A Concise Quality Control Guide on Essential Drugs and other Medicines

Manual

Accompanying The GPHF-Minilab®

Volume II

Thin Layer Chromatographic Tests

GPHF
GLOBAL PHARMA HEALTH FUND E.V.

A Charity Initiated and Sponsored by
Merck Darmstadt · Germany

A Concise Quality Control Guide on Essential Drugs and other Medicines

Volume II · Thin Layer Chromatographic Tests

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About Merck Darmstadt · Germany

Merck Darmstadt · Germany is a global pharmaceutical and chemical enterprise with roots dating back to 1668. Merck manages its operating activities under the umbrella of Merck KGaA, which is listed on the Frankfurt Stock Exchange. Today, around 30% percent of the company's share capital is publicly traded, while the Merck family owns an interest of about 70%. Merck is pursuing a strategy of operating in two major business sectors – Pharmaceuticals and Chemicals.

The Pharmaceuticals business comprises branded prescription drugs, e.g. for the treatment of cancer, neurological and growth disorders, cardiovascular diseases and infertility. The product range of this business sector also includes a wide range of well-known brands for consumer health care.

The Chemicals business sector offers chemicals for sophisticated applications: liquid crystals for displays, effect pigments for industry and cosmetics, analytical reagents and test kits, as well as products and services along the entire process chain of the pharmaceutical and biotech industry.

In 2007, Merck Darmstadt · Germany and the World Health Organization (WHO) in Geneva signed a partnership agreement to control schistosomiasis in African schoolchildren. Under this agreement, Merck will donate 200 million praziquantel 600 mg tablets (Cesol 600®) - a sufficient quantity to treat about 27 million children in the next ten years. This initiative came together with the establishment of the Global Pharma Health Fund (GPHF) in Frankfurt, a charity exclusively sponsored by Merck and driven to improve health and medicines supply in developing countries. The GPHF-Minilab acts as first-line defence against counterfeit and substandard medicines threatening the health of millions of people in developing countries.

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Made by Grimm Grafik Design

GPHF-Minilab® assembled and supplied by Technologie Transfer Marburg, Cölbe, Germany

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* including fixed-dose combination products

1 Introduction

The incidence of counterfeiting pharmaceutical products and the proliferation of substandard quality medicines has been well identified internationally and constitutes serious health hazards. It is primarily flourishing in developing countries where institutional capacity in regulation, inspection and law enforcement is weak and adequate funds for regular drug quality monitoring are missing. Counterfeiting of pharmaceutical products can take all kinds of form, but the end result is, when administered to a patient, that the consequences range from treatment failure, increased toxicity, increased drug resistance to malaria, TB and AIDS, and even outright death as a result of any of the above.

Need for drug quality testing in low-income countries with non-comprehensive supply chains and counterfeit medicines proliferation

Level	Location of testing	Scale of testing	Purpose of testing
1	Health post, rural retail outlets, consumers etc.	Visual screening: inspection of dosage forms, labelling and packaging	Counterfeit medicines detection before consumption
2	Hospitals, medical stores, priority disease programmes, wholesalers, importers, etc.	Basic testing: Colour reactions, thin-layer chromatography, disintegration	Post marketing surveillance, bridging capacity gaps when fully-fledged labs are not available, not in working order etc.
3	Regional/national public laboratories, independent private laboratories, industry labs etc.	Complete testing: pharmacopoeial and other legally accepted methods	Pre- and post-shipment inspections, forensic testing for court actions etc.

It is reasonable to estimate that the prevalence of counterfeit medicines ranges from less than 1 percent of sales in developed countries, to over 10 percent in developing countries, depending on the geographical area. Africa, parts of Asia, and parts of Latin America have areas where more than 30% of the medicines on sale can be counterfeit. Other developing markets, however, have less than 10%; overall, a reasonable estimate is between 10% and 30%. Considering antimalarials, antibacterials and other anti-infective medicines, even one single case can be enough to put thousands of lives at risk. Completely ineffective counterfeit antimalarials containing no drug at all are flooding the markets in Southeast Asia already. The trust of patients into health care and medicines is gradually fading away.

GPHF-Minilab® Need

Owing to the widespread danger of counterfeit medicines, quality control in the distribution system of developing countries has acquired new dimensions today. If adherence to good pharmaceutical manufacture, distribution and trading practice cannot be assumed, a greater number of samples have to be tested in order to maintain an appropriate assurance of drug quality. At the same time, however, pharmacopoeial analyses have become more and more expensive and only a few centres of excellence in some countries are currently available to perform them. The development and use of simple tests should therefore facilitate a balance between the need to increase the extend of drug testing on the one hand, and the need to contain costs on the other.

The Global Pharma Health Fund (GPHF), a charity initiated and maintained by Merck Darmstadt Germany, set out to develop and supply a portable, tropics-compatible and easy-to-use mini-laboratory that could verify the drug's identity and content and thus detect fake medicines by employing inexpensive analytical techniques. The GPHF-Minilab could close the capacity gap on drug quality testing in countries where the means for an effective drug quality-control system are not yet fully in place or where full testing is expensive, hardly accessible or time consuming.

The GPHF-Minilab will enable health facilities responsible for drug purchase, storage and distribution to protect themselves against the menace of dangerous trade in counterfeit medicines. Counterfeit case management is part of the job. Case reporting is entirely voluntary. Once informed, GPHF can point to counterfeit medicines but performs no own investigations. Once substandard quality medicine has been identified, some health care providers might decide not to pay the bill, some others might change the supplier in silent. Minilabs put people not into jail. However, they can trigger off further investigations and instantly protect patients against treatments with ineffective counterfeit medicines. And finally, the sheer likelihood that the crime might get detected even far a field in rural areas might send a warning signal to the smart persons behind the crime and cut down the proliferation in counterfeit medicines already.

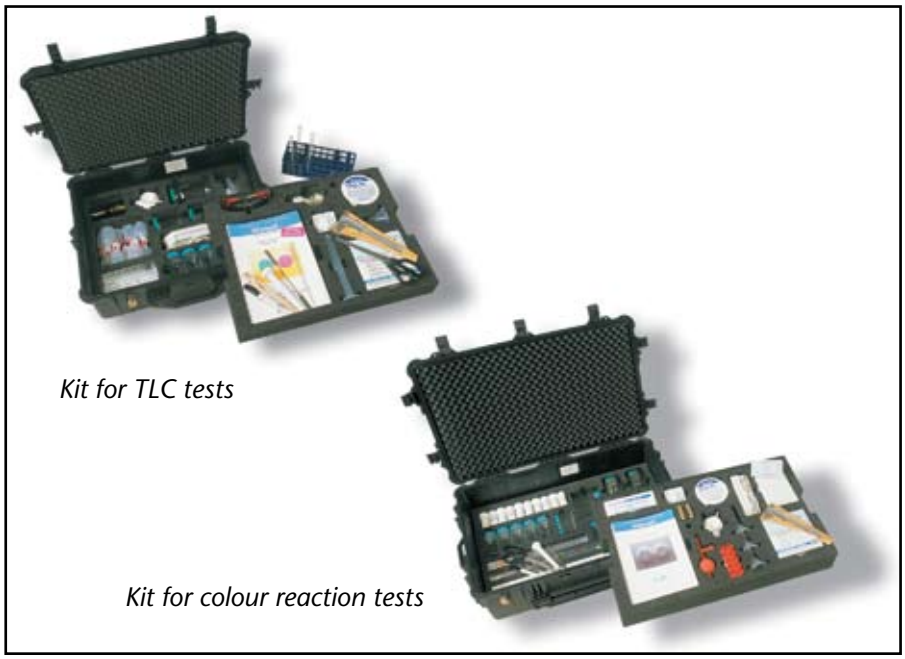
The GPHF-Minilab's current list of applications servicing medicines for priority diseases and childcare in developing countries	
Therapeutic Class	Individual Medicines
Analgesics (pain relievers)	Acetylsalicylic acid, Paracetamol
Antiasthmatics & Antiallergics	Aminophylline, Prednisolone, Salbutamol
Antibacterials	Amoxicillin, Ampicillin, Cephalexin, Chloramphenicol, Ciprofloxacin, Cloxacillin, Erythromycin, Metronidazole, Phenoxymethylpenicillin, Sulfamethoxazole, Tetracycline, Trimethoprim
Antifungals	Griseofulvin
Antihelminthics	Mebendazole, Praziquantel
Antimalarials	Amodiaquine, Artemether, Artesunate, Chloroquine, Lumefantrine, Mefloquine, Primaquine, Pyrimethamine, Quinine, Sulfadoxine
Antituberculosis	Ethambutol, Isoniazid, Pyrazinamide, Rifampicin
Antivirals	Didanosine, Indinavir, Lamivudine, Nevirapine, Oseltamivir, Stavudine, Zidovudine
Others	Furosemide, Glibenclamide

GPHF-Minilab® Applications

The GPHF-Minilab focuses its work on a range of more than forty drugs instantly life-threatened when diluted down to nothing. They have been selected on the basis of prevailing prescription practices, public health interest and existing counterfeit case reports, the current short list consisting of common antimicrobials, antihelminthics, anti(retro)virals, antimalarials, antituberculosis and some other medicines. Extensions of these test methods to other active ingredients are possible. Once counterfeit versions have been detected with the Minilab, drug inspectors, hospitals, medical stores and other health care providers can move on to freeze counterfeit batches for instant patient protection and send additional samples for confirmatory testing to a fully-fledged drug quality control laboratory.

GPHF-Minilab® Content

GPHF-Minilabs contain essential lab ware and chemicals, as well as authentic tablets and capsules for reference purposes. Supplies include sufficient quantities in order to perform about a thousand assays while ensuring that the total material costs for one test run do not exceed two Euros. Two heavy-duty suitcases contain the essential components - a full range of glassware for sample extraction, preparation, pipetting and spotting, high performance chromatographic plates, developing and detection chambers, UV lamps with different wavelengths, a hot plate, a spirit lamp, test tubes, calliper rules and storage containers. Even pens and pencils are included. If needed, a digital pocket balance can easily be added. Of particular importance is a full collection of secondary reference standards for more than forty active ingredients and a set of manuals providing simple operation procedures. Written in a non-scientific format and rich in illustrations, these manuals read more like a cooking recipe than an instruction booklet. Both, this and the manual on colour reaction tests are also available in French and Spanish.



Kit for TLC tests

Kit for colour reaction tests

The GPHF-Minilab's suitcases containing basic lab equipment, manuals and a full collection of more than forty secondary reference standards

GPHF-Minilab® Testing Procedures

The GPHF-Minilab takes the basic drug testing scheme published by the World Health Organization (WHO) some thirty years ago into the 21st century. New test methods have been introduced, and supplied are not only operation manuals printed in different languages, but also a complete range of lab ware, starter kit chemicals and reference standards is included - all suitably packed for global shipment by air. Now, identification of counterfeit medicines containing wrong, too little, or no ingredients at all can be performed instantly anywhere in the world. Results obtained by a set of physical and chemical screening tests must match the product label claims for, at least, drug identity and content. If they do not match or results are inconclusive, then the appropriate batches can be frozen for further investigation. GPHF-Minilabs cannot replace extensive testing on questions of drug release, chemical purity, or microbial burden; those and detailed forensic testing for court actions must be referred to a fully-fledged drug quality control laboratory that employs legally accepted methods. The GPHF-Minilab has been developed for rapid drug quality verification and counterfeit medicines detection only.

The GPHF-Minilab's scheme of physical and chemical testing

Visual Inspection	Disintegration	Colour Reaction	Thin Layer Chromatography
			
1. A visual inspection scheme of solid dosage forms and associated packaging material for an early rejection of the more crudely presented counterfeits.	2. A simple tablet and capsule disintegration test in order to verify label claims on enteric-coating and other modified-release systems.	3. Simplified colour reaction tests for a quick check of any drug present, thus verifying label claims on identity.	4. Easy-to-use thin layer chromatographic tests for a quick check on drug content, thus verifying label claims on potency.

GPHF-Minilab® Staff Requirements

Expert staff with lab experience will be able to use the kit straight away without further assistance. Sometimes they ask for a short refreshment training. Experts are doctors specialised in the field of clinical chemistry, pharmacists with a background in drug analysis and medical and pharmaceutical technicians performing the same jobs on adequate levels in hospitals of low-income countries. Here, pharmacists frequently prefer to be trained as Minilab trainers themselves thus reducing the amount of training otherwise delivered by the Global Pharma Health Fund and its partners. In Africa and Southeast Asia, even law enforcement and customs personnel occasional attends Minilab trainings. But this is then for information only in particular when big country studies for drug quality monitoring purposes are initiated. In such studies, support might be drawn from them for sample collection and freezing in situations where pharmacists are lacking the power of enforcement.

GPHF-Minilab® Procurement, Maintenance and Shipment

As a unique product without direct competition, procurement of GPHF-Minilabs by public institutions can be managed without tendering, which facilitates quick responds to needs in public health programming. As a product assembled for humanitarian use only, the GPHF-Minilab can cross borders with a single item customs tariff number and when partnering with United Nation Organizations shipments are facilitated even further. Non-for-profit sales make Minilabs also affordable for private non-governmental and faith-based health communities. Here, acceptance is even further enhanced by the fact that Minilabs are assembled and shipped by Technologie Transfer Marburg (TTM), a logistics facility within their own community.

Technologie Transfer Marburg is the licensed partner of the Global Pharma Health Fund responsible for Minilab assembly, invoicing and shipment. Quotes for a standard Minilab including lab equipment, reference standards, reagents and test solutions for both, TLC and dye tests, can be

obtained from them (www.ttm-germany.de). Quotes may also include the costs for transport for each destination, however, the costs for clearance cannot be stated and must be investigated locally by the project itself. For Minilab maintenance, global delivery of replacement items is secured through the same supply route. Minilabs can be customised to cater for specific project needs, for example using TLC equipment and reference standards for antimalarial drug quality verification only. Depending on the final specification, the price might then go up or down.

GPHF-Minilab® User, Resources and Project Partners

Priority disease programmes from institutional development assistance are frequently using Minilabs in order to monitor the quality of medicines in malaria-, TB- and AIDS-endemic countries. Promoters and project partners are the World Health Organization (WHO) in Geneva and three major NGOs from the USA, Management Sciences for Health (MSH), the Partnership for Supply Chain Management (PFSCM) and the Drug Quality and Information programme of the United States Pharmacopeia (USP DQI), all being based in Washington DC. Support comes also from the German Technical Cooperation (GTZ) and faith-based organisations, for example, from the Medical Mission Institute Würzburg, the medicines relief organisation *action medeor* and the German Doctors for Developing Countries. In Tanzania, 25 Minilabs are already used as a first-line defence to protect the country's communities against the infiltration of counterfeit medicines.

Since ten years, GPHF-Minilabs are physically and financially accessible on a global scale and are protecting health facilities around the world against the infiltration of counterfeit medicines dangerous to health and life. Over 270 units are now in place in 65 countries. Within the International Medical Product AntiCounterfeiting Taskforce (IMPACT) steered by WHO, GPHF-Minilab test methods are an accepted technology for counterfeit medicines detection and patient protection in developing countries. With this backing and a proven record in global and timely Minilab delivery to almost any destination in the world, governmental and non-governmental advisory and financing bodies, for example The World Bank, The Global Fund, UNDP etc. are able to issue grants and other support to drug quality monitoring projects using Minilabs.

The imagination of the major funding agencies, the enthusiasm of local people, the established logistics and the commitment of the Global Pharma Health Fund will clearly take the Minilab initiative forward over the next ten years. In this scenario, training and teaching at schools of pharmacy, chemistry and medicine can be an additional option.

Important Notice

Counterfeit drugs represent a risk for the health and life of patients. In order to avoid erroneous test results, which could turn out to be potentially dangerous for the patients, it is essential that the instructions and tests given in this manual are carefully studied and closely followed when working with the GPHF-Minilab®

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6 Individual Test Procedures

6.33 Pyrazinamide (including fixed-dose combinations)

Primary Screening via Visual Inspection and Disintegration Test

I. VISUAL INSPECTION

Search for deficiencies on labelling, packaging and dosage forms as described in the opening chapters on general methods and operations. Write down all product particulars using the reporting form as a guide. Each tablet or capsule usually contains 400 or 500 mg of pyrazinamide. Dosage strenghts of a 100 to 300 mg of pyrazinamide are known to exist in particular in fixed-dose combinations with other antituberculosis medicines.

II. DISINTEGRATION TEST

All quick release pyrazinamide tablets and capsules must pass the disintegration test as described in the opening chapters on general methods and operations. They should disintegrate in water at 37 °C in less than 30 minutes. It's a major defect if a drug product doesn't pass this test.

III. RESULTS & ACTIONS TO BE TAKEN

Drug products from unusually cheap sources, drug products with missing or incorrect accompanying documents and drug products with defective dosage forms, packaging or with incomplete, damaged or missing labels or with labels written in a foreign language should be subjected to a thin layer chromatographic test.

Verification of Drug Identity and Content via Thin Layer Chromatography

I. PRINCIPLE

Pyrazinamide is extracted from tablets and capsules with methanol and determined by TLC with reference to an authentic secondary standard. When combined with other antituberculosis drugs, all compounds can be extracted and analysed simultaneously.

II. EQUIPMENT AND REAGENTS

1) Pestle
2) Aluminium foil
3) Funnel
4) Label tape
5) Marker pen
6) Pencil
7) 10-ml vials
8) Set of straight pipettes (1 to 25 ml)
9) Set of laboratory glass bottles (25 to 100 ml)
10) Merck TLC aluminium plates pre-coated with silica gel 60 F 254, size 5x10 cm
11) Glass microcapillaries (2-µl filling capacity)
12) TLC developing chamber (500-ml jar)
13) Hot plate
14) Filter paper
15) Pair of scissors
16) Pair of tweezers
17) UV light of 254 nm
18) Iodine chamber
19) Methanol
20) Toluene
21) Ammonia solution 25%
22) Secondary reference standard, for example, pyrazinamide 500 mg tablets

III. PREPARATION OF THE STOCK STANDARD SOLUTION

The preparation of the stock standard solution requires an authentic drug product for reference purposes, for example, tablets containing 500 mg of pyrazinamide. Wrap up one reference tablet into aluminium foil and crush it down to a fine powder using a pestle. Carefully empty the aluminium foil over a 100-ml laboratory glass bottle and wash down all residual solids with 50 ml of methanol using a straight pipette. Close the bottle and shake for about three minutes until most of the solids are dissolved. Allow the solution to sit for an additional five minutes until undissolved residues settle below the supernatant liquid. The solution obtained should contain 10 mg of total drug per ml and be labelled as *'Pyrazinamide Stock Standard Solution'*. Freshly prepare this solution for each test. Continue to work with the clear or hazy supernatant liquid.

IV. PREPARATION OF THE WORKING STANDARD SOLUTION 100% (UPPER WORKING LIMIT)

Pipette 1 ml of the stock standard solution into a 10-ml vial and add 7 ml of methanol. Close and shake the vial. The solution obtained should contain 1.25 mg of total drug per ml and be labelled as *'Pyrazinamide Working Standard Solution 100%'*.

This higher working standard solution represents a drug product of good quality containing 100 % of pyrazinamide.

V. PREPARATION OF THE WORKING STANDARD SOLUTION 80% (LOWER WORKING LIMIT)

Pipette 1 ml of the stock standard solution into a 10-ml vial and add 9 ml of methanol. Close and shake the vial. The solution obtained should contain 1.0 mg of total drug per ml and be labelled as *'Pyrazinamide Working Standard Solution 80%'*.

This lower working standard solution represents a drug product of poor quality containing just 80% of the amount of pyrazinamide as stated on the product's label. In the current investigation, this drug level represents the lower acceptable limit for a given product.

VI. PREPARATION OF THE STOCK SAMPLE SOLUTION FROM A PRODUCT CLAIMING TO CONTAIN 100 MG OF PYRAZINAMIDE PER UNIT

Take one whole tablet or capsule from an appropriate drug product sampled in the field. As usual, tablets are wrapped up into aluminium foil and crushed down to a fine powder. Transfer all the powder obtained into a 25-ml laboratory glass bottle. Powder obtained from a sample capsule should be transferred directly into the bottle adding the cap and body shells last. For extraction, add 10 ml of methanol using a straight pipette, close the bottle and shake for about three minutes until most of the solids are dissolved. Allow the solution to sit for an additional five minutes until undissolved residues settle below the supernatant liquid.

300 MG OF PYRAZINAMIDE PER UNIT

Take one whole sample tablet or capsule and extract the powder obtained with 30 ml of methanol using a straight pipette and a 40-ml laboratory glass bottle as sample container. Continue to work as above.

400 MG OF PYRAZINAMIDE PER UNIT

Take one whole sample tablet or capsule and extract the powder obtained with 40 ml of methanol using a straight pipette and a 100-ml laboratory glass bottle as sample container. Continue to work as above.

500 MG OF PYRAZINAMIDE PER UNIT

Take one whole sample tablet or capsule and extract the powder obtained with 50 ml of methanol using a straight pipette and a 100-ml laboratory glass bottle as sample container. Continue to work as above.

All stock sample solutions produced should finally contain 10 mg of total drug per ml and be labelled as *'Pyrazinamide Stock Sample Solution'*. Freshly prepare these solutions for each test. Continue to work with the clear or hazy supernatant liquids.

VII. PREPARATION OF THE WORKING SAMPLE SOLUTION

Pipette 1 ml of the stock sample solution into a 10-ml vial and add 7 ml of methanol. Close and shake the vial and label as *'Pyrazinamide Working Sample Solution'*.

The expected concentration of pyrazinamide in this working sample solution is 1.25 mg per ml and should match the concentration of pyrazinamide of the higher working standard solution produced above.

VIII. SPOTTING

Mark an origin line parallel to and about 1.5 cm from the bottom edge of the chromatoplate and apply 2 µl of each test and standard solution as shown in the picture opposite using the microcapillary pipettes supplied.

Up to five spots can be placed on a plate. Check the uniformity of all spots using UV light of 254 nm. All spots should be circular in shape and equally spaced across the origin line. Although their intensities might differ, their diameters never should. Different intensities are due to residual amounts of tablet and capsule excipients or different drug concentrations in the sample solutions. A difference in spot size, however, relates to poor spotting. Repeat this step if homogeneous spotting is not achieved first time.

IX. DEVELOPMENT

Pipette 12 ml of methanol, 10 ml of toluene and 0.5 ml of concentrated ammonia solution into the jar being used as TLC developing chamber. Close the chamber and mix thoroughly. Line the chamber's wall with filter paper and wait for about 15 minutes thus ensuring saturation of the chamber with solvent vapour. Carefully place the loaded TLC plate into the jar. Close the jar and develop the chromatoplate until the solvent front has moved about three-quarters of the length of the plate, the developing time being about 20 minutes. Remove the plate from the chamber, mark the solvent front and allow any excess solvent to evaporate using a hot plate if necessary.

X. DETECTION

Dry off all residual solvent and observe the chromatoplate under UV light of 254 nm using the battery-driven lamp supplied. Use this method of detection for both, identification and quantification purposes. Further verification of pyrazinamide identity and content can be achieved when observing the plate at daylight after iodine staining.

In case ethambutol is present, stain the chromatoplate with ninhydrin for its detection. Consult pages 26 and 90 to see how to perform the staining process. Note that this method of detection will make it impossible to further observe pyrazinamide or isoniazid spots under UV light of 254 nm and rifampicin spots at daylight.

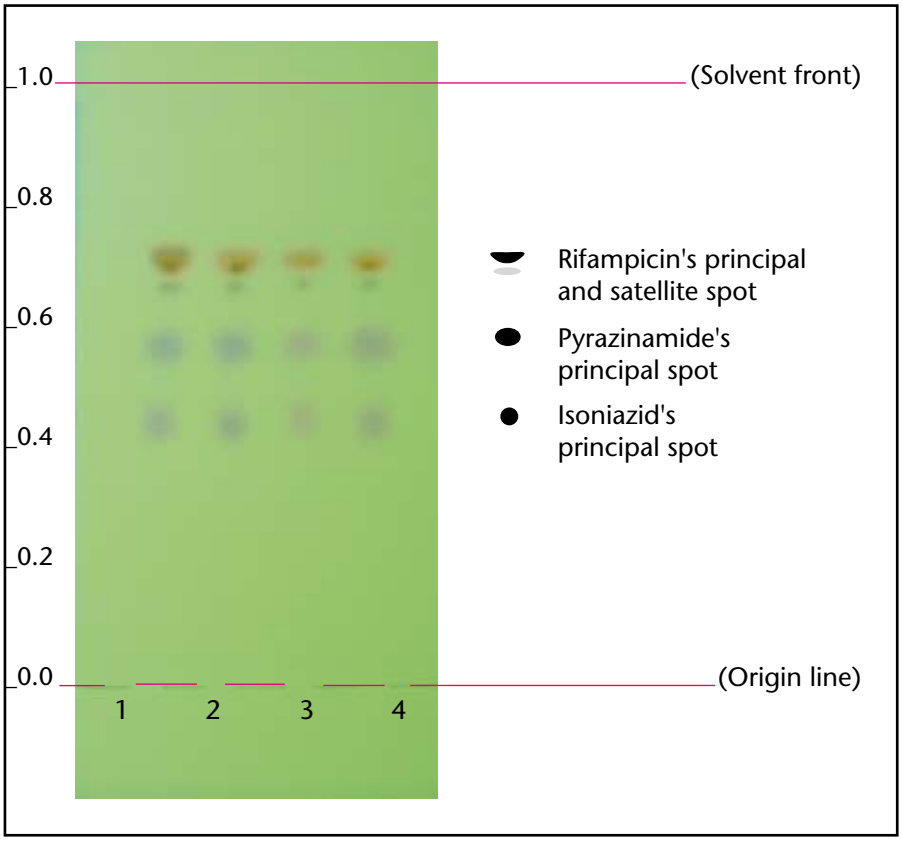
XI. CHROMATOPLATE OBSERVED UNDER UV LIGHT OF 254 NM

Run No.1:
A standard solution representing 100% of total pyrazinamide, isoniazid and rifampicin as upper working limit.

Run No. 2:
A pyrazinamide fixed-dose combination product of good quality.

Run No.3:
A pyrazinamide fixed-dose combination product of poor quality.

Run No.4:
A standard solution representing 80% of total pyrazinamide, isoniazid and rifampicin as lower working limit.



XII. OBSERVATIONS MADE AT 254 NM

A blue-violet spot at a travel distance of about 0.56 indicates the presence of pyrazinamide in the test solution. When combined with isoniazid and rifampicin, two more principal spots are visible below and above the pyrazinamide spot at a travel distance of about 0.45 and 0.71, respectively. Additional strong spots generated by the test solution would point at other drugs or pyrazinamide degradation, the latter case being more likely when associated with a smaller principal spot. Auxiliary agents incorporated in the different tablet or capsule formulations might cause some fainter spots emerging near or on the origin line. Fixed-dose combination products containing also ethambutol would require staining with ninhydrin solution as this drug cannot be detected with UV light of any wavelenght whatsoever.

XIII. OBSERVATIONS MADE AT DAYLIGHT AFTER IODINE STAINING

When exposing the chromatoplate to iodine vapour, all pyrazinamide spots already observed at 254 nm are now turning orange-brown. Still observe the plate when iodine evaporates already. Spots reflecting poor quality products will disappear first gradually followed by the reference spots representing a drug content of an 80 and 100 percent, respectively.

XIII. RESULTS & ACTIONS TO BE TAKEN

The pyrazinamide spot in the chromatogram obtained with the test solution must correspond in terms of colour, size, intensity, shape and travel distance to that in the chromatogram obtained with the lower and higher standard solution. This result must be obtained for each method of detection. If this is not achieved, repeat the run from scratch with a second sample. Reject the batch if the drug content cannot be verified in a third run. For a second opinion, refer additional samples to a fully-fledged drug quality control laboratory. Retain samples and put the batch on quarantine until a final decision on rejection or release has been taken.

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