LANDSCAPE ANALYSIS OF TECHNOLOGIES TO DETECT COUNTERFEIT DRUGS: SUPPORTING INFORMATION

UNIVERSITY OF WASHINGTON GLOBAL HEALTH START PROGRAM
REPORT TO THE BILL & MELINDA GATES FOUNDATION

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PURPOSE

This report supplements a technology comparison table developed by the University of Washington Global Health Strategic Analysis and Research Training Program (START) team in response to the Bill & Melinda Gates Foundation's (the Foundation) work order *Landscape Analysis of Technologies to Detect Counterfeit and Substandard Drugs.* Included are a description of the methods used to identify technologies, the definitions of columns in the comparison table, and summary comparisons of the technologies. This report has two objectives:

Objective 1. Describe methods used to identify technologies for detecting counterfeit and substandard drugs.

Objective 2. Compare technologies (Appendix 1).

INTRODUCTION

Counterfeit or falsified and substandard drugs are a global problem and are estimated to account for 10% of all pharmaceuticals on the market (WHO 2012). The WHO defines a counterfeit drug as any pharmaceutical product that is deliberately mislabeled with respect to identity and/or source. Counterfeit drugs may include branded and generic products, drugs with the correct ingredients or with the wrong ingredients; without active pharmaceutical ingredient (API), with insufficient active pharmaceutical ingredients (API) or with fake packaging (WHO 2012). WHO estimates that counterfeit or falsified drugs cost the pharmaceutical industry over $75 billion in 2010 (WHO 2012). Beyond the financial costs of counterfeit drugs are the public health concerns. Use of counterfeit malaria drugs may be threatening gains made to control the disease due to increasing resistance to antimalarial drugs (Nayyar, Breman et al. 2012). For example, in a study of 1437 samples of malaria drugs from Southeast Asia, 35% failed chemical analysis (Nayyar, Breman et al. 2012). Because of these problems associated

with counterfeit drugs in the market, technologies that can correctly identify counterfeit, falsified and substandard products are critically needed. To address this urgent need, the U.S Institute of Medicine convened a committee to gather information and make recommendations on how best to mitigate the global problem of counterfeit, substandard and falsified pharmaceutical products (Insitute of Medicine 2012). These recommendations will be available in early 2013 for use by the global community. The landscape of technologies to detect counterfeit and substandard drugs is constantly evolving, thus these results are representative of our findings from our searches in January 2013.

OBJECTIVE 1: IDENTIFYING TECHNOLOGIES FOR DETECTING COUNTRFEIT DRUGS

METHODS FOR OBJECTIVE 1

Technologies for detecting counterfeit and substandard drugs were identified using two methods. First, literature reviews were conducted using databases such as PubMed, Web of Science, and Google Scholar. Second, selected key informant interviews were performed in which additional technologies were identified. Details of the technologies were gathered directly from the manufacturer or developer, when available.

Key words used in the literature searchers include "Technologies Detecting Counterfeit Drugs", "Mass Spectrometry Counterfeit Drugs", "Colorimetry counterfeit", "Gas chromatography counterfeit", "Liquid chromatography counterfeit". Many technologies had multiple articles, and in some articles multiple technologies were combined to create a new device. For example, one article discusses the successful combination of Direct Analysis in Real Time (DART) technology with Time of Flight (TOF) technology to create a new mass spectrometry device called AccuDART (Fernandez, Cody et al. 2006). For the purposes of the table, DART and TOF are presented as separate technologies, and AccuDART is presented as an example of a specific type of TOF device. Because technologies are often combined or used together, we presented the technologies separately and noted where they have been or could have been combined with other technologies. We included technologies if it was noted in the relevant literature that they were specifically designed for counterfeit drug use, pharmacokinetics, or if they could be plausibly used in counterfeit drug detection. No time bounds were used for searches in order to maximize the number of technologies captured.

RESULTS FOR OBJECTIVE 1

Through the literature review we identified 35 specific technologies, and an additional three technologies were identified through key informant interviews for a total of 38 specific technologies. The specific technologies are grouped into broad categories including: mass spectrometry (18), light based spectroscopy (3), colorimetry (1), electrophoresis (1), chromatography (9), fluorescent/phosphorescent approaches (1), nuclear magnetic resonance (1), nuclear quadrupole resonance (1), X-ray diffraction and radio waves (1), nanotechnology with multidimensional atomic force microscopy (1), and check list tools (1).

OBJECTIVE 2: CREATING TABLE OF TECHNOLOGIES FOR COMPARISON

METHODS FOR OBJECTIVE 2

The results of the literature review are presented in table form in the Appendix 1. Each row represents a single technology for detecting counterfeit or substandard drugs. Each column describes a unique attribute of the technology. Columns are grouped by general description, scientific properties, logistics of use, economic considerations and other considerations. Below is a description of the information included in each columns in the table:

General Description:

Technology's Purpose: All technologies were grouped by general purpose within the broader algorithm for detecting counterfeit and substandard products including chemical profiling and identification and quantification of active ingredients.

*General Technology***:** All technologies are grouped by general mechanism of action for detecting counterfeit and substandard drugs.

Specific Technology: This column subdivides the general technology into groups. For example, there are several different types of mass spectrometry including quadruple MS and time of flight MS.

Trade Name: For many technologies multiple instruments are available. For example, there are 24 different gas chromatography with mass spectrometry products on the market. In the table we only provided the details for one of each of the specific technologies while noting how many different instruments are available.

Manufacture: For many technologies there are multiple producers. For example, there are 14 companies that manufacture gas chromatography with mass spectrometry devices. In the table, where multiple producers exist for one product, we provide the total number of manufactures but details for only one specific manufacturer.

General Description: This column provides greater detail on how the specific technology works.

Stage of Development: The choices for the column include: under development (still theoretical), proof of concept paper published (i.e. the technology works), and commercially available.

Scientific Properties:

Mechanism of Action: This column defines how the technology detects the substance being measured. For example, mass spectrometers measure a mass to charge ratio in order to properly identify the substance being tested.

Screening vs. Confirmatory: This column dichotomizes technologies into those that can only screen pharmaceuticals as potentially counterfeit, and those tests which can confirm that a substance matches the label. Confirmatory technologies can be used to bring legal cases against counterfeiters where screening tests will need confirmatory test before legal action could be taken.

Sample Preparation Needed: Many technologies cannot test solids such as pills directly, but, instead, require the solid substance to be dissolved into a solution or heated to high temperatures and vaporized into a gas state.

Drugs that can be analyzed: Certain technologies such as mass spectrometers and light spectroscopy can be used to test any substance for which a validated chemical signature exists within the device's library allowing for essentially any drug to be tested. Other technologies such as MiniLab provide a limited number of reagents so only the 40 essential WHO medicines can be examined.

Temperature and Humidity Requirements: Some devices are very sensitive to high temperatures and/or humidity and therefore lose accuracy outside narrow temperature ranges.

Performance: Within the tables, technologies within the same general technology category are compared with regard to their relative sensitivity and specificity for detecting counterfeit drugs. Comparisons across broader technology categories are contained in the results section.

Logistical Considerations:

Laboratory Supplies: Some technologies need reagents, additional software, or supplies to function.

Speed: Refers to the time needed to analyze a single substance.

Throughput Batch or Serial: Dichotomizes technologies into those that must run samples serially and those that can run a batch of tests at once.

Need Electricity: Some technologies require an external electricity supply, others are battery-powered, others do not require electricity.

Level of Training Required: This captures the education and/or training requirements needed to utilize the technology. For example, mass spectrometry requires a highly trained chemist to operate the instrument while light spectroscopy requires little technical expertise and is used by boarder patrol officers.

Facility Requirements: Some technologies require specialized laboratories with a consistent supply of electricity and the ability to store flammable gasses, while other technologies can be utilized in any laboratory.

Portable: Dichotomizes technologies that can be used in the field and require no laboratory and those that must be housed in a laboratory.

Economic Considerations:

Set-up Costs: These costs include one-time costs of purchasing the device, any needed training, and/or infrastructure improvements.

Warrantee: Provides information about warrantees offered by the producer for the device.

Additional Costs: These include all marginal costs associated with running the device. Where possible, this is presented as a cost per test. Additional costs include: reagents and other laboratory supplies needed. Labor costs were not included in this calculation because they vary by geographical location.

Other:

Other Considerations: This column is used to note anything else of importance concerning the specific technology.

Funded by the Bill & Melinda Gates Foundation: Notes which technologies have been developed with funding from the Foundation.

Key Citation(s)/Websites: Any scientific articles, or links to product information from the manufacturer about the technology are listed in this column.

RESULTS FOR OBJECTIVE 2

Details for the 38 technologies identified are presented in Appendix 1 as an Excel spreadsheet.

BACKGROUND ON GENERAL TECHNOLOGIES

Spectroscopy

Spectroscopy-based technologies measure the diffraction of light by a substance and its corresponding spectra. These spectra are unique to the substance being sampled and can be used for chemical analysis – structure and contents - of suspected counterfeit drugs. Different types of spectroscopes use lasers to cause the molecules of a sample to vibrate and measure the readmitted light spectrum. Devices specific to counterfeit drug detection, such as the Raman spectrometer, can be made portable and many are able to sample products without removing the packaging. These devices are therefore often used in the field and require minimal training compared with other laboratory-based techniques. Devices range in prices from $1000-50,000.

Nuclear Magnetic Resonance (NMR)

Identification of compounds using NMR is based on the unique responses of different elements to changes in an external magnetic field. NMR is similar to spectroscopy in that a compound of interest is stimulated with electromagnetic energy and the reemitted energy can be used to identify and quantify the compound. NMR differs from other technologies because the wavelength of incident energy is very long (in the radiowave frequency), and because an energy pulse is required to assess how the compound responds to a perturbation. NMR is only able to detect atoms that contain an odd number of protons and/or neutrons. In counterfeit drug detection this means that NMR can identify APIs that consist of organic compounds containing ^{1}H and ^{13}C, either alone or in a mixture, but will not detect certain mineral ingredients. These instruments are expensive and have numerous requirements, such as training and electrical supply, for proper operation.

Colorimetry

Colorimetry is similar in concept to spectrophotometry, but reduces the possible results to remain within the realm of visible color change. Colorimetry can be used to identify drug components through simple chemical reactions that may result in color changes, identifying the presence of an active ingredient. Semi-quantification of the substance after the reaction can be conducted using an ultraviolet (UV) detector. Colorimetry is relatively inexpensive and some counterfeit drug testing kits include sets of color-change dye tests.

Chromatography

Chromatography is a mechanism by which mixtures can be separated into their component parts. Commonly, chromatography is used to prepare a chemical mixture before identification of the components is conducted through spectroscopic methods. The mixture (such as a tablet) is dissolved in a liquid or gas "mobile" phase and carried through a solid, "stationary" phase. Molecules are retained differentially within the solid phase, separating similar from dissimilar components. Types of chromatography are distinguished based on the shape of the diffusion bed (column or planar), the type of mobile phase, and the mechanism of separation. Several planar (thin layer) chromatography techniques have been developed specifically for counterfeit drug identification. Capillary electrokinetic chromatography and anion exchange chromatography are mechanisms of separation in the stationary phase that have also been used for API quantification. Both gas and liquid mobile phases are available, although the more advanced high performance liquid chromatography (HPLC) is the most commonly cited chromatographic method in the literature for counterfeit drug testing, per our PubMed review.

Mass Spectrometry

Mass spectrometry (MS) is an analytical technique that compares the mass to charge ratio of ions of a given substance in order to produce a unique mass spectra of the given sample. For the purposes of detecting counterfeit drugs, MS devices can identify and quantify APIs, expedients and adulterants in order to determine if an unknown sample contains the labeled API, if the amount of the API is correct, and if there are any contaminants present. A specific type of MS device called Isotope Ratio MS can also determine the location of production of the sample and therefore develop linkages between counterfeit samples and identify their source.

All MS devices contain three modules: an ion source, a mass analyzer and a detector. For all MS devices, ions of the sample must be created from either a gas, liquid or solid source. Ionizing techniques that can make ions from solid samples (needing no sample preparation) include DESI and DART. Other techniques such as inductively coupled plasma (ICP) require liquid samples. Mass analyzers use either static or dynamic magnetic or electric fields in order to separate ions by their mass or charge ratio. For example, time of flight (TOF) analyzers use an electric field to accelerate ions. Ions of lower mass will reach the detector faster than heavier ions. The final component of the MS device is the detector which records either the charge produced or the current produced when and ion hits the surface. MS devices can be configured to contain almost any ion source, mass analyzer or detector. In addition, MS can be combined with gas chromatography or liquid chromatography techniques.

In general, MS devices are very expensive (exceeding $100,000) and require highly trained personnel and well equipped research laboratory settings.

COMPARISONS ACROSS TECHNOLOGIES

The technologies for detecting counterfeit or falsified and substandard drugs can be divided into four approaches: visual examination of packaging materials and product; chemical profiling; identification and quantification of APIs, expedients and adulterants; and identifying the location of production of counterfeit samples (Yong, Lau et al. 2012).

Examination of packaging and product through check lists or optical microscopy can identify counterfeit products by finding defects in the design of the package or in the presentation of the capsules. This can be the first step in the identification of suspected counterfeit products, but cannot definitively

determine counterfeits. As counterfeit producers improve packaging, these techniques will be further limited. Finally, these technologies cannot identify whether or not the appropriate API is included at the correct dosage or if adulterants are present.

Chemical profiling technologies include all light spectroscopy technologies such as Raman and are able to compare profiles of unknown products against the profiles of authentic products. These technologies can be used in the field to rapidly provide information on APIs and adulterants. Although these techniques are not able to definitively confirm the identity of a product, improvements in these technologies have allowed them to perform almost as well as mass spectrometry-based technologies without requiring any specimen preparation. While the costs for these devices are much higher than chromatography and colorimetric techniques, there are no marginal costs associated with using these devices, in contrast with techniques that require reagents (Martino, Malet-Martino et al. 2010; Fernandez, Hostetler et al. 2011).

Additional technologies for detecting chemical profiles include colorimetry and thin layer chromatography (TLC). These tests can be performed cheaply and easily but consume both reagents and the sample. These methods can be used in the field, but in piloting, the most common field based technology, MiniLab, was only able to detect grossly substandard products (Fernandez, Hostetler et al. 2011).

Mass spectrometry techniques can be used for confirmatory testing of any product deemed suspect through examination of packaging, spectroscopy and chromatography techniques. MS is used for the **identification and quantification of APIs**, expedients and adulterants. Mass spectrometers are expensive devices requiring trained personnel and well-equipped laboratories. Newer technologies including DART and DESI can be performed on solid samples requiring no sample preparation (Fernandez, Hostetler et al. 2011). Isotope ratio mass spectrometry (IRMS) is able to provide linkages between counterfeits samples and is the best techniques for providing forensic evidence of the **location of production** for counterfeit drugs (Santamaria-Fernandez, Hearn et al. 2009).

ALGORITHM FOR DETECTING COUNTERFEIT AND SUBSTANDARD DRUGS

In order to efficiently and effectively identify counterfeit and substandard drugs, the Counterfeit Drug Forensic Investigation Network (CODFIN) developed an algorithm (Appendix 2). The Algorithm starts with examining packaging, quantitative HPLC screening and Ramen, NIR or colorimetric testing to ensure that the appropriate API is present. These tests may be done in the field utilizing technologies such as the MiniLab and WHO checklist. If the wrong the API is detected by these methods, ambient mass spectrometry analysis using technologies such as DART and DESI mass spectrometry should be used to gain an accurate fingerprint of suspected counterfeit. If a counterfeit substance is confirmed, isotope ratio mass spectrometry may be used to determine the location of counterfeit product's production.

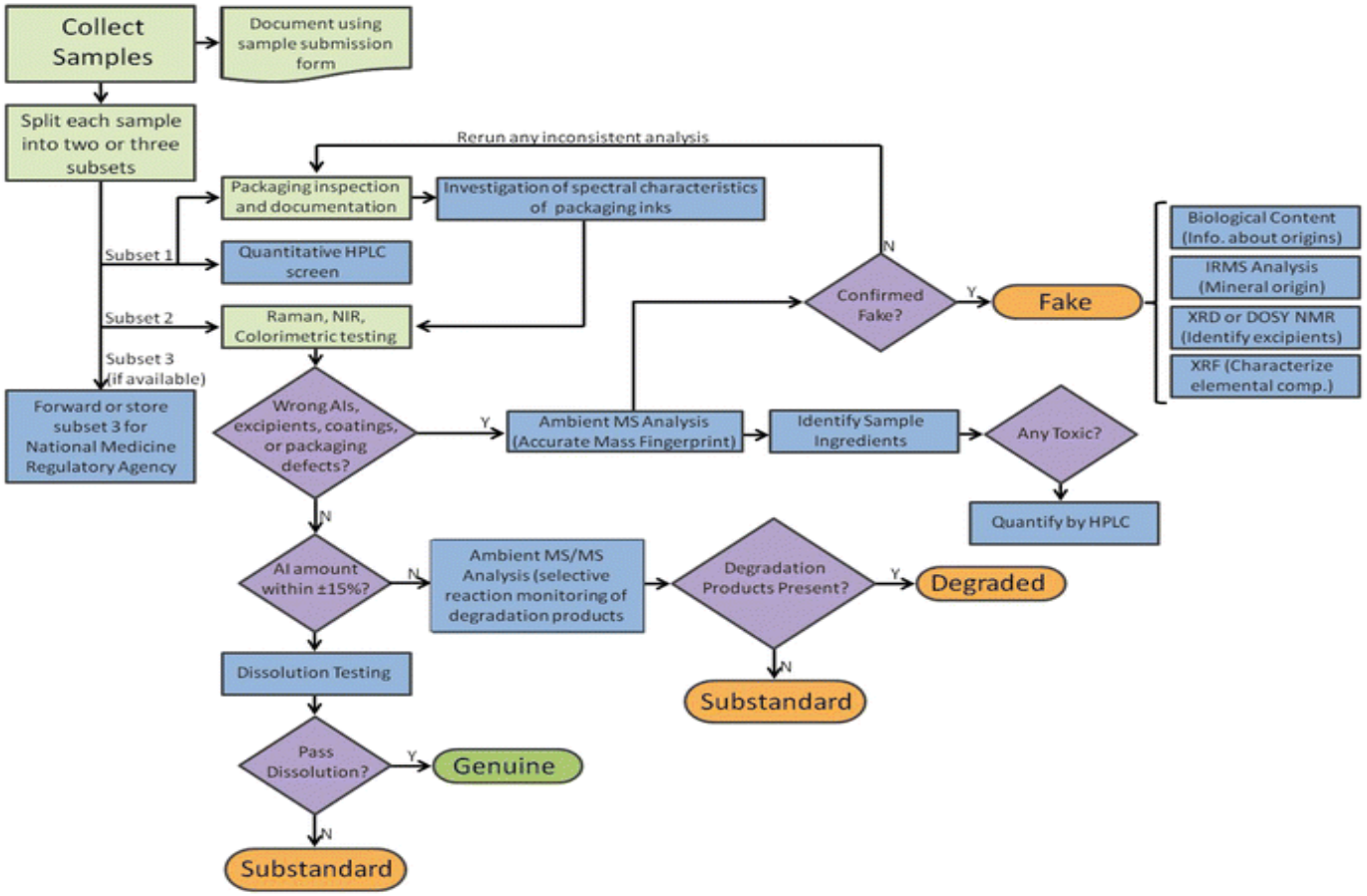
For those products with the correct active ingredient present, the next step is to ensure that the product has the correct levels of the active ingredient using HPLC. If the amount of the active ingredient is with 15% of the labeled value, the drug should be tested using dissolution testing. If the percentage of active ingredient is below 15% of the expected value, then further testing is needed to determine if the product is degraded due to improper storage or if it is substandard. Mass spectrometry techniques and nuclear magnetic resonance (NMR) can both be used with NRM being less sensitive but does not require chemical standards (Fernandez, Hostetler et al. 2011).

APPENDIX 1: TABLE OF TECHNOLOGIES TO DETECT COUNTERFEIT, SUBSTANDARD AND FALSIFIED DRUGS

SEE EXCEL SPREADSHEET ATTACHMENT

APPENDIX 2: COUNTERFEIT DRUG ANALYSIS ALGORITHM

Analytical workflow currently in use by CODFIN to test samples collected in country-level drug quality surveys (Fernandez, Hostetler et al. 2011). Steps colored with light green background can be performed in the field.



APPENDIX 3: LIST OF KEY INFORMANTS

Name	Organization	Technology
David Goodlet, PhD	University of Washington	SAWN, SAWN with DART
Chip Cody, PhD	JEOL	DART
Kevin Wheeler	Thermo Scientific	Orbitrap
Andy Stergachis, PhD	University of Washington	CD#3, WHO checklist
Bill Johnson	Agilent Technologies	GC-MS

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