. The MMF of zero indicates a perfect match. By comparing the spectra of DPs removed from packaging (e.g., blister pack/capsule) with packaged DPs, it was possible (although interferences were observed) to generate DP specific information through the packaging in many cases. It was also found that, by covering the bottom of a small vial with the DP substance of interest (at least 1 mm high), quality NIR data could be collected through the bottom of the vial. The instrument was able to identify several of the APIs in the various products (artemether, lumefantrine amoxicillin, rifampicin, isoniazid, ethambutol, pyrazinamide). For the gels and liquids, quality data could not be collected from these samples due to interference from water.

However, the instrument has some general limitations. The unit is fragile and likely to be damaged if dropped. It is also heavy and designed to be pressed up against large surfaces rather than to have small DP samples pressed up against the analysis window. A simple redesign could make this instrument much more user friendly for quality screening of DPs. Although spectra can be viewed on the unit, there is no onboard ID software. For identification, spectra must be transferred to a separate computer, and all identification methods must be developed using third-party software. The instrument operating software is not intuitive. Some bugs were identified, the most serious of which was that the instrument became inoperable after creating a project name with more than 20 characters.

The field evaluation showed that most medicine regulatory inspectors, chemists, laboratory analysts, and pharmacists with various levels of technical experience from two countries, Zambia and Indonesia, could become either basic, intermediate, or advanced users of the technology within 2 weeks. Trek functioned well in the field: running on lithium batteries, collecting data quickly, and presenting results on the instrument screen. One challenge encountered in the field was that the Trek software was not particularly user friendly: there was no overlay of spectra on the instrument screen for comparison purposes of the samples.

Acknowledgments

The authors would like to acknowledge the following for their guidance, contribution, support, and feedback in the development of this report:

- USP Review of Surveillance and Screening Technologies for the Quality Assurance of Medicines Expert Panel
- National Agency of Drug and Food Control of Indonesia (BBPOM)
- Zambia Medicines Regulatory Authority (ZAMRA)

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Acronyms

AL	artemether–lumefantrine
AMX	amoxicillin
API	active pharmaceutical ingredient
CD	chlorhexidine digluconate
DP	drug product
ID	identification
IR	infrared
MMF	mismatch factor
NIR	near infrared
NLT	no less than
NMT	no more than
RH	rifampicin–isoniazid
RHE	rifampicin–isoniazid–ethambutol
RHZE	rifampicin–isoniazid–pyrazinamide–ethambutol
ST	sulfamethoxazole–trimethoprim
USP	U.S. Pharmacopeial Convention
WHO	World Health Organization

1. Introduction

Assuring the quality of medicines along all points of the supply chain is vital for promoting positive health outcomes for patients around the world [1]. The importance of medicine quality screening technologies as part of this endeavor is becoming increasingly recognized [2], and USP has launched the Technology Review Program, an initiative guided by a technical expert panel established through the organization's collaborative and volunteer-driven governance. The Technology Review Program works toward four objectives:

1. Develop standards and guidelines for evaluating medicine quality screening technologies.
2. Generate and disseminate tailored information on the capabilities of these technologies through a two-step review process: a laboratory-based technical performance evaluation and a collaborative field-based utility evaluation.
3. Build the knowledge of key stakeholders to appropriately procure and sustainably utilize screening technologies for the purposes of combating substandard and falsified medicines.
4. Foster the development and enhancement of new and emerging screening technologies.

This report contributes directly to objectives 2, 3, and 4, and is part of an ongoing series evaluating the capabilities of various promising screening technologies.

Advances in near infrared (NIR) spectroscopy over the last decade have led to the development and commercialization of an increasing number of handheld and portable spectrometers, some of which can be used in low- and middle-income country settings to screen the quality of suspect medicines. NIR screening technologies measure the absorption of NIR radiation diffusely reflected from samples. All NIR screening technology instruments employ a 180° data collection orientation, with contact generally occurring between the sample and device window (typically made of sapphire). NIR radiation probes the combination and overtone vibrations of the fundamental modes probed by infrared (IR) and, as a result, the NIR signal is much weaker and less resolved than IR. NIR penetration depth for solid dosage form medicines can extend ~1–5 mm, enabling a more representative bulk evaluation of the formulation than IR or Raman. The penetration depth and lower absorption of NIR radiation compared to IR also enables through-package analysis. Unlike IR-based screening technologies, the signal measured by NIR screening technologies is strongly dependent on particle size and packing density. Trek[1] is one of the handheld NIR spectrometers on the market with a spectral range of 350 nm–2500 nm. It was selected for the first NIR review because of claims regarding its technical capabilities, novelty, and simplicity of use. With input from the expert panel and other stakeholders, the Technology Review Program decided to review it.

[1] The Trek used for the review was purchased from ASD Inc., a brand of Malvern Panalytical, in 2017.

2. Methodology

2.1. General Information

Table 1 provides general information on Trek and its functions, manufacturer, basic specifications, and upfront and recurring costs. All data in this section were collected through email exchange, telephone conversations, and review of the vendor's website and invoices between July 2017 and May 2018.

Table 1: General Information

Technology	Trek is a handheld NIR spectrometer that delivers a full range of spectral measurements through a handheld system. It has an integrated internal light source, onboard GPS, voice audio recorder for expanded sample descriptions, internal white reference for optimization and calibration, three lightweight rechargeable lithium ion batteries, automated internal wavelength validation, integrated computer, and LCD display. The instrument comes with a built-in vial holder and a point-and-shoot adapter. Trek is supplied by ASD Inc., a brand of Malvern Panalytical. Information about the company is available on its website (https://www.malvernpanalytical.com/en/).
Specifications*	*Dimensions:* 31 cm (H) x 10 cm (W) x 30 (D) *Weight with battery:* 2.5kg (5.5lbs) *Weight without battery*: 2.0kg (4.3lbs) *Power source:* 3 Li-OIN rechargeable batteries and 3 battery chargers *Spectral range:* 350 nm–2800 nm *Languages*: English, Spanish, Chinese
Cost*	*Upfront costs* • 1 unit: $53,500 USD* • Lenovo Think Pad X200 Field Instrument controller: $1,836 • QualitySpec Trek Webinar Training: $500 • GRAMS IQ Stand Alone Software: $1,027 • ASD Inc. Chemometric Training at customer site: $7,740 *Recurring costs* • Replacement bulb: $135 • White reference discs: $58 • Performance checks(recalibration/inspection): $526

*Source: ASD Inc.

Table 2: List of Samples

AL1	artemether+lumefantrine tablets (20/120 mg), brand 1
AL2	artemether+lumefantrine tablets (80/480 mg), brand 2
AMX1	amoxicillin capsules (250 mg), brand 1
AMX2	amoxicillin capsules (500 mg), brand 1
AMX3	amoxicillin tablets (500 mg), brand 2
CD1	chlorhexidine (4% w/w) digluconate gel, brand 1
CD2	chlorhexidine (4% w/w) digluconate gel, brand 2
OX1	oxytocin (10IU) injection, brand 1
RH1	rifampicin+isoniazid tablets (150/75 mg), brand 1
RHE1	rifampicin+isoniazid+ethambutol tablets (150/75/275 mg), brand 1
RHZE1	rifampicin+isoniazid+pyrazinamide+ethambutol tablets (150/75/400/275 mg), brand 1
RHZE2	rifampicin+isoniazid+pyrazinamide+ethambutol tablets (150/75/400/275 mg), brand 2
ST1	sulfamethoxazole+trimethoprim for oral suspension (200/40 mg), brand 1

Additional details about equipment and samples used can be found in Annexes 1 and 2.

Trek Operating Procedure

1. Before using Trek for the first time, fully charge the battery.
2. Make sure the instrument window is clean.
3. Open the disk cover and make sure the disk is clean.
4. Place the white side of the disk over the window. Magnets hold the disk in place.
5. Press the power button.
6. Watch the startup process on the screen. The power LED turns green. The startup process is displayed on the screen and takes about 2 minutes to complete.
7. When the main menu appears, remove the disk.
    - The instrument is now ready to collect data.
    - The instrument comes with two locations configured, and data collection can commence using those locations. However, the vendor recommends configuring the instrument and locations to match the user's preference, then synching the configuration using Trek Manager prior to data collection.
8. Navigate the screen using the main menu items.

Sample Analysis

- **Glass vial analysis.** The sample was placed in a 2 mL glass vial. The instrument was positioned facing up on a table and held in place by hand. The glass vial was held on top of the instrument window, and a notch on the top of the instrument window served to guide it into position. The instrument is not designed to be positioned facing up, and it must be held upright during analysis. A control experiment was conducted by collecting spectra of an empty glass vial.
- **"As is" analysis.** The sample was placed on a thick round Spectralon surface provided by the manufacturer. The instrument was carefully aligned over the sample window and held in place as the weight of the instrument pressed down on the sample. Centering the instrument window over the sample was a bit awkward, as the face plate is quite large compared to the window and obstructs the view. To more easily place the instrument window over the sample, the operator sat with eyes at sample/bench level during analysis. In the case of the AL drug products (DPs), the heat of the window was warm enough to melt elements of the tablet (most likely artemether, with a melting point of 87°C), leaving a residue on the window. In some cases, the small AL1 tablet stuck to the window when removing the instrument after analysis. Any residue on the sapphire window could easily be cleaned by wiping with a lint-free cloth. The window takes time to reach its equilibrium temperature while in operation (perhaps 30 minutes), and this should be taken into consideration for temperature-sensitive materials. Care must be taken for "as is" analyses of capsule formulations, since the weight of the instrument can permanently indent the capsules.
- **Packaging analysis.** For tablets analyzed in the original packaging, the instrument was placed over the packaging, similar to what was done for "as is" analysis. No Spectralon surface was placed below the sample (packaging was by aluminum foil (nontransparent) and always larger than sampling window). A control experiment was conducted by collecting spectra of the packaging with the tablets removed.

- **Plastic bag analysis.** This is analogous to "as is" analysis, with the sample placed in a plastic bag (as the bag is transparent, a neutral background such as Spectralon is needed). Analyzing samples in a plastic bag may be preferred to keep the instrument window clean and reduce the heat transferred to the sample. A control experiment was conducted by collecting spectra of the packaging with the tablets removed.
- **Tablets (powdered).** Crushed and ground tablets were placed in a glass vial for glass vial analysis.
- **Capsule (powdered).** Emptied and ground capsules were placed in a glass vial for glass vial analysis.
- **Tablets ("as is").** Blister pack tablets were removed for "as is" analysis.
- **Capsule ("as is").** Capsules were removed from the container for "as is" analysis.
- **Gels and liquids.** Gels and liquids were placed in a glass vial for glass vial analysis. These samples had high water content, and a control experiment was conducted by filling a glass vial with water for glass vial analysis. High-quality data could not be collected due to interference from water.
- **Degradation conditions.** Part of the AL and RHZE tablets were exposed to 105°C for 17 hours prior to testing.

ASD QualitySpec Trek Manager Software version 1.0.0.90 was used in two Trek instruments, and the spectra were preprocessed using ViewSpec Pro Version 6.2. The instrument data collection range was from 350 cm to 2500 cm^{-1}. The method was designed such that 100 scans were acquired for each sample. Background scans were acquired automatically by the instrument. A vendor-provided Spectralon surface was used as a white reference, and data are presented in units of reflectance by the instrument. The ID method involved applying a match factor ID metric following spectral preprocessing. A correlation coefficient match factor, termed a mismatch factor (MMF), ID algorithm was applied successfully using a sensitivity and selectivity threshold of no more than (NMT) 5 and no less than (NLT) 15, respectively. The sensitivity and specificity thresholds are indicated by green and red lines in the MMF graphs. The NIR data were compared using an MMF, where zero indicates a perfect match. The accuracy or diagnostic accuracy of a screening ID method is described by its sensitivity and selectivity. Sensitivity and selectivity are dependent on the quality of data collected/processed, discriminating power of the ID metric, and structuring of the ID threshold.

Methodology Limitations

Certain limitations were encountered during this performance review, which were inevitable given the nature of the technology and the objectives of the review. They are identified below:

1. Seven different DP samples were analyzed. One product (oxytocin injection) could not be analyzed due to known interference from water. Although most of these products are on the World Health Organization's (WHO) Essential Medicines List [3], they represent only a small fraction of the list. Ideally, many more samples would be analyzed. However, these seven samples represented a variety of therapeutic indications, fixed-dose combinations dosage forms, and dosage strengths to enable broader conclusions about the utility of the Trek.

2. No actual substandard or falsified medicines were obtained for the evaluation. Instead genuine products were subjected to an environmental chamber or oven at 105°C for 17 hours, or different dosage strengths were used to mimic substandard or falsified medicines. There were no significant changes in spectra after exposure to the above conditions. Future evaluations could look at the possibility of collaborating with genuine manufacturers to obtain either placebo (no active pharmaceutical ingredient (API)) or low-dose versions of their products and subject the samples to harsher environmental conditions to simulate substandard medicines.
3. Chemical analyses of excipient profiles of different brands of the same product were not performed. Future work could perform such an evaluation to determine whether minor match score differences between brands are due to variances in excipient profiles.

3. Results

3.1. General Information

This section provides general information about the technology of interest, including data; access, handling, maintenance, and repair; durability; and use and results of the evaluations.

Data

Trek is available in English, Spanish, and Chinese for the instrument but not for the accompanying PC Manager software. The instrument does not have internet or Bluetooth capabilities. However, it has the ability to record an audio note per sample and an onboard GPS to automatically populate accurate coordinate and elevation data for every measurement taken in a certain area. Although spectra can be viewed on the unit, there is no onboard ID software. For ID, spectra must be transferred to a separate computer via a micro-USB cable, and all ID methods must be developed using third-party software.

Access, Handling, Maintenance, and Repair

Trek is commercially available globally but can only be purchased directly from ASD Inc., a brand of Malvern Panalytical. While issues can be diagnosed over the phone, all service and repairs are provided by their offices in Longmont, CO, USA. The user should perform the built-in daily performance verification check prior to use.

Durability

Trek is a compact and portable instrument, with a rugged packaging design that allows portability in the field. It is water resistant but should be protected from moisture as much as possible. The keypad and screen should be kept from getting wet.

Use

Trek can theoretically analyze solids and liquids. Such samples may need to be placed in a glass vial to perform a glass vial analysis. However, the high water content in gels and liquids makes it impossible to collect high-quality data due to interference.

3.2. Performance Evaluation

Performance evaluation involved review of Trek's performance characteristics in the laboratory. Variables were controlled to evaluate the instrument's analytical qualitative capabilities as per Application II of the Proposed USP General Chapter <1850>: *Evaluation of Screening Technologies for Assessing Medicine Quality [4]* to ensure a structured, effective approach to performing a pragmatic review of the technology.

Application II involves identification of bulk drug substances or APIs in finished pharmaceutical products. All data below were collected between April and September 2018.

The samples selected to evaluate the capabilities and challenge the instrument were all products from the current WHO Essential Medicines List and represent different therapeutic indications, fixed-dose combinations, dosage forms, and dosage strengths.

Artemether + Lumefantrine (AL) Tablets

High-quality spectra were collected from AL1 and AL2 samples in their original packaging. Comparing the spectra of the AL sample in its original packaging (packed) with the AL prepared tablet powder and tablet "as is" (placed on a white reference surface) revealed little interference from the packaging. The spectra of AL1 and AL2 appeared similar, which was expected considering their similar composition, but they differed from all other DPs tested. Using the determined sensitivity and selectivity thresholds, the developed ID method was able to correctly identify the two AL DPs with respect to the other DPs tested for both powdered and "as is" analysis (see Figures 1 and 2). Exposure of the AL1 and AL2 tablets to 105°C for 17 hours produced no significant change in spectra.

Figure 1: AL1 and AL2 powdered match factors results

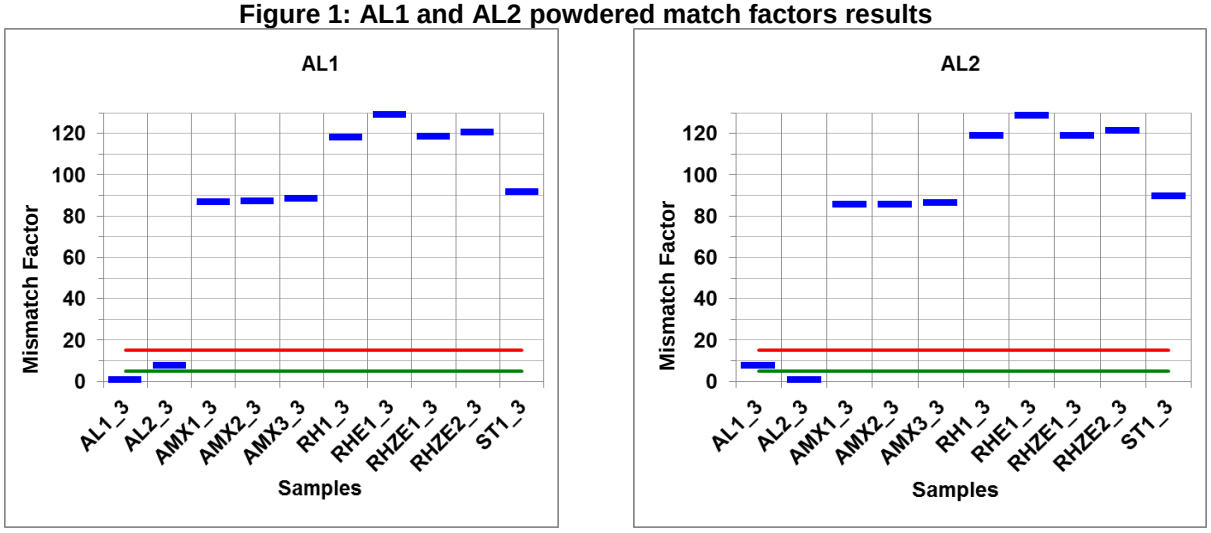
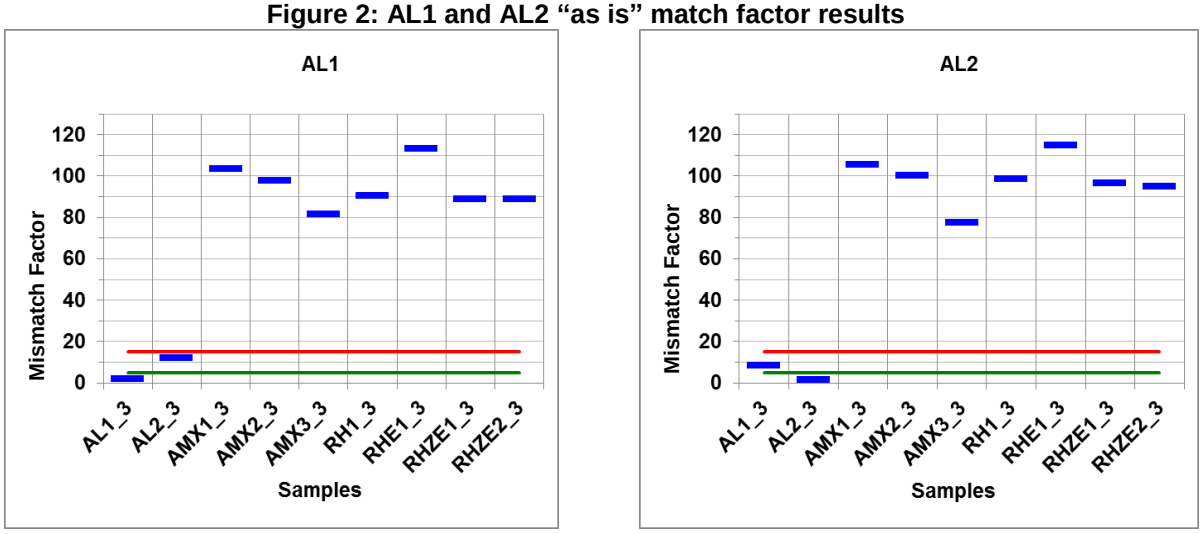


Figure 2: AL1 and AL2 "as is" match factor results



Green line: sensitivity threshold (MMF NMT 5)
Red line: specificity threshold (MMF NLT 15)

Rifampicin + Isoniazid + Pyrazinamide + Ethambutol (RHZE) Tablets

High-quality spectra were acquired from both RHZE1 and 2 tablets "as is." In contrast to the "as is" spectra of AL1 and 2, the spectra obtained from RHZE1 and 2 tablets "as is" were significantly different. However, a comparison of RHZE1 and 2 powdered spectra yielded similar results, indicating the difference between these two DPs could be due to the coatings. Although through-package analysis was possible for RHZE1, significant interference was observed in the case of RHZE2. Match factor analysis of the powdered and "as is" spectra for RHZE1 and 2 are shown in Figures 3 and 4. The match factor analysis identifies the powdered samples as similar but the "as is" sample as different, consistent with the spectral variations observed. Exposure of the RHZE1 and 2 tablets to 105ºC for 17 hours produced similar spectra, indicating no significant spectral changes upon exposure.

Figure 3: RHEZ1 and 2 powdered match factor results

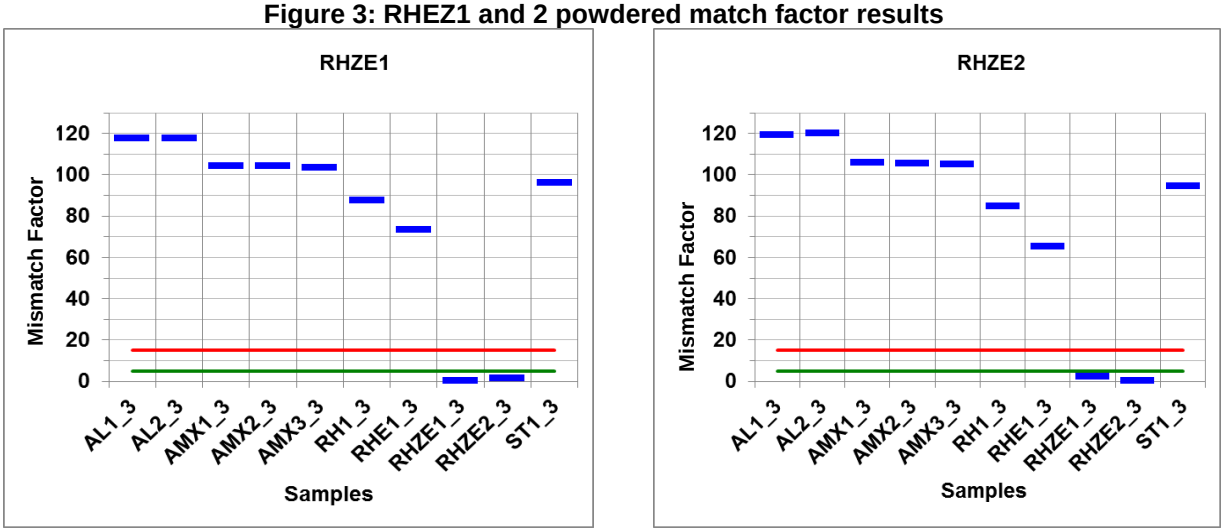
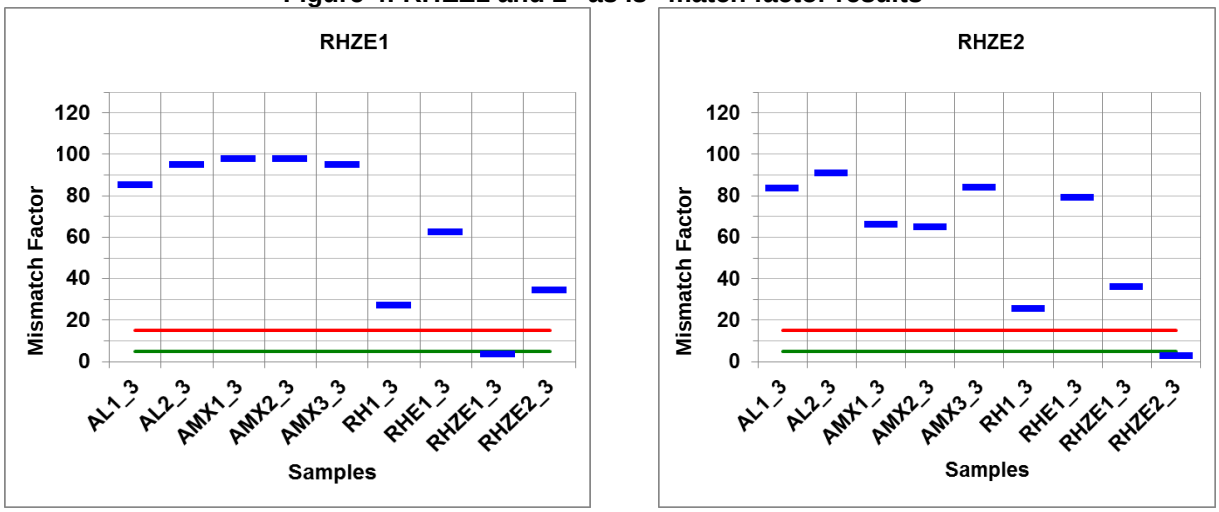


Figure 4: RHEZ1 and 2 "as is" match factor results



Amoxicillin (AMX) Capsules and Tablets

High-quality spectra were obtained from all AMX DPs "as is." A comparison of the AMX powdered and "as is" spectra indicated the capsule shell interferes significantly with the spectra of the capsule contents. The "as is" spectrum of AMX3 agrees well with the spectra of AMX3 powdered, as this sample is a tablet (i.e., without a capsule shell). The spectra of AMX1 and 2 "as is" show some similarities with the spectra of AMX1 and 2 powdered, indicating the contents of the capsule are being probed in the "as is" analysis. The AMX DP powdered spectra all look very similar and are within the match factor sensitivity threshold (see Figures 5 and 6). The match factor results for all AMX DP "as is" spectra reflect the interference from the capsule (see Figure 7).

Figure 5: AMX1, 2, and 3 powdered

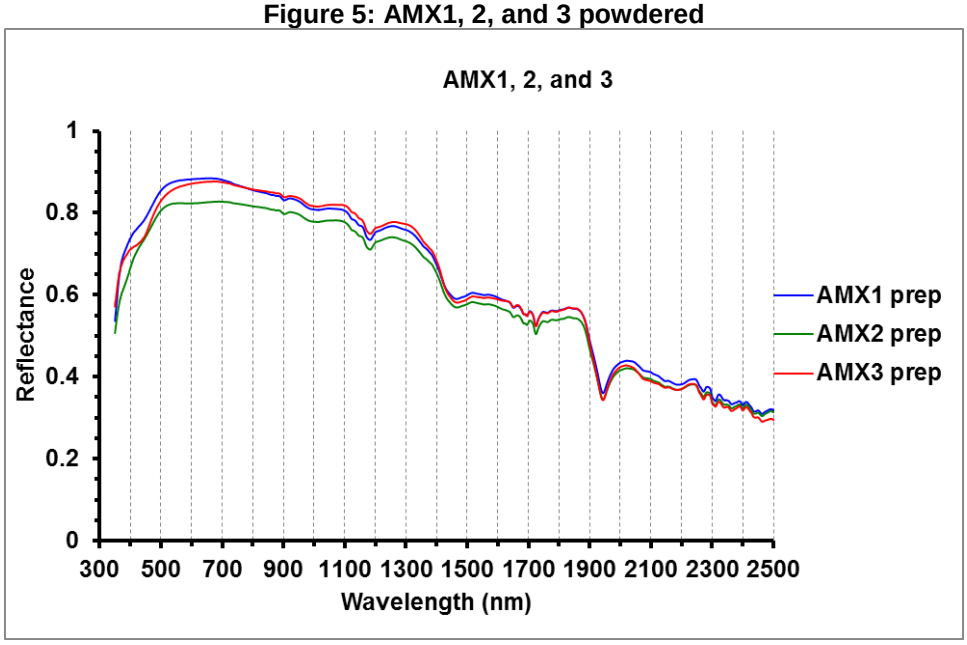


Figure 6: AMX1, 2, and 3 powdered match factor results

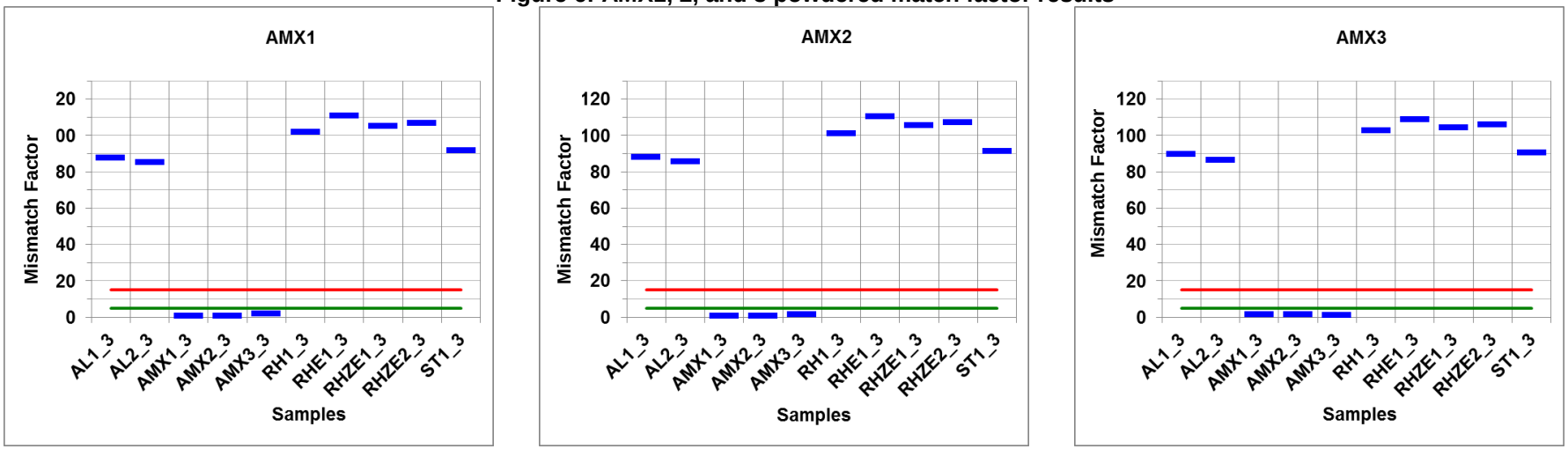
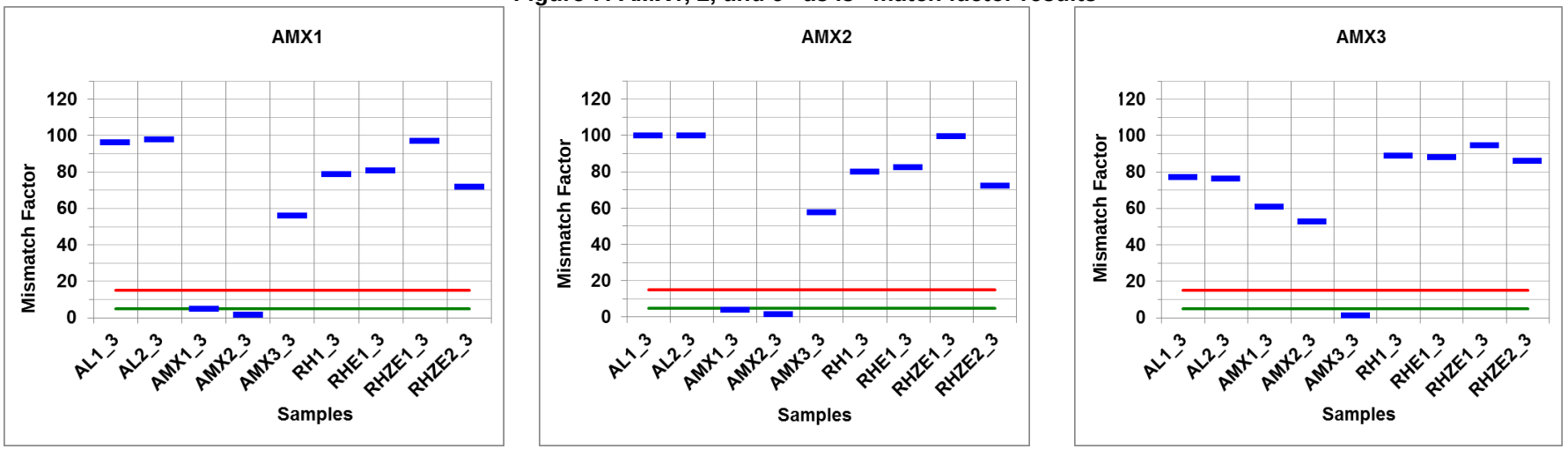


Figure 7: AMX1, 2, and 3 "as is" match factor results



Rifampin + Isoniazid (RH) Tablets

High-quality spectra were acquired for the RH1 DP packed samples, although some interference with the packaging was observed. All RH1 spectra packed "as is" and powdered have similar features, indicating the contents of the tablets being probed in all scenarios. The match factor results for RH1 are shown in Figure 8 and 9, and accurate identification was achieved with respect to all DPs.

Figure 8: RH1 powdered match factor results

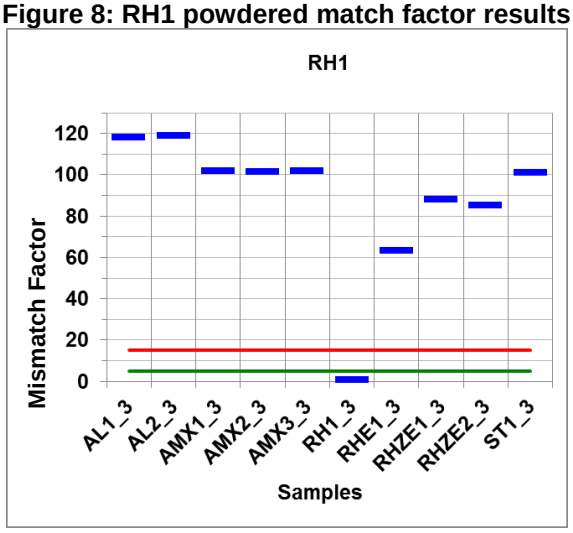
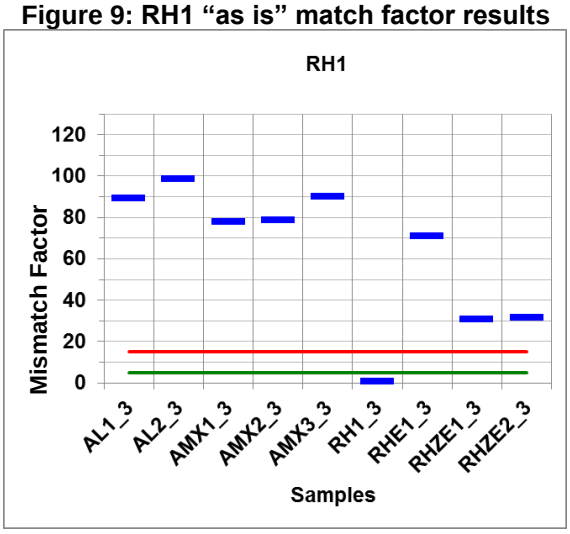


Figure 9: RH1 "as is" match factor results



Rifampicin + Isoniazid + Ethambutol (RHE) Tablets

High-quality spectra were obtained from the RHE1 DP "as is." However, significant interference was observed with through-package analysis, indicating such analysis is not feasible. "As is" analysis produced similar spectra to the powdered analysis, indicating "as is" analysis probes the tablet contents sufficiently with little coating interference. The match factor results for RHE1 are shown in Figures 10 and 11 for powdered and "as is" analysis, respectively. Accurate ID was achieved with respect to all DPs.

Figure 10: RHE1 powdered match factor results

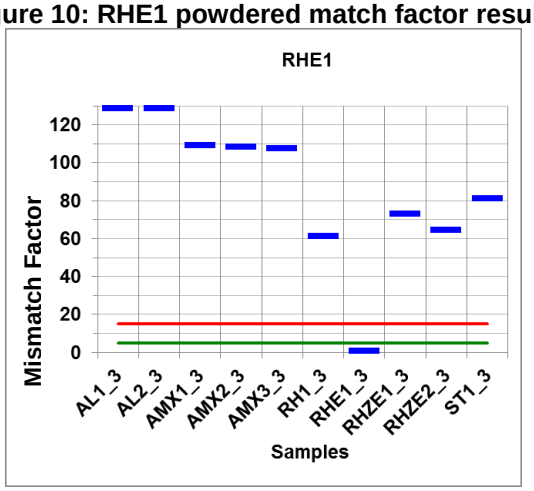
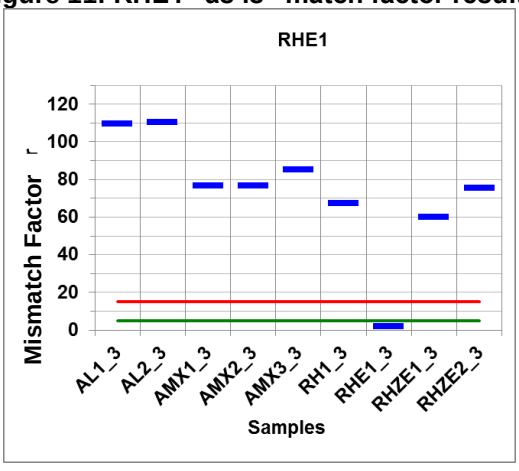


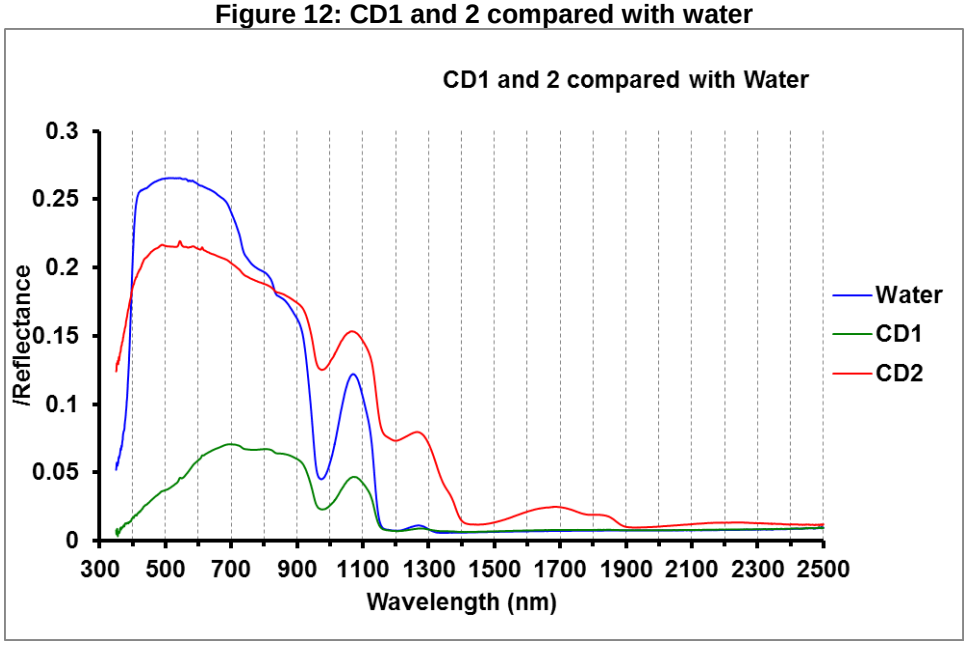
Figure 11: RHE1 "as is" match factor results



Chlorhexidine Digluconate (CD) Gel

High-quality spectra could not be obtained from the CD DPs because of strong interference from water and not the active ingredient. A comparison of spectra acquired from samples in glass vials and water spectra is shown in Figure 12.

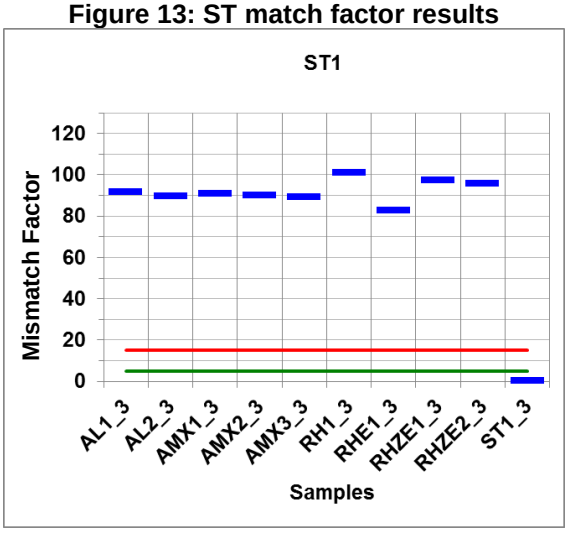
Figure 12: CD1 and 2 compared with water



Sulfamethoxazole + Trimethoprim (ST) Oral Suspension

High-quality spectra were obtained from ST by glass vial analysis. Very good agreement was achieved among duplicate data collections, as was the case for all data collected. Some deviation was observed in the region below 450 cm^{-1}, which is the reason to avoid the region below 450 cm^{-1} when developing an ID method. Match factor analysis indicates ST was accurately identified using the developed method (see Figure 13).

Figure 13: ST match factor results



3.3. Field Evaluation

The field evaluation was performed in Zambia and Indonesia on May 28–June 8, 2018, for two major parameters: training requirements and field utility. Zambia and Indonesia were selected because they represent two countries with different regulatory environments, where screening technologies have not been used extensively in the past but have the potential to be deployed effectively to combat substandard and falsified medicines.

Training Requirements

This first component of the field evaluation involved working with and training local medicine regulatory body staff in Zambia and Indonesia to assess the amount of training required to enable staff to reliably and productively utilize Trek in the field. The training involved 2 full days of work both in Zambia and Indonesia, which included 1 day of hands-on and theoretical work followed by 1 day in the field collecting and testing products for practical use of the instrument. Across both countries, 24 total staff, most of them from the National Agency of Drug and Food Control of Republic of Indonesia (BBPOM) and Zambia Medicines Regulatory Authority (ZAMRA) were trained, including 15 laboratory staff (either microbiologists or chemists), 6 inspectors, 2 retail pharmacists, and 1 customs official. To evaluate the perceived training timeframes for three levels of use of the instrument (basic, intermediate, and advanced), two data sources were used to develop a training timeframe requirements matrix: (1) a survey completed by trainees following the training and (2) the trainer observations. Two variables were used to develop the matrix:

1. User experience (prior to training):
    a. *Non-technical experience*: a trainee with no prior laboratory experience and no background in one of the physical sciences (e.g., chemistry, biology).
    b. *Technical experience*: a trainee with prior experience working in a laboratory and/or a background in one of the physical sciences.
    c. *Specialized experience*: a trainee with theoretical and practical experience utilizing the technology or the technique underpinning the technology.
2. User type (following training):
    a. *Basic user*: a user with the ability to follow a standard operating procedure or work instruction to set up and run the instrument and collect data.
    b. *Intermediate user*: a user with the ability to develop and modify methods and evaluate and interpret results.
    c. *Advanced user*: a user with the ability to train other staff and perform basic troubleshooting.

Table 3 provides recommended training timeframes for trainees to reach one of three user levels—basic, intermediate, or advanced—based on performance and field evaluations, the survey given to trainees and local staff, and trainer observations.

Table 3: Training Timeframe Requirements

User Experience	User Type		
	Basic	***Intermediate***	***Advanced***
Non-technical	Between 1 and 2 days	1 week	2 weeks
Technical	1 day	Between 1 day and 1 week	1 to 2 weeks
Specialized	1 to 2 hours	1 day	Less than 1 week

Field Utility

The second component of the field evaluation involved running samples using Trek in field settings and determining the utility of the instrument in these environments. It also included identifying any challenges associated with traveling with Trek.

No problems were encountered during routine international air transportation, which included security checks on the checked-in luggage storage on long-haul flights.

However, the lithium ion batteries must be removed from the instrument and carried into the cabin during flights, since the instrument is carried as checked-in luggage as per current airline regulations. Travel by vehicle to various sampling sites also did not involve any challenges, and the instrument withstood temperatures between room temperature and high temperatures (e.g., 40°C). The rugged travel case and a holster supplied with the instrument made it convenient to transport and carry the instrument in the field. The instrument was taken to a rural health outlet, a general hospital, pharmacies, and warehouses, where samples were collected and analyzed onsite. The trainees completed this work by themselves, the collection of scans was accomplished in minutes, and the users could see the spectra on the instrument screen. However, the transfer of spectra between the instrument and the PC (synching) was not successful at this point, which limited the users to visual comparisons of the spectra. Visual comparison was done in the field by individually (alternatingly) opening a sample and known files and comparing spectral features. Even with this limited procedure, the trainees were able to identify samples that corresponded to the known spectra. Later, after additional discussion with the instrument manufacturer, some of the spectra collected in the field were downloaded and evaluated, and examples of these field spectra can be seen in Figures 18, 19, and 20. These files show the field spectra were very similar to spectra collected in the laboratory.

Some other issues observed with the instrument and noted include:

- An error pops up when trying to export files.
- Calibration checks after few scans normally taking a couple minutes.
- Field use challenges arise due to the orientation of the instrument.
- The software not user friendly in data processing and analysis, as it requires determination of a threshold and a data file format that must be changed to allow for text numbers.

Figure 14: Spectra collected using Trek during field evaluation

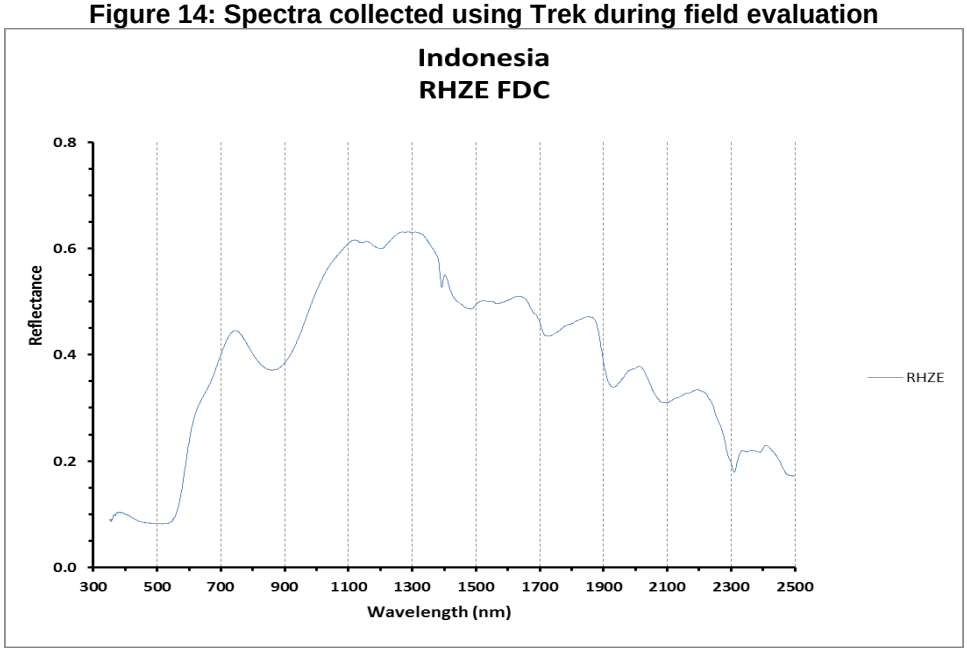


Figure 15: Spectra collected using Trek during field evaluation

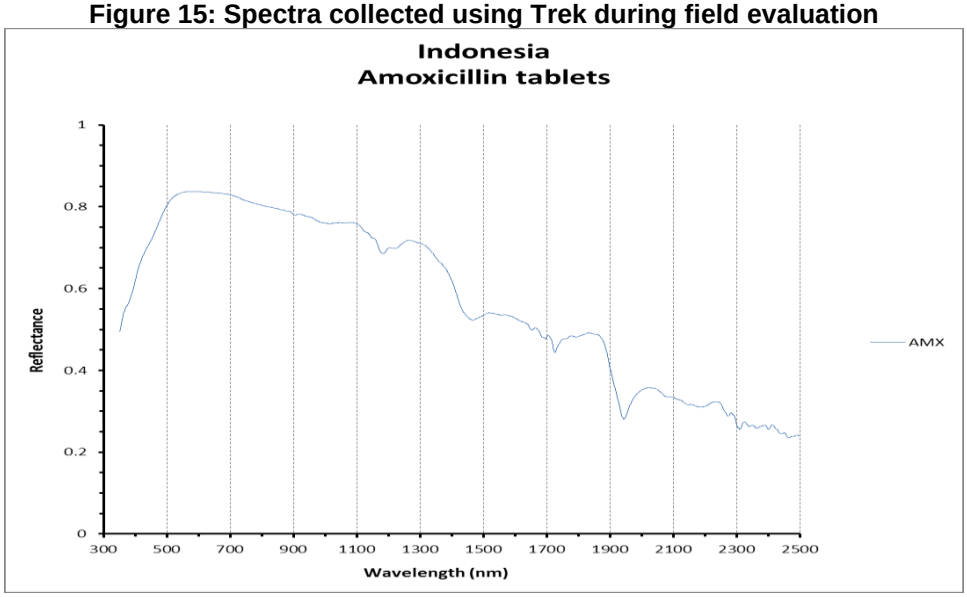
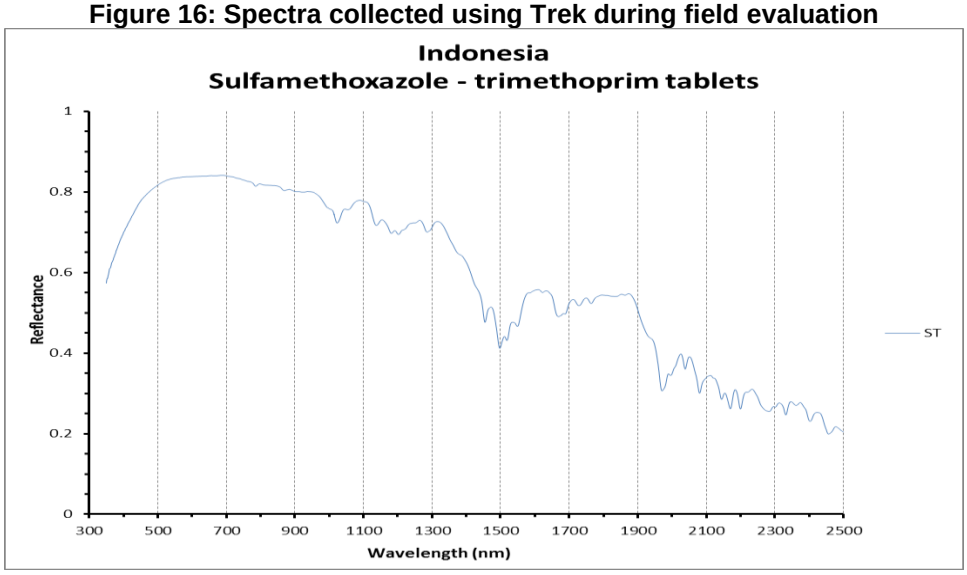


Figure 16: Spectra collected using Trek during field evaluation



Use of Trek during field evaluation in Zambia

4. Review and Conclusions

4.1. Performance Evaluation

Trek provides quality NIR data for DP ID, with distinct advantages over other vibrational spectroscopies such as Fourier transform infrared and Raman. NIR penetration depth for solid dosage form medicines can extend ~1–5 mm, enabling a more representative bulk evaluation of the formulation than IR or Raman. The penetration depth and lower absorption of NIR radiation compared to IR also enables through-package analysis. Also, unlike IR screening technologies, the signal measured by NIR screening technologies is strongly dependent on particle size and packing density. All of the DPs produced high-quality spectra, except for oxytocin and chlorhexidine digluconate gel, which did not due to strong interference from water. By comparing spectra of DPs removed from packaging (e.g., blister pack/capsule) with packaged DPs, it was possible (although interferences were observed) to generate DP-specific information through the packaging in many cases. Excellent agreement was found between the two NIR instrument-collected spectra, allowing data to be compared on both instruments. It was found that by covering the bottom of a small vial with the DP substance of interest (at least 1 mm high), high-quality NIR data could be collected through the bottom of the vial. Tablet coating may also impact the results due to the light penetration depth.

Exposure of AL and RHZE tablets to 105°C for 17 hours produced the same spectra, indicating no significant spectral changes upon exposure. Further work is needed to ascertain the threshold (amount of degradation) at which Trek would identify a substandard product. This should be corroborated using confirmatory analysis to assay the content of API and degradation products.

High-quality spectra were acquired from both RHZE 1 and 2 tablets, but they were significantly different, indicating the difference between the two DPs was the tablet coatings. A comparison of RHZE1 and 2 spectra when powdered indicated the products are similar. High-quality spectra were also obtained from all AMX DPs, but a comparison of the AMX powdered and “as is” spectra indicate the capsule interferes significantly with the capsule contents spectra. There was strong interference, and high-quality spectra could not be obtained for products containing water.

4.2. Field Evaluation

Based on feedback from trainees and ongoing observations of trainers, the training required to become a basic, intermediate, or advanced user of the instrument was manageable. More specifically, most staff with either technical or non-technical backgrounds can become immediate or advanced users within 2 weeks of training. The Trek Manager software was easy to download onto an external computer through a vendor-provided attachment. Transfer of data and development of spectral libraries were not very simple during the training and at the field due to software problems. The reference spectra library also needs to be carefully built and maintained, since the usefulness of the results depends on the software.

The instrument is not small: field use was challenging because of its orientation, and it may need two people to operate. The advantage is that it does not need any external consumables, making it particularly suitable for use in field settings where electricity may not be reliable since the instrument comes with three batteries. Additional work would need to evaluate the feasibility of enhancing the instrument by developing a function that allows overlay of spectra on the screen.

5. References

[1] PQM, *Annual Performance Report FY 2017*, Promoting the Quality of Medicines program, Washington, DC, 2017.

[2] IOM, *Countering the Problem of Falsified and Substandard Drugs*, Institute of Medicine (now the National Academies of Sciences, Engineering, Medicine), Washington, DC, 2013.

[3] WHO, *WHO Model List of Essential Medicines, 20th List (March 2017)*, March 2017b. [Online]. Available at http://www.who.int/medicines/publications/essentialmedicines/20th_EML2017.pdf?ua=1. [Accessed 10 December 2018].

[4] USP Review of Surveillance and Screening Technology for the Quality Assurance of Medicines Expert Panel, "Proposed USP General Chapter <1850>: Evaluation of Screening Technologies for Assessing Medicine Quality (USP PF 43 (5))." September 2017.

Annex 1. Equipment Used During Performance Evaluation

Item	Acronym	Manufacturer / Source	Expiry Date	Other details
QualitySpec® Trek – Unit 1	Trek1	ASD Inc.	N/A	NRIR-0003. ASD part # A170803 (Instrument 3)
QualitySpec® Trek – Unit 2	Trek2	ASD Inc.	N/A	NRIR 0004. ASD part # A170803 (Instrument 4)
Trek Manager software	Trek PC Manager software	ASD Inc.	N/A	
Lenovo Think Pad X200 Series		Lenovo	N/A	Field Instrument Controller
Vacuum Oven	OV	Yamato Scientific	N/A	Model: ADP-21 Serial No: A3700054
Environmental Chamber	EC	Weiss Technik	N/A	Model: WKL 34/+10 Unit Not: 56246010530010

Annex 2. Sample Materials Used During Performance Evaluation

Item	Acronym	Manufacturer / Source	Product #	Lot No.
Amoxicillin (250 mg) capsules	AMX1	Sandoz	0781-2020-01	HG9361
Amoxicillin (500 mg) capsules	AMX2	Sandoz	0781-2613-01	GS0051
Amoxicillin (500 mg) tablets	AMX3	Teva	0093-2263-01	35442174A
Artemether (20 mg) + Lumefantrine (120 mg) tablets	AL1	Ipca Laboratories	18901079017052	DY1466166
Artemether (80 mg) + Lumefantrine (480 mg) tablets	AL2	Novartis	30760 U57	K0050
Chlorhexidine (4% w/w) Digluconate gel	CD1	Lomus Pharma.	Kawach Gel	616
Chlorhexidine (4% w/w) Digluconate gel	CD2	NA	Umbilica Gel	326L15
Oxytocin injection (10 units/mL)	OX1	PT Ethica	GKL8606703943A1	15G0497
Rifampicin (150 mg) + Isoniazid (75 mg) tablets	RH1	Phapros	Pro TB 2	6159001
Rifampicin (150 mg) + Isoniazid (75 mg) + Ethambutol HCl (275 mg) tablets	RHE1	Macleods Pharma.	DD/376	ERD2706B
Rifampicin (150 mg) + Isoniazid (75 mg) + Pyrazinamide (400 mg) + Ethambutol HCl (275 mg) tablets	RHZE1	Lupin Ltd.	499	A603606
Rifampicin (150 mg) + Isoniazid (75 mg) + Pyrazinamide (400 mg) + Ethambutol HCl (275 mg) tablets	RHZE2	Macleods Pharma.	DD/Drugs/DD/376	ERC6690C
Sulfamethoxazole (200 mg) + Trimethoprim (40 mg) for oral suspension	ST1	BDH Industries	608	D-10217

Note: OX1 sample was not analyzed due to known interference from water.