USP Technology Review: Target-ID™

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Executive Summary

A technology review was carried out on the Smiths Detection Target-ID a portable Fourier-transform infrared (FTIR) spectrometer. The objective of the review was to determine whether Target-ID can feasibly be used as a first-line screening technology to identify the presence of active pharmaceutical ingredients (APIs) in drug products (DPs).Infrared (IR) screening technologies measure the absorption of IR radiation and are most sensitive to polar bonds, thereby making the IR technique most responsive to functional groups. The IR instrument employs diamond attenuated total reflection (ATR) due to its robustness and ease of use. By pressing the sample material against the diamond ATR element, the IR probe beam penetrates the surface approximately 1–5 μm. Liquid samples may simply rest on the ATR element. While other IR techniques require sample dilution, the low penetration depth for ATR enables “as is” sample analysis.

The performance evaluation of Target-ID involved the analysis of four co-formulated tablet samples (artemether + lumefantrine, rifampicin + isoniazid + pyrazinamide + ethambutol, rifampicin + isoniazid + ethambutol, and rifampicin + isoniazid), single API capsules and tablets (amoxicillin), one co-formulated oral suspension sample (sulfamethoxazole and trimethoprim), one gel formulation (chlorhexidine digluconate gel), and one injection (oxytocin). The instrument was able to reliably identify several of the APIs in single API drug products. However, it encountered challenges identifying the presence of multiple APIs in co-formulated products, specifically artemether + lumefantrine tablets, rifampicin + isoniazid tablets, and rifampicin + isoniazid + pyrazinamide + ethambutol tablets. It was also unable to detect the presence of APIs in water-based formulations (e.g. the oxytocin injection and chlorhexidine digluconate gel) where the spectra obtained was that of water and not of the API. The Target-ID software restricts visual comparisons of the test sample spectra to only three ranked spectra in the library (by match factor computation).

The field evaluation showed that most inspectors, chemists, and laboratory analysts with various levels of technical experience from the regulatory authorities of two countries, Zambia and Indonesia, could become proficient users of the technology in two weeks. Target-ID functioned well in the field, with one lithium battery able to last four hours. The major limitation was about the data transfer from the instrument to the personal computer (PC). The USB port has delicate pins, which can malfunction and inhibit data transfer to the PC; however, a mini USB cable can also be used. Also, during the data transfer, some spectral libraries could not be located on the PC software, requiring the user to contact the vendor.

Acknowledgments

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- Zambia Medicines Regulatory Authority (ZAMRA)

Acronyms

AL	artemether–lumefantrine
AMX	amoxicillin
API	active pharmaceutical ingredient
ATR	attenuated total reflection
CC	correlation coefficient
CD	chlorhexidine digluconate
DP	drug product
ID	identification
IR	infrared
NLT	no less than
RH	rifampicin–isoniazid
RHE	rifampicin–isoniazid–ethambutol
RHZE	rifampicin–isoniazid–pyrazinamide–ethambutol
RS	reference standard
SF	substandard falsified
ST	sulfamethoxazole–trimethoprim
FTIR	near-fourier transform infrared
USP	U.S. Pharmacopeial Convention
WHO	World Health Organization

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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]. USP 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 towards 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 lab-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 (SF) medicines.
4. Foster the development and enhancement of new and emerging screening technologies.

This report contributes directly to objectives two, three, and four and is the fourth in an ongoing series evaluating the capabilities of various screening technologies.

Advances in near-Fourier Transform Infrared (FTIR) 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 countries to screen suspected SF medicines.

Infrared screening technologies (IRSTs) measure the absorption of infrared (IR) radiation. IR spectroscopy is most sensitive to polar bonds, making this technique most responsive to functional groups. All IRST instruments employ diamond attenuated total reflection (ATR) due to its robustness and ease of use. By pressing the sample material against the diamond ATR element, the IR probe beam penetrates the surface approximately 1-5 µm. While other IR techniques require sample dilution, the low penetration depth enables "as is" sample analysis. However, the low penetration depth of IR-based screening technologies inhibits analysis through coating, capsules, and packaging (e.g., blister packs). In general, tablet and capsule dosage forms must be transformed into fine powders to generate reproducible measurements. Powders are more suitable for IR analysis as rigid samples introduce variations in the amount of pressure that can be applied across the ATR element surface, creating signal intensity variations. Also, the very strong IR absorption of water interferes with IR spectroscopy.

Although the intention is to eventually evaluate all commercially available FTIR instruments, the Target-ID was selected for the first FTIR review because of its cost, simplicity, and claimed technical capacities.

2. Methodology

2.1. General Information

Table 1 provides the following general information on Target-ID: functionality, basic specifications, the manufacturer, and the upfront and recurring costs of using the instrument. All data in this section were collected between July 2017 and September 2018 through email exchange, telephone conversations, and review of the vendor's website.

Table 1: General Information

Technology	Target-ID is a FTIR spectroscopy analyzer specifically designed to produce identification results in a matter of seconds. It has a high contrast, full color LCD display, which allows for high viewing angles and visibility indoors or outdoors. An intuitive, color-coded user interface guides the operator through each step of the sample preparation and analysis process. The instrument has a diamond ATR sensor, with an integrated press for solids and direct placement for liquids. The software includes a library of up to 2,500 substances, including new synthetic designer drugs, and the ability to add up to 500 user collected spectra.
Specifications	*Dimensions:* 25.5 cm (H) x 15.62 cm (W) x 9.83 cm (D) (10.05 in x 6.15 in x 3.87 in) *Weight with battery:* 2.45 kg (5.4 lbs) *Weight without battery*: 2.0 kg (4.3 lbs) *Power source:* Rechargeable lithium-ion battery (four hours of operation); disposable 123A battery compatible *Display:* High-contrast 4.3 in LCD color display *Color*: Blue *Spectral range: 650-4000 cm^{-1}* *Languages*: English, German, Spanish, Portuguese, Russian, French, Chinese, Korean, Japanese, Thai
Cost	*Upfront costs* • One unit: $28,065 USD • Operator training at customer site: $3,850 USD *Recurring costs* • No recurring costs but some optional costs: Service agreements and sampling items such as alcohol wipes, spatulas, vials, etc.

2.2. Performance Evaluation

Table 2: List of samples and reference standards tested

AL1	artemether + lumefantrine tablets (20/120 mg), brand 1
AL2	artemether + lumefantrine tablets (80/480 mg), brand 2
ARR	USP Artemether Reference Standard
AMR	USP Amoxicillin Reference Standard
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
CDR	USP Chlorhexidine Reference Standard
ETR	USP Ethambutol Hydrochloride Reference Standard
INR	USP Isoniazid Reference Standard
LUR	USP Lumefantrine Reference Standard
OX1	oxytocin (10 IU) injection
OXR1	USP Oxytocin Reference Standard
PYR	USP Pyrazinamide Reference Standard
RH1	rifampicin + isoniazid tablets (150/75 mg)
RHE1	rifampicin + isoniazid + ethambutol tablets (150/75/275 mg)
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
RIR	USP Rifampicin Reference Standard
ST1	sulfamethoxazole + trimethoprim (200/40 mg) for oral suspension
SUR	USP Sulfamethoxazole Reference Standard
TMR	USP Trimethoprim Reference Standard

Additional details of samples, standards, and equipment used can be found in Annexes 1, 2, and 3.

Target–ID Operating Procedure

The instrument is supplied with a manual that gives instructions on how to operate.

Preparation of Samples, Solutions, and Standards

All powders, gels, liquids (OX1), and oral suspensions (ST1) were analyzed “as is.” All tablet dosage forms were crushed and ground to fine powder using a pestle and mortar before taking an aliquot for analysis (enough to cover the crystal or approximately 1 mg). All capsules were emptied and their contents ground using a pestle and mortar.

Note: The tablets and some capsules were also analyzed “as is.” However, the instrument sample holder was not designed to analyze such samples, and this procedure is not recommended for

routine use. For tablets and capsules analyzed “as is,” the designation “as is” is added to the spectrum file name.

For the powder and oral suspension samples, the material was placed on the ATR element and pressed with the Target-ID steel clamp press. If a good signal was not obtained before data collection (an infrequent occurrence), the powder was rearranged on the element and re-pressed until an excellent signal was obtained. For the gel and liquid samples, a drop was placed directly on the ATR element without pressing beforehand (use of a press is not recommended for such materials). For tablets analyzed “as is,” the sample was placed on the ATR element and pressed continuously by hand throughout the acquisition, as the clamping mechanism could not completely engage for these larger samples. For capsule samples, the clamp was able to engage as long as the capsule deformed completely and adapt its shape to the ATR element under the pressure of the press.

Two FTIR Target-ID spectrometers were used for the evaluation, with FTIR-0017 as the master and FTIR-0016 as the slave. The instruments have a resolution of 4cm-1 from 650-4000 cm-1 and are equipped with a signal strength indicator which is color coded as red, yellow, or green indicating poor, good, or excellent signal strength prior to data collection. Auser library was created using spectra of the samples and USP Reference Standards (RSs).

Picture 1. Sample being placed on the diamond ATR element for pressing during analysis

Degradation of Samples

Degradation experiments were performed on AL, RHZE, and CD. However, data was not reported as no evidence of degradation was detected by the Target-ID. The degradation conditions tested were 105℃ for 17 hours (AL and RHZE only), 80℃ for 17 hours, and 60℃ for 10 days. In a previous experiment, using HPLC under similar conditions, the samples were shown to degrade. Because samples must be ground prior to analysis the preferential degradation that occurs at the surface of the tablets is diluted making detection more difficult.

Match Score

Target-ID employs a correlation coefficient (CC) match factor identification (ID) metric, which scales from 0 to 1, with 1 being a perfect match and 0 being a perfect mismatch. Previous work in the USP Compendial Development Laboratory had demonstrated that an appropriate two-ID threshold scheme using a CC match factor could be achieved on a single instrument using a sensitivity and selectivity threshold of 0.99 and 0.95, respectively.

Methodology Limitations of the instrument

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. The Target-ID software restricts visual comparisons of the test sample spectrum to only the top three ranked spectra in the library (by match factor computation). Thus, comparisons of DP with corresponding USP RS(s) were not possible unless those spectra happened to be ranked in the top three matches. Also, the Target-ID software limits match factor reporting to the top ten library matches and does not allow for determination of peak position. Therefore, all peaks noted in texts and figures are approximated from the provided axis.
2. When comparing different brands, minor match score differences may be obtained between brands, which can be attributed to variances in excipient profiles.

Limitations of the review process

3. Eight different DP samples were analyzed. Although most 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 eight samples deliberately represented a variety of therapeutic indications, dosage forms, and dosage strengths to enable broader conclusions about the utility of the Target-ID to be made.
4 No actual SF medicines were obtained for the evaluation. Future evaluations could include a collaboration with manufacturers to obtain placebo (no API) or low-dose versions DPs to formulate and test SF medicines.

3. Results

3.1. General Information

Data

Target-ID instructions are available in ten languages as listed on the specification list. A library of spectra was created on the instrument and used to compare with ID test sample spectra collected on the same instrument. The library included a single spectrum of each DP. Tablet and capsule dosage forms were prepared as powders for analysis and, if possible, analyzed "as is." The library also included a spectrum of each USP RS analyzed "as is." The instrument has a resolution of 4 cm^{-1} from 650–4000 cm^{-1}. It is equipped with a color-coded signal strength indicator, and before data collection, a color of either red, yellow, or green indicates poor, good, or excellent signal strength, respectively.

Access, Handling, Maintenance, and Repair

Target-ID is commercially available globally and can be purchased directly from Smith's Detection Inc. All major services and repairs are provided by Smith Detection offices at their main service depot in Edgewood, Maryland, USA. Smaller depots are also located in UK, Australia, and Singapore. The instrument should have a performance validation done before use.

Durability

Target-ID is a lightweight and portable instrument which allows for portability in the field. The instrument is neither waterproof nor is it completely sealed, so dust ingress is possible. The instrument has an operating temperature range of -10ºC to 46ºC and a storage temperature range of -20ºC to 60ºC. It can operate in up to 99% humidity.

Use

Target-ID can theoretically analyze solids and liquids. However, water has a significant absorbance spectrum in the IR region and can interfere with IR analysis. For example, only water absorption was apparent in the spectrum of oxytocin; thus, this IR-based technology is not suitable for selective identification of oxytocin injection or other samples that contain high water content.

The instrument brochure and further details can be found at the manufacture website: https://www.smithsdetection.com/products/target-id/

3.2. Performance Evaluation

Application II: Identification of Bulk Drug Substances or Active Pharmaceutical Ingredients in Finished Pharmaceutical Products

Application II is defined in the USP General Chapter <1850>: *Evaluation of Screening Technologies for Assessing Medicine Quality [4]*. All data below were collected between April 2017 and September 2018.

Twenty-two scans and a background spectrum were acquired for each sample, and data was transferred from the instrument to a PC installed with Target-ID software version 1.6.0.2.4 and firmware version 2.4.

The samples selected to evaluate the capabilities of the instrument are all products from the WHO Essential Medicines List and represent different therapeutic indications, dosage forms, and dosage strengths.

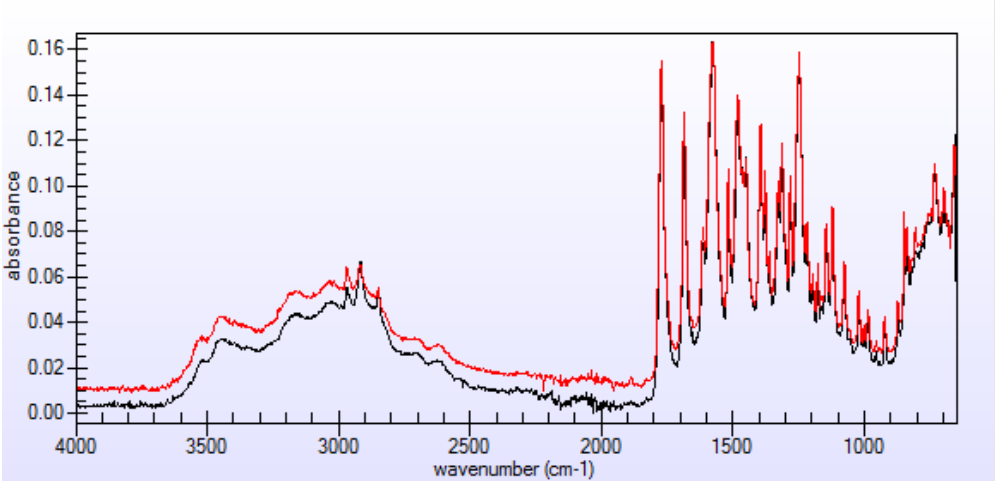
Reproducibility and Reliability

ID methods were successfully developed for all DPs, except CD and OX, which lacked selectivity. The spectra of CD and OX were not specific due to interference from water absorption hence, water content can change the results. All other DPs exhibited strong absorptions with high inherent selectivity (i.e., many different IR absorptions appeared across the entire spectral range). All API spectra acquired from USP RS material (Annex 3) also exhibited strong absorptions with high inherent selectivity. The match factor was not less than (NLT) 0.996 for DP spectra collected on the same instrument (master), and NLT 0.985 for DP spectra collected on a different instrument (slave). Thus, the instrumental error is approximately 0.01. Considering the instrumental error, a sensitivity threshold of 0.98 is expected to enable accurate ID of DPs using a master/slave type ID method. Evaluation of the data shows that the lowest match score, which indicates some significant similarity between the library and test spectrum, is approximately 0.80.

Amoxicillin

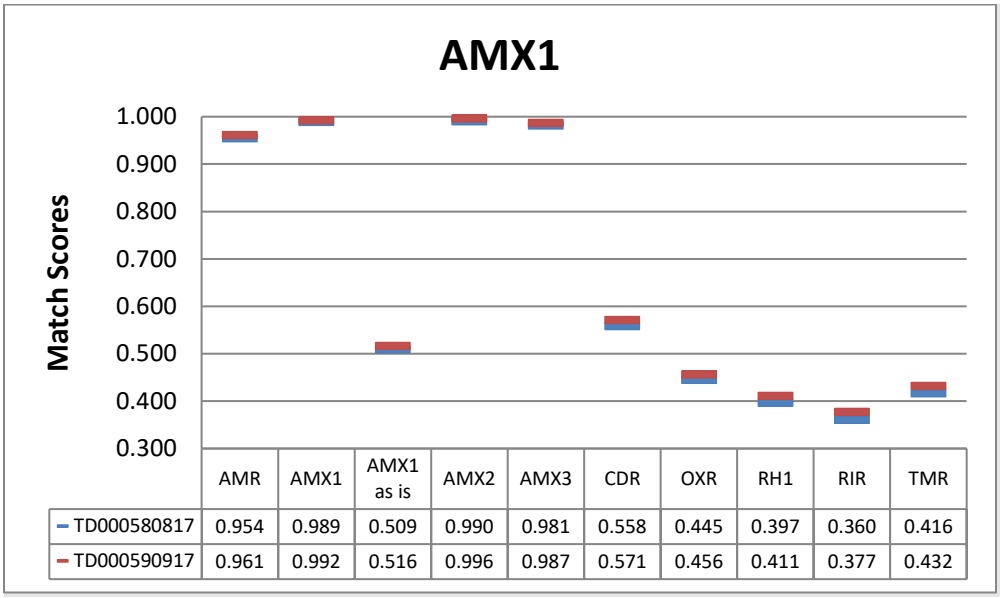
Individual spectra were collected for all three amoxicillin samples using the two instruments. Figure 1 shows an example of one of the spectra collected, and Figure 2-4 provides a match score comparisons of the samples against the other samples between the two instruments. The spectra of AMX express a high degree of inherent selectivity, with many peaks appearing across the spectral range. The selectivity of the AMX spectra for the API also appeared high. All AMX DPs were identified accurately using both instruments with match factors NLT 0.981. It should be noted that the match factor, as expected, is not impacted by the strength of the AMX DPs. The AMX “as is” spectrum generates a very low match score of not more than (NMT) 0.54, indicating that only the capsule shell was detected. AMX1, AMX2, and AMX3 generated high match scores since the DP was analyzed after the capsule was emptied, and the tablet was crushed and ground.

Figure 1. Visual comparison of AMX1 and AMX2 spectra



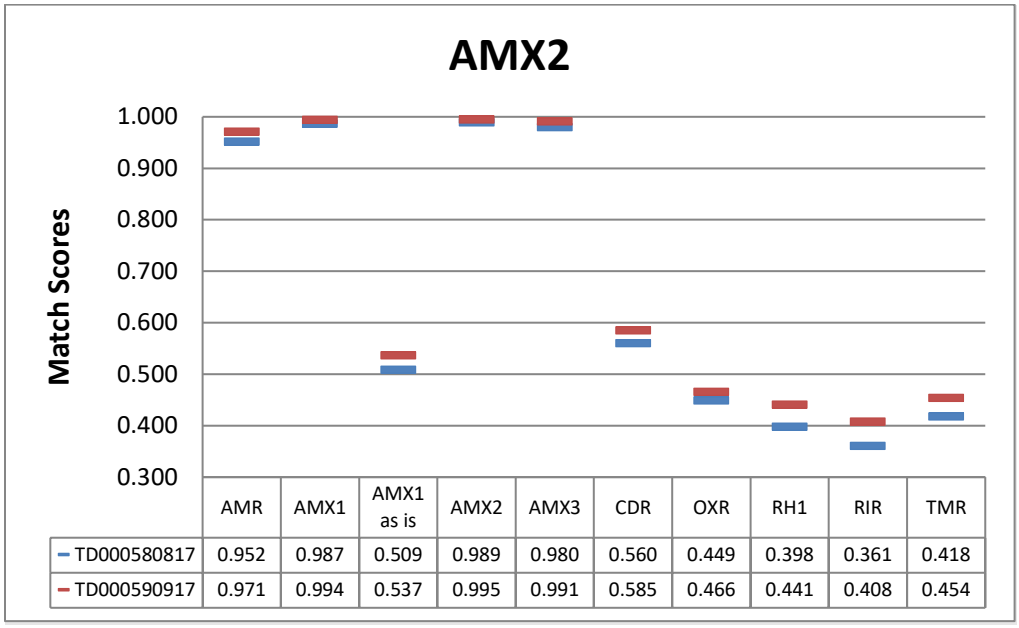
The spectra for the amoxicillin products appear similar.

Figure 2. Match scores of AMX1 compared to several DP samples and USP RSs



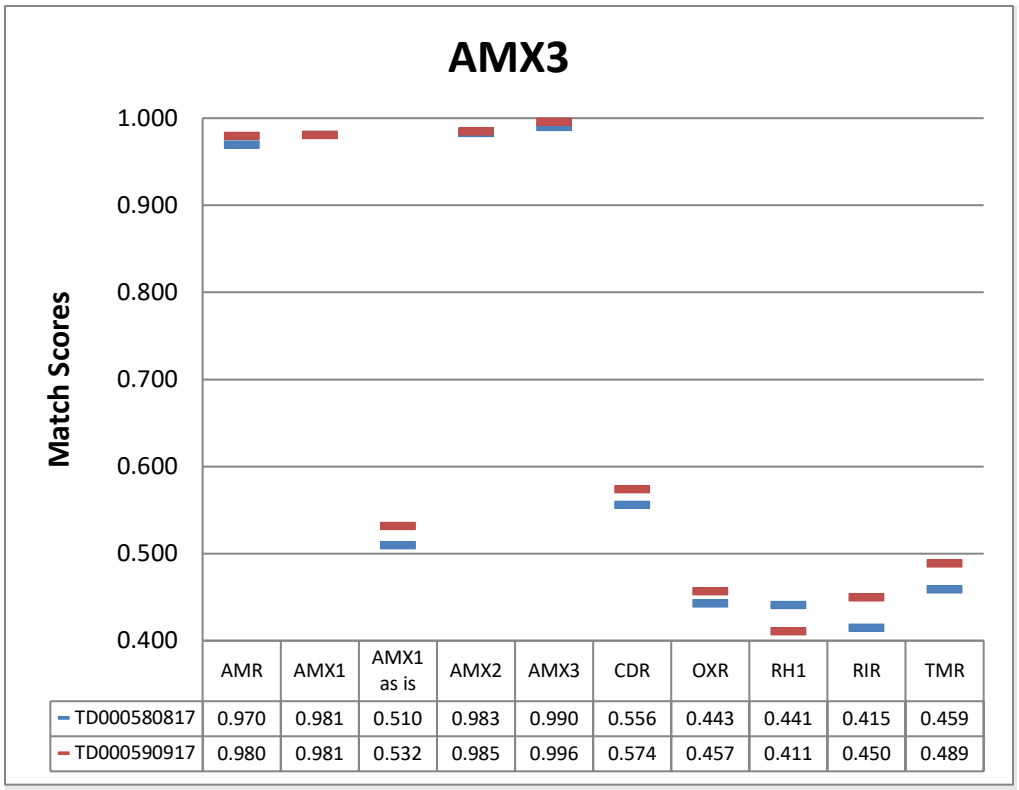
	AMR	AMX1	AMX1 as is	AMX2	AMX3	CDR	OXR	RH1	RIR	TMR
TD000580817	0.954	0.989	0.509	0.990	0.981	0.558	0.445	0.397	0.360	0.416
TD000590917	0.961	0.992	0.516	0.996	0.987	0.571	0.456	0.411	0.377	0.432

Figure 3. Match scores of AMX2 compared to several DP samples and USP RSs



	AMR	AMX1	AMX1 as is	AMX2	AMX3	CDR	OXR	RH1	RIR	TMR
TD000580817	0.952	0.987	0.509	0.989	0.980	0.560	0.449	0.398	0.361	0.418
TD000590917	0.971	0.994	0.537	0.995	0.991	0.585	0.466	0.441	0.408	0.454

Figure 4. Match scores of AMX3 compared to several DP samples and USP RSs



	AMR	AMX1	AMX1 as is	AMX2	AMX3	CDR	OXR	RH1	RIR	TMR
TD000580817	0.970	0.981	0.510	0.983	0.990	0.556	0.443	0.441	0.415	0.459
TD000590917	0.980	0.981	0.532	0.985	0.996	0.574	0.457	0.411	0.450	0.489

Artemether + Lumefantrine

A sample Target-ID spectrum obtained for AL containing DPs 1 and 2 are shown in Figure 5, and the match scores for various DPs tested are shown in Figures 6 and 7. The spectra of AL express a high degree of inherent selectivity, with many peaks appearing across the spectral range. AL1 and AL2 were identified accurately using both instruments, with match factors NLT 0.99. Unlike the AMX DPs, significant differences in match factor, as low as 0.94, were computed between the two different AL DPs, and significant spectral differences were observed between the two. The significant spectral differences appear to be related to the presence of peaks in regions near 1050, 1550, 3275, and 3450 cm^{-1}. A match factor NLT 0.89 was computed between the library spectra of AL DPs analyzed as a ground powder and "as is," indicating that some spectral similarities are present. The differences in the spectra appear to be primarily due to baseline shifts, which are likely a result of physical differences in the surfaces between the two samples, rather than because of chemical differences. The USP Artemether RS and Lumefantrine RS were not the top match with either of AL DPs, an indication that the equipment is unable to identify each APIs in co-formulated products.

Figure 5. Visual comparison of AL1 and AL2 spectra

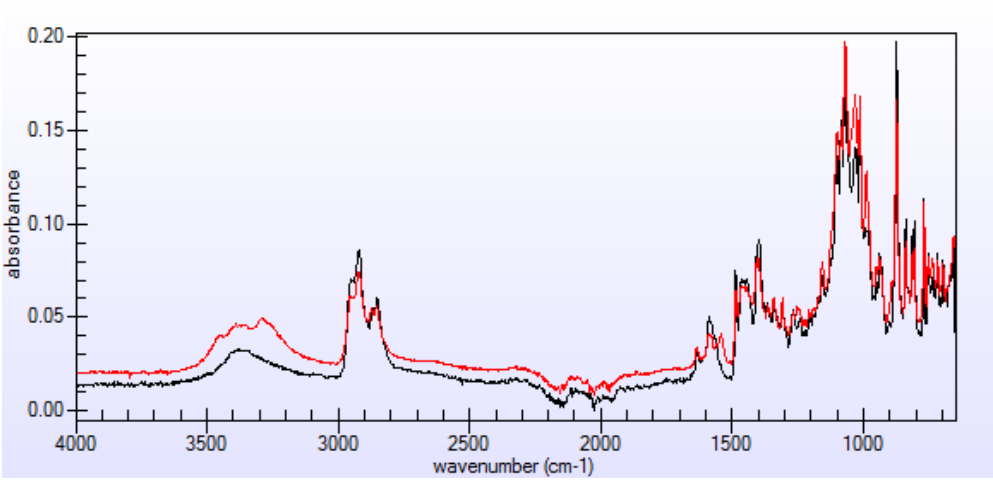
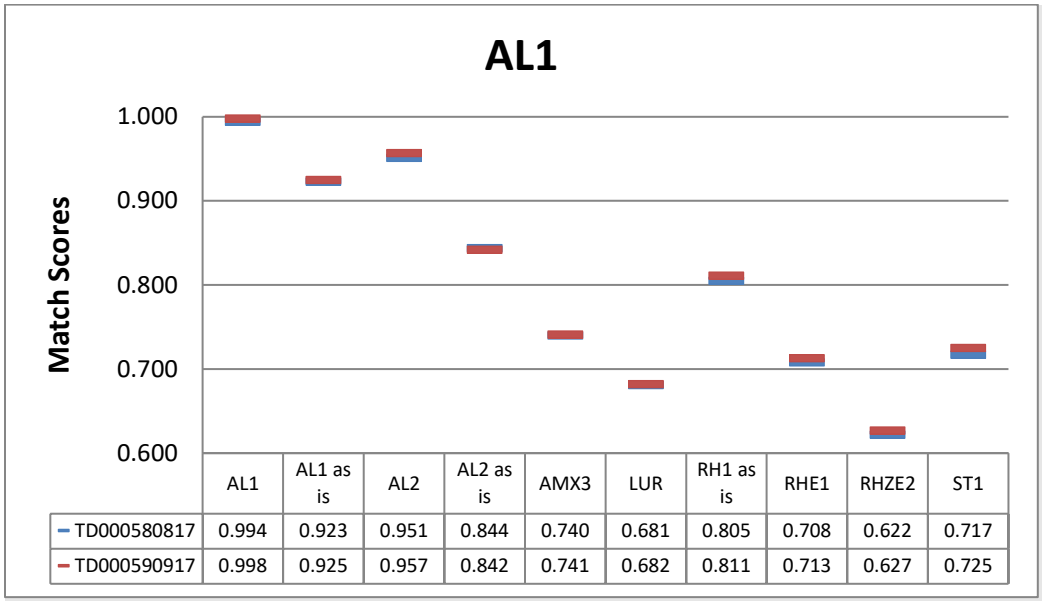
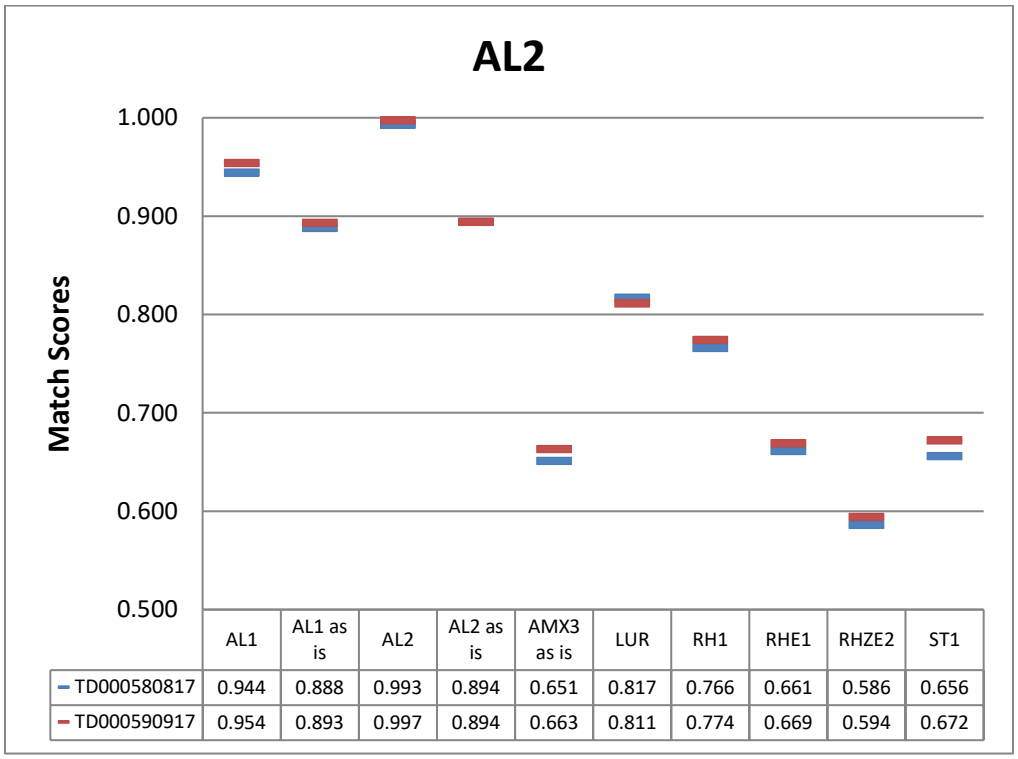


Figure 6. Match scores of AL1 compared to several DP samples and LUR



	AL1	AL1 as is	AL2	AL2 as is	AMX3	LUR	RH1 as is	RHE1	RHZE2	ST1
TD000580817	0.994	0.923	0.951	0.844	0.740	0.681	0.805	0.708	0.622	0.717
TD000590917	0.998	0.925	0.957	0.842	0.741	0.682	0.811	0.713	0.627	0.725

Figure 7. Match scores of AL2 compared to several DP samples and LUR



	AL1	AL1 as is	AL2	AL2 as is	AMX3 as is	LUR	RH1	RHE1	RHZE2	ST1
TD000580817	0.944	0.888	0.993	0.894	0.651	0.817	0.766	0.661	0.586	0.656
TD000590917	0.954	0.893	0.997	0.894	0.663	0.811	0.774	0.669	0.594	0.672

Chlorhexidine (4% w/w) Digluconate Gel

Target-ID spectra for CD1 and CD2 are shown in Figure 8. The spectra of chlorhexidine digluconate DPs are dominated by water absorption, and only a few weak peaks from species other than water are observed in the fingerprint region. While CD1 and CD2 both show peaks at 1410, 1490, and 1550 cm^{-1}, CD1 shows an additional peak at 1050 cm^{-1}. In Figure 10, the dominance of the water absorption is reflected in the high match factors for water for all products, which is NLT 0.98 for all products (Note: The spectrum of OX1 is also dominated by water absorption). A similar result was obtained when CD2 was compared to several other DPs. The selectivity of the method is thus not suitable for accurate identification of CD.

Figure 8. Visual comparison of CD1 spectra and CD2 sample

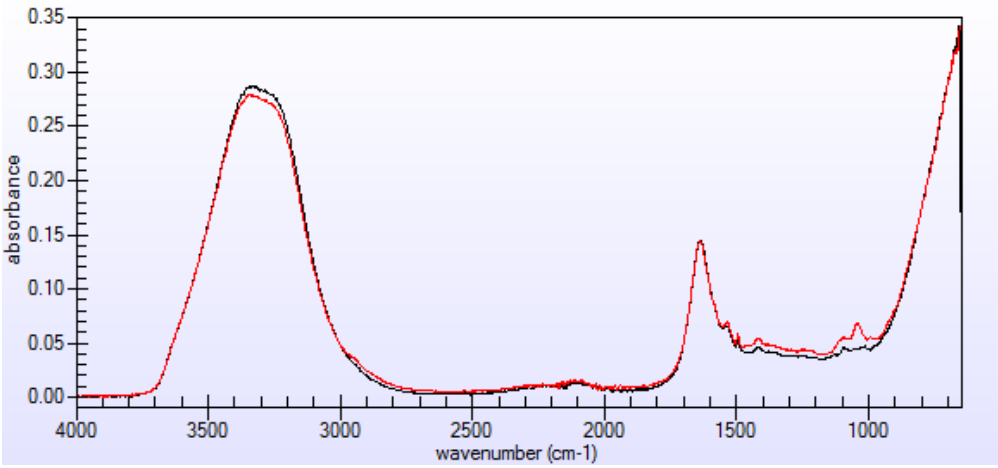


Figure 9: Water sample spectra

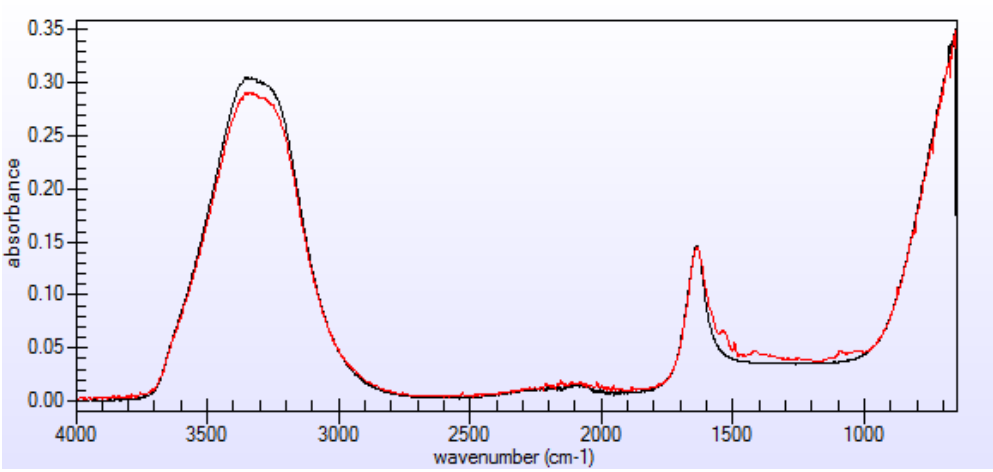
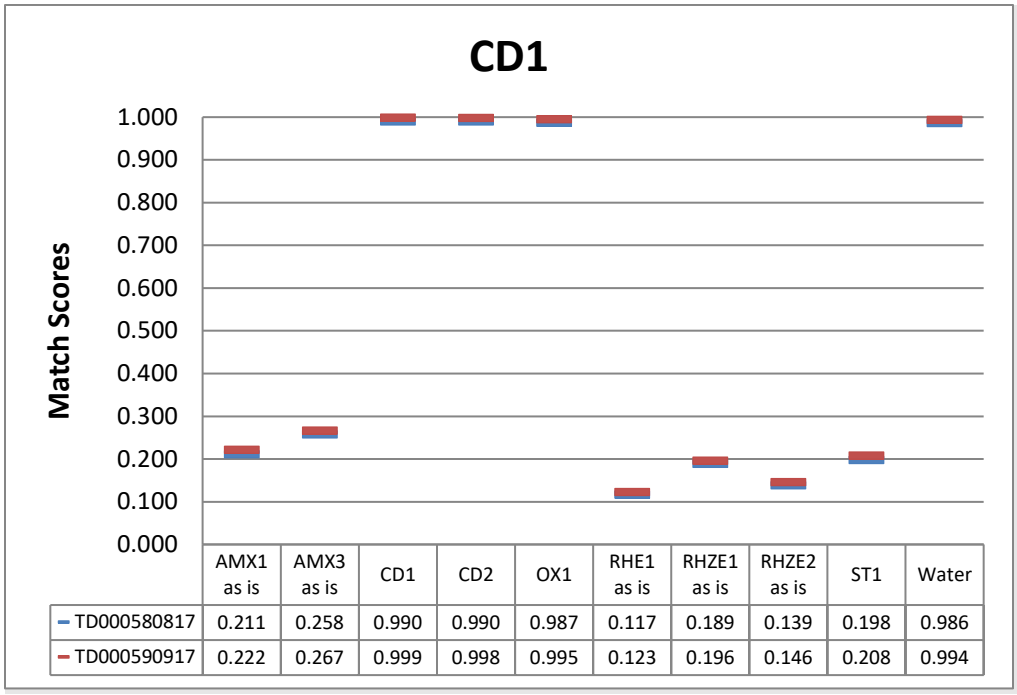


Figure 10. Match scores of CD1 compared to several DP samples and water



	AMX1 as is	AMX3 as is	CD1	CD2	OX1	RHE1 as is	RHZE1 as is	RHZE2 as is	ST1	Water
TD000580817	0.211	0.258	0.990	0.990	0.987	0.117	0.189	0.139	0.198	0.986
TD000590917	0.222	0.267	0.999	0.998	0.995	0.123	0.196	0.146	0.208	0.994

Oxytocin (10 IU) Injection

The Target-ID report for OX1 is shown in Figure 11. Only water absorption is apparent in the spectrum of OX1; thus, IR is not a suitable technique for selective ID of oxytocin, which can also be seen by the corresponding match factors in Figure 12.

Figure 11. Visual comparison of OX1 and water sample spectra

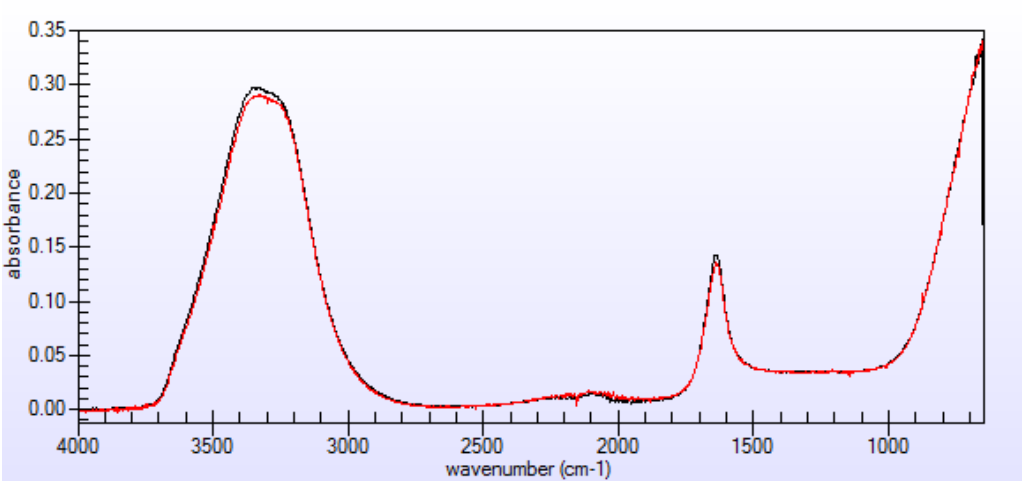
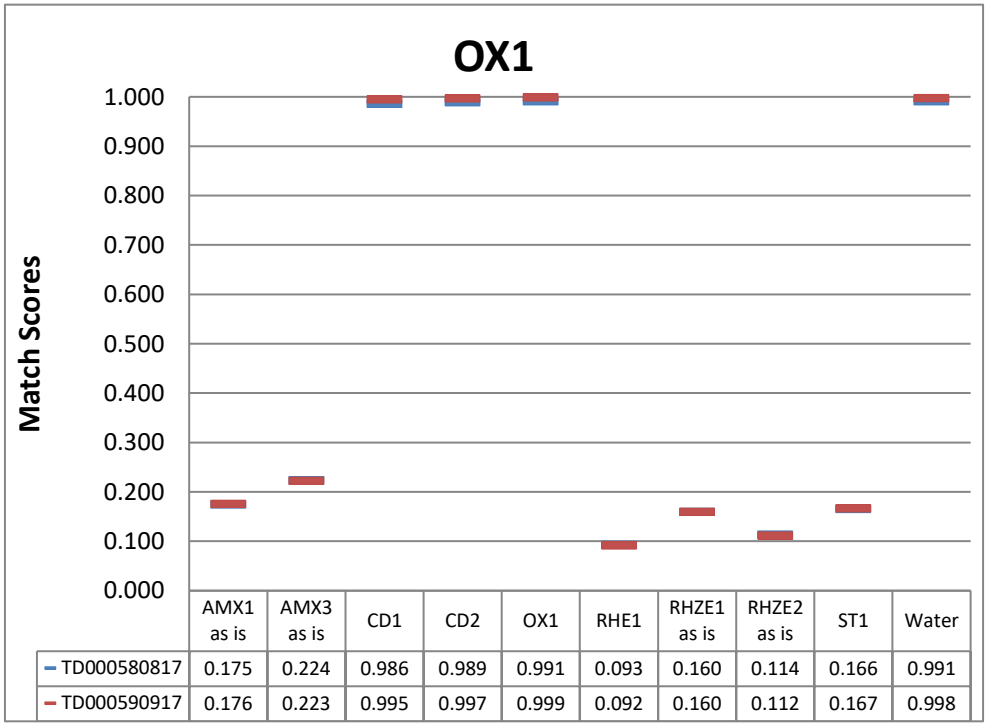


Figure 12. Match scores of OX1 compared to several DP samples and water



	AMX1 as is	AMX3 as is	CD1	CD2	OX1	RHE1	RHZE1 as is	RHZE2 as is	ST1	Water
TD000580817	0.175	0.224	0.986	0.989	0.991	0.093	0.160	0.114	0.166	0.991
TD000590917	0.176	0.223	0.995	0.997	0.999	0.092	0.160	0.112	0.167	0.998

Rifampicin + Isoniazid

The Target-ID report for RH1 is shown in Figure 13. The spectrum of RH1 expresses a high degree of inherent selectivity, with many peaks appearing across the spectral range. The selectivity of the RH1 spectrum for the API also appears high, and several peaks from INR and RIR can be seen in the RH1 spectrum. RH1 was identified accurately on both instruments with match factors NLT 0.98, see Figure 14.

Figure 13. Visual comparison of RH1 spectra and RH1 sample

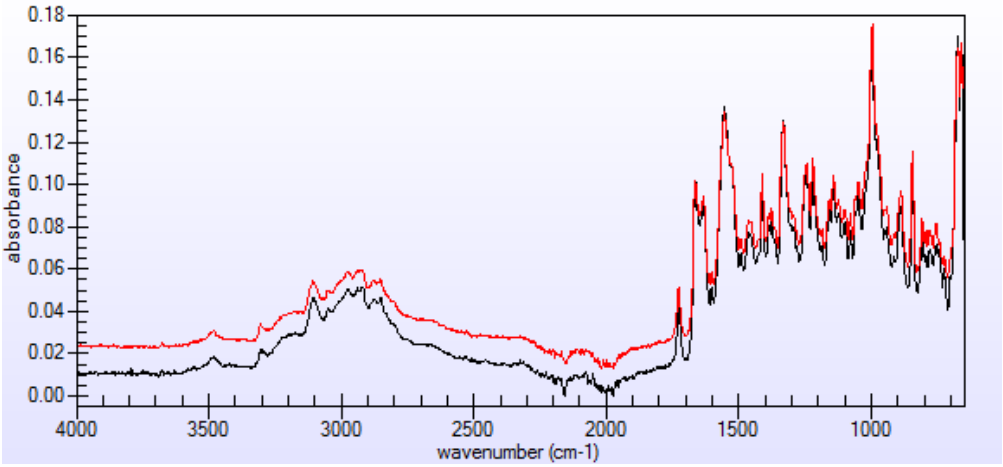
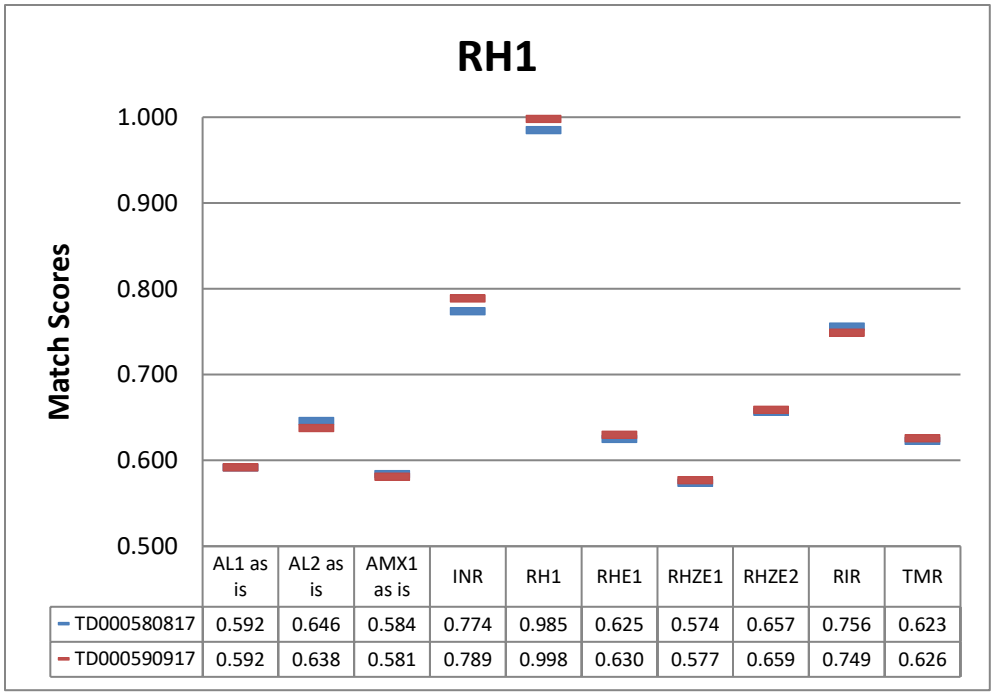


Figure 14. Match scores of RH1 compared to several DP samples and USP RSs



	AL1 as is	AL2 as is	AMX1 as is	INR	RH1	RHE1	RHZE1	RHZE2	RIR	TMR
TD000580817	0.592	0.646	0.584	0.774	0.985	0.625	0.574	0.657	0.756	0.623
TD000590917	0.592	0.638	0.581	0.789	0.998	0.630	0.577	0.659	0.749	0.626

Rifampicin + Isoniazid + Ethambutol

The Target-ID report for RHE1 is shown in Figure 15. The spectrum of RHE1 expresses a high degree of inherent selectivity, with many peaks appearing across the spectral range. RHE was identified accurately on both instruments, with match factors NLT 0.99, see Figure 16.

Figure 15. Visual comparison of RHE1 spectra and RHE1 sample

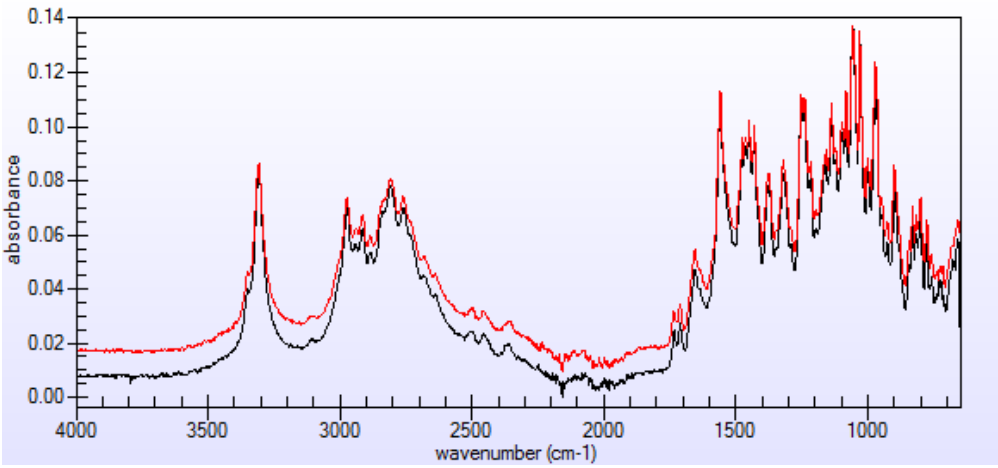
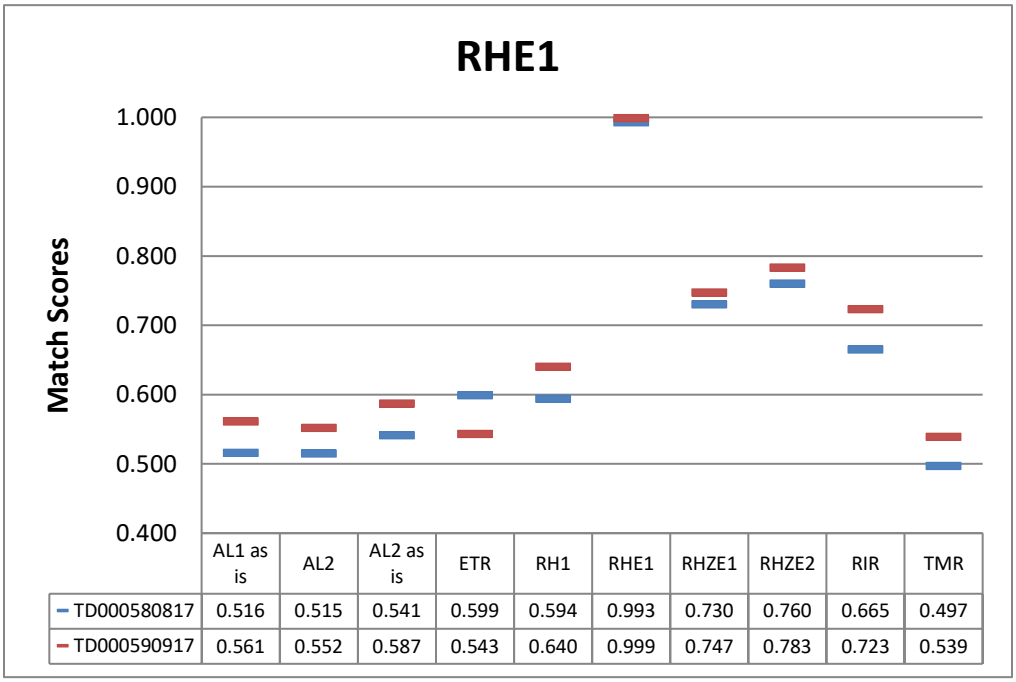


Figure 16. Match scores of RHE1 compared to several DP samples and USP RSs



	AL1 as is	AL2	AL2 as is	ETR	RH1	RHE1	RHZE1	RHZE2	RIR	TMR
TD000580817	0.516	0.515	0.541	0.599	0.594	0.993	0.730	0.760	0.665	0.497
TD000590917	0.561	0.552	0.587	0.543	0.640	0.999	0.747	0.783	0.723	0.539

Rifampicin + Isoniazid + Pyrazinamide + Ethambutol

The Target-ID report for RHZE1 is shown in Figure 17. The spectrum of RHZE expresses a high degree of inherent selectivity, with many peaks appearing across the spectral range. RHZE1 and RHZE2 were identified accurately on both instruments, with match factors NLT 0.97, see Figures 18 and 19.

Figure 17. Visual comparisons of RHZE1 spectra and RHZE1 sample

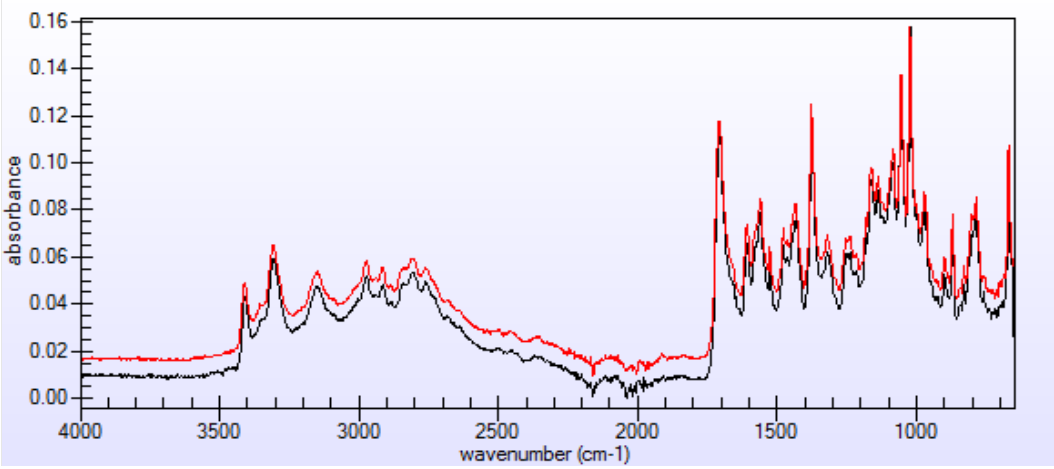
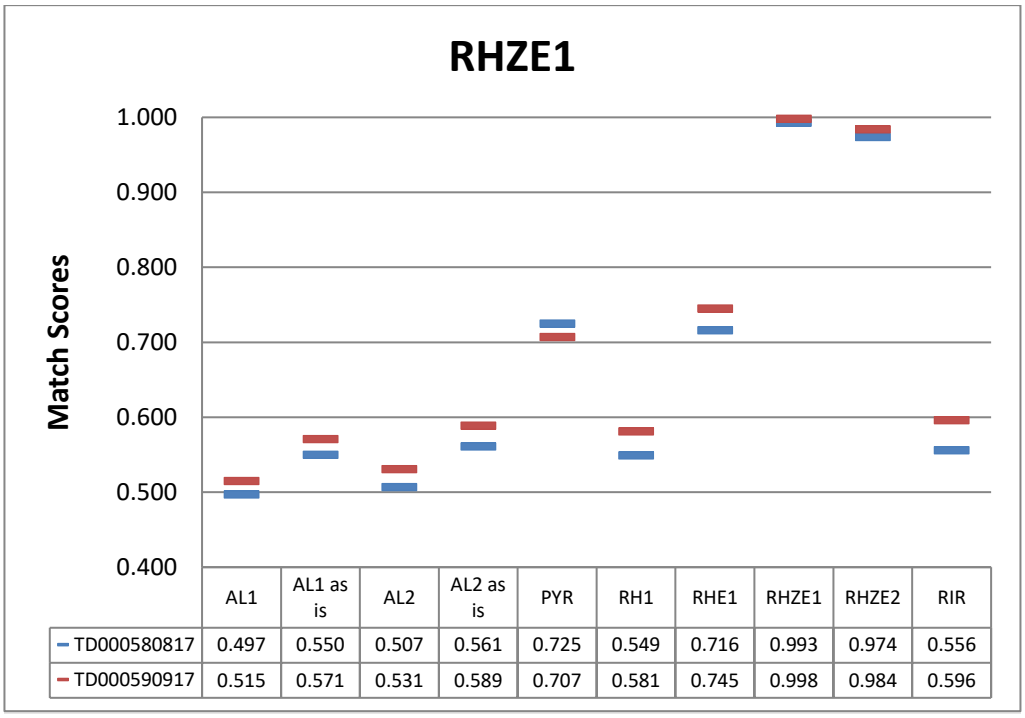
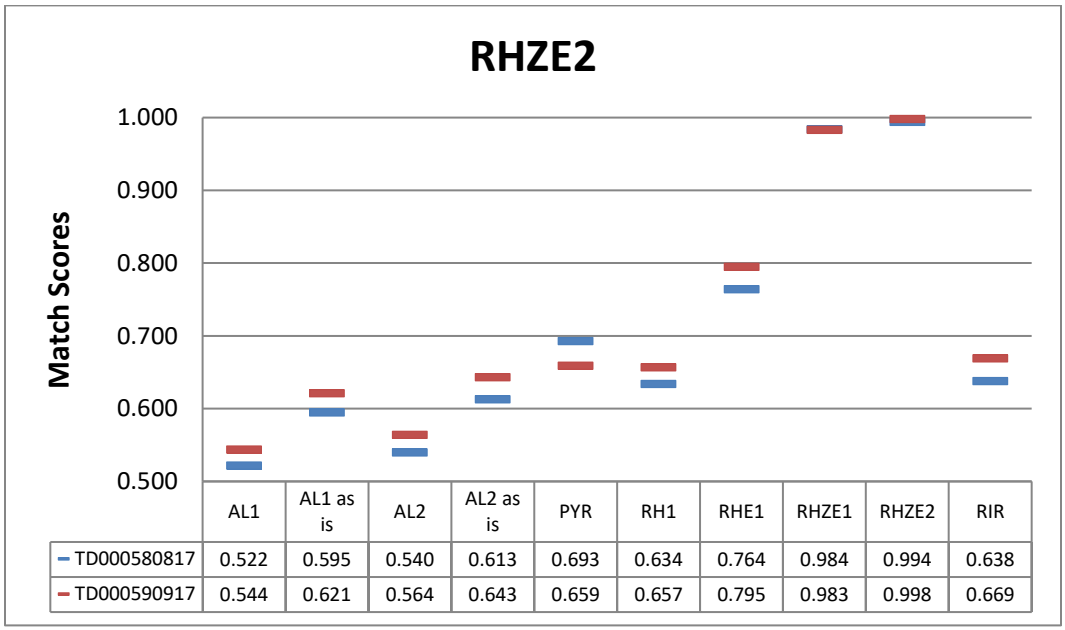


Figure 18. Match scores of RHZE1 compared to several DP samples and USP RSs



	AL1	AL1 as is	AL2	AL2 as is	PYR	RH1	RHE1	RHZE1	RHZE2	RIR
TD000580817	0.497	0.550	0.507	0.561	0.725	0.549	0.716	0.993	0.974	0.556
TD000590917	0.515	0.571	0.531	0.589	0.707	0.581	0.745	0.998	0.984	0.596

Figure 19. Match scores of RHZE2 compared to several DP samples and USP RSs

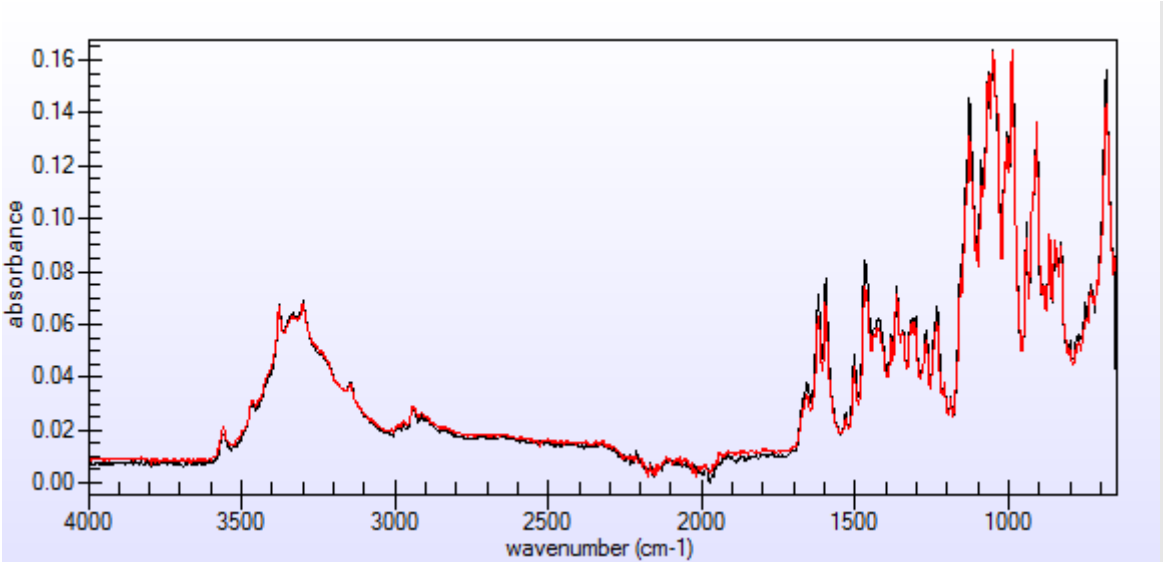


	AL1	AL1 as is	AL2	AL2 as is	PYR	RH1	RHE1	RHZE1	RHZE2	RIR
TD000580817	0.522	0.595	0.540	0.613	0.693	0.634	0.764	0.984	0.994	0.638
TD000590917	0.544	0.621	0.564	0.643	0.659	0.657	0.795	0.983	0.998	0.669

Sulfamethoxazole + Trimethoprim

The Target-ID report for ST1 is shown in Figure 20. The spectrum of ST1 expresses a high degree of inherent selectivity with many peaks appearing across the spectral range and ST1 was identified accurately on both instruments with match factors greater than 0.98. Only one brand of ST1 was used. Both Sulfamethoxazole and Trimethoprim reference standards (SUR and TMR) also gave low match scores, similar case with all co-formulated products

Figure 20: ST1 spectrum



3.3. Field Evaluation

The field evaluations were performed in Zambia and Indonesia between May 28 and June 8, 2018, for two major parameters, training requirements and field utility. Zambia and Indonesia were selected because they are 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 SF medicines.

Training Requirements

The first component of the field evaluation involved working with and training local staff from Zambia's and Indonesia's national medicines regulatory authorities (NMRAs), retail pharmacies, and customs to assess the amount of training required to enable staff to reliably and productively use Target-ID in the field.

The training involved two full days of work, which included one day of hands-on and theoretical work, followed by one day of collecting and testing samples in the field. Across both countries, 24 trainees participated, with 21 trainees being from either The National Agency of Drug and Food Control of Republic of Indonesia (Badan POM) or Zambia Medicines Regulatory Authority (ZAMRA). Of these, 15 were laboratory staff (either microbiologists or chemists), and six were pharmaceutical inspectors. Of the other three trainees, two were retail pharmacists and one was a government custom official.

To evaluate the perceived training timeframes needed for three levels of instrument proficiency (basic, intermediate, and advanced), the following 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 (before training):
    a. *Non-technical experience*: A trainee with no prior laboratory experience and no background in one of the physical sciences (e.g., chemistry).
    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 using the technology or the technique underpinning the technology.
2. User level[1] (following training):
    a. *Basic user*: A user with the ability to follow a standard operating procedure (SOP) or work instruction to set up and run the instrument and collect data.

[1] The user type abilities build upon the previous level. (E.g., an advanced user can perform the functions of an advanced user, as well as a basic and intermediate user.)

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 provides recommended training timeframes for trainees to reach each user level depending on the user's experience. Recommendations are based on the performance evaluation, field evaluation, trainer observations, and surveys given to trainees and local staff.

Table 3. Training Timeframe Requirements

User Experience	User Type		
	Basic	***Intermediate***	***Advanced***
Non-technical	1 to 2 days	1 week	2 weeks
Technical	1 day	1 day to 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 Target-ID in field settings and determining the utility of the instrument in these environments. It also included identifying any challenges associated with traveling with Target-ID.

No problems were encountered during routine international air transportation, which included security checks and hand luggage storage on long distance flights. Due to its size, the instrument was carried as hand luggage on the flights. The unit is light and portable, making it easy to carry, especially to the field. However, according to the manufacturer, the unit is fragile and cannot be dropped without the possibility of damage. Travel by vehicle to various sampling sites also did not involve any challenges, and the instrument withstood temperatures between room temperature and approximately 40℃. The instrument's batteries ran for approximately 4 hours.

Spectra were collected in the instrument, and the trainees could see the match scores on the instrument screen. Afterwards, the spectra libraries were transferred from the instrument to PC. Spectral libraries were developed at the training venues in both countries, and the instrument was taken to a rural health facility, retail pharmacies, wholesalers, and central medical stores (CMS), where samples were collected and analyzed onsite. Trainees undertook the exercise and completed the work themselves.

The samples collected and analyzed in the field include amoxicillin tablets, rifampicin + isoniazid tablets, rifampicin + isoniazid + pyrazinamide tablets, rifampicin + isoniazid + pyrazinamide + ethambutol tablets, ciprofloxacin tablets, sulfamethoxazole and trimethoprim tablets, and a sulfamethoxazole and trimethoprim oral suspension.

Also, during the field evaluation in Indonesia, an error was encountered where stored spectra libraries were not displaying, and the last spectrum collected became the spectrum for all of the previous samples. The vendor was contacted by email, responded within 24 hours, and remotely diagnosed the problem as an internally disconnected wire.

Picture 2. Use of Target-ID during field evaluation in Indonesia

4. Review and Conclusions

4.1. Performance Evaluation

Results from the evaluation indicated that the instrument can identify APIs in solid and powder dosage forms containing one API but not able to identify individual APIs in fixed dose formulations. The equipment does not distinguish between brands of the same medicine, as was shown when comparing different brands of samples with the same API. This also seems to imply that there may be no significant difference in excipient profiles between brands strong enough for Target-ID to differentiate brands, which is a limitation of the equipment.

All DPs tested generated match factors NLT 0.985 for their corresponding library spectrum. The data suggest an appropriate sensitivity threshold for the Target-ID is 0.98 if using a slave instrument (0.99 for the master). The data also indicate the lowest match score, indicating some significant similarity between the library and test spectrum, is approximately 0.80. This “similarity threshold” was determined by comparing various match scores and provided spectra for a number of DPs.

When analyzing the powders, there was good agreement between the obtained spectra and the library spectra, as opposed to analyzing the sample as a whole tablet, a capsule, or with primary packaging. This means, when using the instrument, it is advisable to crush the tablets or empty the capsules to obtain a better spectrum. The instrument sample holder was not designed to analyze such samples, and is hence, not recommended. In addition, Target-ID was not able to distinguish between different dosage strengths of AMX and AL tablets. For example, 20 mg/120 mg AL tablets and 80 mg/480 mg AL tablets had very similar spectra.

For RHZE, RHE, and RH, the spectrum and match scores were different from each other. This demonstrates that a falsified RHZE medicine without any one of the four APIs (rifampicin, isoniazid, pyrazinamide, or ethambutol) may be correctly identified using the Target-ID.

The advantage of a FTIR spectrometer is that it does not separate energy into individual frequencies for measurement, making data collection faster. In addition, an FTIR instrument allows more energy to reach the sample, making the signal-to-noise ratio high. Higher signal-to-noise means the sensitivity of small peaks will be greater, and details in a sample spectrum will be clearer than and more distinguishable from the dispersive spectrum of the same sample.

Also, an FTIR spectrometer requires the use of a laser to control the velocity of the moving mirror and to time the collection of data points throughout the mirror stroke length for each scan. The laser wavelength is a constant value, and the x-axis data points of the FTIR spectrum are automatically referenced to this known value to maintain internal precision and accuracy of the wavelength positions. This capability is not available on a dispersive IR system, and external calibration standards are required to control the accuracy of a dispersive instrument, making spectra less comparable due to instrumental unknowns during and between scans. Usually, accuracy and precision in IR spectra are much higher when collected on an FTIR instrument.

4.2. Field Evaluation

Based on the feedback survey from the trainees and the ongoing observations by the trainers, the training required to become a basic, intermediate, or advanced user of the instrument was manageable. More specifically, most of the trainees (20/24 or 83%), with both technical and non-technical backgrounds, can become either intermediate or advanced users within two weeks of training. Trainees were able to obtain spectra for samples obtained in the field, and match with some created spectral libraries. Transfer of the data and development of spectral libraries were also simple, with trainees developing libraries within a few minutes and analyzing samples within a few seconds at pharmacies, wholesalers, CMS, and public health facilities. The instrument is lightweight, portable, and self-contained, functioning with one battery, which can last for four hours and packaged in a rugged box. This makes it easy to carry and use in remote settings. Furthermore, it does not need any external consumables, making it particularly cheaper in the long run since there are rarely replaceable items. To avoid damaging the power cable, additional work would need to be done to replace the delicate pins on the power cable with better ones.

References

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

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

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

[4] USP. USP 43–NF 38. <1850>: EVALUATION OF SCREENING TECHNOLOGIES FOR ASSESSING MEDICINE QUALITY. Rockville, MD. United States Pharmacopeial Convention; To be official May 2020.

Annex 1. Equipment Used During Performance Evaluation

Item	Acronym	Manufacturer/ Source	Additional Details
Target-ID – Master	FTIR-0017	Smith Detection	Serial No. TD000590917
Target-ID – Slave	FTIR-0016	Smith Detection	Serial No. TD000580817
Target-ID manager software		Smith Detection	Version 1.6.0.2.4
Vacuum oven	OV	Yamamoto Scientific	Model: ADP-21 Serial No. A3700054
Environmental chamber	EC	Weiss Technik	Model: WKL 34/+10 Unit No. 562460 10530010

Annex 2. Samples Materials Used During Performance Evaluation

Item	Acronym	Manufacturer / Source	Product No.	Lot No.
Amoxicillin capsules (250 mg)	AMX1	Sandoz	0781-2020-01	HG9361
Amoxicillin capsules (500 mg)	AMX2	Sandoz	0781-2613-01	GS0051
Amoxicillin tablets (500 mg)	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	N/A	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 (150 mg) + ethambutol HCL (275mg) tablets	RHE1	Macleods Pharmaceuticals Ltd.	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 Pharmaceuticals Ltd.	DD/Drugs/DD/376	ERC6690C
Sulfamethoxazole (200 mg) + trimethoprim (40 mg) oral suspension	ST1	BDH Industries	608	D-10217

Annex 3. USP Reference Standard Materials

Product Description	Abbrev.		Product No.	Lot No.
Amoxicillin	AMR		1031503	L0K359
Artemether	ARR		1042780	H0M313
Chlorhexidine	CDR		1111103	l1L484
Ethambutol Hydrochloride	ETR		1257007	H1J063
Isoniazid	INR		1349706	R013N0
Lumefantrine	LUR		1370746	R041X0
Oxytocin	OXR1		1491296	F0I056
Pyrazinamide	PYR		1585006	R030C0
Rifampin	RIR		1604009	R039N0
Sulfamethoxazole	SUR		1631001	J1F148
Trimethoprim	TMR		1692505	L0M053