

Chemistry and Toxicology Devices
April 25, 2013

Strip Test, Isoniazid - unclassified

Executive Summary

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Executive Summary

I. *Introduction*

The purpose of this meeting is to determine the appropriate regulatory classification for diagnostic devices known as Isoniazid Test Strips. Isoniazid Test Strips are considered pre-amendment devices since they were in commercial distribution prior to May 28, 1976 when the Medical Device Amendments became effective but were not classified. Isoniazid Test Strips are currently regulated under the heading of “Strip Test, Isoniazid” Product Code MIG, as unclassified under the 510(k) premarket notification authority. The Food and Drug Administration (Agency) is seeking panel input on the safety and effectiveness of Isoniazid Test Strips in order to classify these devices.

Isoniazid Test Strips are a qualitative assay used for detecting isonicotinic acid and its metabolites in urine to determine compliance of isoniazid (INH) medication. The Food and Drug Administration (Agency) is seeking panel input on the safety and effectiveness of Isoniazid Test Strips in order to classify the device.

II. *Regulatory History*

The Agency classifies medical devices into Class I, II, or III generally determined by the risks or hazards to the patient or user associated with the device. Class I devices are those devices which are considered low risk and present minimal potential harm to a user. The risks from harm of a Class I device can be adequately mitigated by general controls which include the following:

- Establishment registration and listing;
- 510(k) premarket notification;
- Good Manufacturing Practices (GMPs); and
- Other regulatory controls, e.g., labeling adverse event reporting, misbranding, adulteration of the device, and others.

Subsequently, many of the Class I devices have been exempted from the 510(k) premarket notification procedures due to their low risk. However, they have not been exempted from other general controls.

Class II devices are those devices which are considered to have moderate risk such that general controls alone are not sufficient to mitigate the risks of harm to a user and for which there is sufficient information to establish special controls, existing methods specific to the device that can control the risks not controlled by the general controls. Special controls for medical devices may include:

- performance standards;

- post-market surveillance;
- patient registries;
- guidelines;
- design controls; and
- other appropriate actions deemed necessary for mitigating the risks of the device.

Class III devices are those devices considered to be high risk and whose risk may not be completely mitigated by general and special controls alone. For Class III devices there is insufficient information to establish a reasonable assurance of safety and effectiveness so data from a well-controlled, statistically significant clinical study is often needed. These devices are typically life sustaining or life supporting of substantial importance in preventing impairment of human health, or present an unreasonable risk of illness or injury. In addition, manufacturers cannot make any changes to the Class III device or to the labeling without notifying and receiving approval from FDA.

Isoniazid Test Strips were not identified during the device classification process carried out in the 1970's and therefore were not assigned a device classification. These devices were identified later and established to have pre-amendments status. Over the course of over 30 years, one device (cleared under k912888) was found to be substantially equivalent to a pre-amendment device and was cleared in 1992. Though these strips are still available, they are not widely used.

III. *General Device Description*

Isoniazid Test Strips are a qualitative, chemical assay for detecting isonicotinic acid and its metabolites in urine to determine compliance of isoniazid (INH) medication. INH therapy is prescribed for persons with active or latent tuberculosis. The course of treatment with the drug can extend to 6 months in latent TB cases. Isoniazid Test Strips are used to monitor the compliance of individuals undergoing INH treatment in order to reduce the number of disruptions in therapy, thereby reducing the risk of developing INH resistance.

Screening tests for Isoniazid or its metabolites in urine are based on the color reaction of isonicotinic acid and isonicotinoyl glycine with gaseous cyanogen chloride and benzidine. Chloramine -T, potassium thiocyanate, citric acid, and barbituric acid are impregnated into absorbent paper strips and dried. The strips are then dipped into urine of the person receiving INH. The presence of a blue, purple or green color on the strip after 15-30 minutes is indicative of a positive result for INH.¹ Positive and negative control materials are commercially available and sold separately from the device.

There is a second screening test for INH called the "Arkansas Method", a method first described in 1970. The difference between the paper strip tests and the Arkansas Method is that the latter is performed in a test tube using modified reagents from the test strip method, and the color development takes place within minutes after the addition of the patient's urine to the reagents as opposed to a 15-30 minute color development time for the pre-amendment or cleared INH test strip. A positive result is indicated by a dark blue or turquoise color and a negative test will be yellow.²

High-performance liquid chromatography (HPLC) is available for accurate serum Isoniazid concentration determinations, but these are expensive and very labor intensive.³ In lieu of performing HPLC, compliance with INH therapy is often accomplished through direct observation of the person taking Isoniazid, or self-reporting.

IV. *Indications for Use for Isoniazid Test Strips*

The indications for use, in general, is a description of the disease or condition the device will diagnose, treat, prevent, cure or mitigate, including a description of the patient population for which the device is intended.

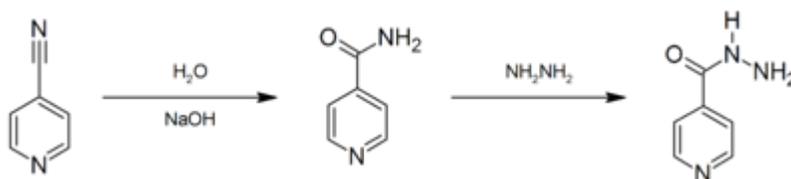
Isoniazid Test Strips are indicated for use in detecting isonicotinic acid and its metabolites in urine to determine compliance of isoniazid (INH) medication.

V. *Overview of the Measurand, Isoniazid*

Isoniazid History and Medical Use

Isoniazid (Laniazid, Nydrazid), also known as isonicotinylhydrazine (INH), is an organic compound that is the first-line medication in prevention and treatment of tuberculosis. The compound was first synthesized in the early 20th century⁴, but its activity against tuberculosis was first reported in the early 1950s. Three pharmaceutical companies attempted unsuccessfully to simultaneously patent the drug⁵ (the most prominent one being Roche, which launched its version, Rimifon, in 1952). With the introduction of isoniazid, a cure for tuberculosis was first considered reasonable.

Isoniazid may be prepared by the base hydrolysis of 4-cyanopyridine to give the amide, followed by displacement of ammonia by hydrazine.⁶



Mechanism of action

Isoniazid is a prodrug and must be activated by a bacterial catalase-peroxidase enzyme that in *M. tuberculosis* is called KatG.⁷ KatG couples the isonicotinic acyl with NADH to form isonicotinic acyl-NADH complex. This complex binds tightly to the enoyl-acyl carrier protein reductase known as InhA, thereby blocking the natural enoyl-AcpM substrate and the action of fatty acid synthase. This process inhibits the synthesis of mycolic acid, required for the mycobacterial cell wall. A range of radicals are produced by KatG activation of isoniazid, including nitric oxide,⁸ which has also been shown to be important in the action of another antimycobacterial prodrug PA-824.⁹

Isoniazid is bactericidal to rapidly dividing mycobacteria, but is bacteriostatic if the mycobacteria are slow-growing.¹⁰ It also inhibits the cytochrome P450 system.¹¹

Metabolism

Isoniazid reaches therapeutic concentrations in serum, cerebrospinal fluid, and within caseous granulomas. It is metabolized in the liver via acetylation. Two forms of the enzyme are responsible for acetylation, so some patients metabolize the drug more quickly than others. Hence, the half-life is bimodal, with peaks at one and three hours in the US population. The metabolites are excreted in the urine. Doses do not usually have to be adjusted in case of renal failure.

Dosing

The standard dose of isoniazid in adults is 5 mg/kg/day (max 300 mg daily). When prescribed intermittently (twice or thrice weekly), the dose is 15 mg/kg (max 900 mg daily). Patients with slow clearance of the drug (via acetylation as described above) may require reduced dosages to avoid toxicity. The recommended dose for children is 8 to 12 mg/kg/day.¹²

Side effects

Adverse reactions include rash, abnormal liver function tests, hepatitis, sideroblastic anemia, high anion gap metabolic acidosis, peripheral neuropathy, mild central nervous system (CNS) effects, drug interactions resulting in increased phenytoin (Dilantin) or disulfiram (Antabuse) levels, intractable seizures (status epilepticus) and drug-induced lupus erythematosus.

Peripheral neuropathy and CNS effects are associated with the use of isoniazid and are due to pyridoxine (vitamin B6) depletion, but are uncommon at doses of 5 mg/kg. Persons with conditions in which neuropathy is common (e.g., diabetes, uremia, alcoholism, malnutrition, and HIV infection), as well as pregnant women, and persons with a seizure disorder, may be given pyridoxine (vitamin B6) (10–50 mg/day) with isoniazid.

Hepatotoxicity of INH is by nitrogen group in its chemical structure, as it is metabolized in the liver and gets converted to an ammonium molecule, which causes hepatitis. Hepatotoxicity can be avoided with close clinical monitoring of the patient, to be specific, nausea, vomiting, abdominal pain, and appetite. Isoniazid is metabolized by the liver mainly by acetylation and dehydrazination. The N-acetylhydrazine metabolite is believed to be responsible for the hepatotoxic effects seen in patients treated with isoniazid. The rate of acetylation is genetically determined. Approximately 50% of blacks and Caucasians are slow inactivators; the majority of Inuit and Asians are rapid inactivators. The half-life in fast acetylators is one to two hours, while in slow acetylators, it is two to five hours. Elimination is largely independent of renal function, but the half-life may be prolonged in liver disease. The rate of acetylation has not been shown to significantly alter the effectiveness of isoniazid. However, slow acetylation may lead to higher blood concentrations with chronic administration of the drug, with an increased risk of toxicity. Fast acetylation leads to higher blood levels of the toxic metabolite acetylisoniazid and thus to an increase in toxic reactions - hepatitis which is 250 times more common than in slow acetylators. Isoniazid and its metabolites are excreted in the urine with 75 to 95% of the dose excreted in 24 hours. Small amounts are also excreted in saliva, sputum, and feces. Isoniazid is removed by hemodialysis and peritoneal dialysis.¹³

Headache, poor concentration, weight gain, poor memory, and depression have all been associated with isoniazid use. All patients and healthcare workers should be aware of these serious adverse effects, especially if suicidal thinking or behavior are suspected.^{14,15,16}

VI. *Literature Search*

A systematic literature review was conducted to assess the safety and effectiveness of urine Isoniazid testing by searching and evaluating the existing clinical and *in vitro* diagnostic literature. The scope of the review addressed the following questions:

1. What is the evidence for the effectiveness of colorimetric qualitative detection of Isoniazid by reagent strip testing in individuals with active or latent tuberculosis?
2. What are the reported adverse events associated with the use of qualitative colorimetric reagent strip testing for the detection of Isoniazid in individuals with active or latent tuberculosis?

The literature search was conducted through PubMed in October of 2012 for Isoniazid Testing. The specific methods used are discussed in detail in the full report (Appendix A). Articles were excluded if one or more of the following conditions applied: (1) not relevant to the Isoniazid Test Strip device per indication; (2) not relevant to Isoniazid screening (includes outdated citations), and (3) non-clinical study (i.e., editorials, commentaries, discussions, or overviews).

VII. *Literature Overview*

There was a paucity of literature using the pre-amendment device, Difco Bacto INH Strip and Control, or the cleared device, Mycodyn Uritec Test Strips (k912888); however, the following summary encompasses articles that evaluated the effectiveness of qualitative, colorimetric testing in urine samples of individuals receiving INH therapy for active or latent TB.

Effectiveness of INH Screening

The effectiveness of INH screening depends, in part, on the stability of the isonicotinic acid metabolite to withstand variations in sample storage and handling. An evaluation of 28 adults and adolescents (26 self-reported taking INH within 48 hrs of testing, 2 negative controls) determined that isonicotinic acid, as detected by the Arkansas Method, was stable for 7 days when stored at 21-23° C, for 28 days when stored at 2-6° C, and 9 months when stored at -12 to -16° C.¹⁷

Literature describing interference from other compounds having metabolites similar to isonicotinic acid are few. The effects of simultaneous Rifampin, Pyrazinamide and/or Ethambutol intake with INH therapy have been not been extensively evaluated.

An investigation by Sirgel, *et al* retrospectively assessed qualitative methods to monitor the ingestion of anti-tuberculosis drugs isoniazid, rifampicin and rifapentine compared to HPLC in 691 urine samples from 46 individuals taking all three medications. The results showed 100% correlation between INH screening tests and HPLC. The authors concluded that qualitative

assays measure isoniazid ingestion with an efficiency similar to HPLC. Whitfield's, *et al* 2004 study¹⁸ included 186/191 urine samples of individuals who were taking Rifampin and INH together. Urine specimens were collected within 36 hours of medicating. Positivity for Rifampin seemed to peak 3 hours after ingestion. INH was positive in 94.5% of samples up to 24 hours and in 80% (16/20) of samples between 24 and 30 hours post dosage. There was no discussion for the negative results.

A study conducted by Guerra, *et al*¹⁹ of 144 patients (94 on INH, 50 controls) showed high sensitivity [{94.7% } 95% CI (91.0-98.4)] and specificity [{98.0% } 95% CI (95.7-100)]. However, 5 individuals for whom INH ingestion was confirmed tested negative. The investigators could not determine whether the negative results were due to accelerated INH clearance, smoking, or interference from other medications.

Hanifa, *et al*²⁰ conducted a study to specifically address the effect of nicotine derivatives in the urine of TB patients who smoked using INH test strips. Urine specimens were collected from in-patients taking INH as part of tuberculosis treatment at 6, 12 and 24 hr after a directly observed 300 mg oral dose. As a control group, a single urine specimen was collected from surgical in-patients not taking INH. Specimens were tested for INH using a commercially available dipstick. A total of 153 patients on INH and 60 controls were recruited. The sensitivity of the test was 93.3% (95%CI 88.1–96.8%) at 6 hr post INH, 93.4% (95%CI 88.2–96.8%) at 12 hr and 77% (95%CI 69.1–83.7%) at 24 hr. The specificity of the test was 98.3% (95%CI 91.1–99.9%). Urine specimens from 27 individuals in the TB group who smoked within 48 hours of being tested for INH showed no interference from nicotine. There was no association between smoking status and color change of positive results.

An additional study conducted by Nicolau *et al*²¹ seemed to support Hanifa's earlier study that nicotine derivatives present in the urine from smoking did not affect outcomes of the INH screening test. The former's study examined the effects of possible nicotine derivatives from smoking in the urine of 54 patients receiving INH of whom 10 were self-reported smokers. Using the Arkansas Method, sensitivity and specificity were found to be 93.2% [95% CI (80.3, 98.2)] and 98.7% [95% CI (94.8, 99.8)], respectively.

VIII. Risks and Mitigations of Isoniazid Test Systems

For the purposes of classification, the FDA considers the following items, among other relevant factors, as outlined in 21 CFR 860.7(b):

1. The persons for whose use the device is represented or intended;
2. The conditions of use for the device, including conditions of use prescribed, recommended, or suggested in the labeling or advertising of the device, and other intended conditions of use;
3. The probable benefit to health from the use of the device weighed against any probable injury or illness from such use; and
4. The reliability of the device.

Part (g)(1) of this regulation further states that it “is the responsibility of each manufacturer and importer of a device to assure that adequate, valid scientific evidence exists, and to furnish such evidence to the Food and Drug Administration to provide reasonable assurance that the device is safe and effective for its intended uses and conditions of use. The failure of a manufacturer or importer of a device to present to the Food and Drug Administration adequate, valid scientific evidence showing that there is reasonable assurance of the safety and effectiveness of the device, if regulated by general controls alone, or by general controls and performance standards, may support a determination that the device be classified into class III.”

Reasonable Assurance of Safety

According to 21 CFR 860.7(d)(1), there is reasonable assurance that a device is safe when it can be determined, based upon valid scientific evidence, that the probable benefits to health from use of the device for its intended uses and conditions of use, when accompanied by adequate directions and warnings against unsafe use, outweigh any probable risks. The valid scientific evidence used to determine the safety of a device shall adequately demonstrate the absence of unreasonable risk of illness or injury associated with the use of the devices for its intended uses and conditions of use.”

Reasonable Assurance of Effectiveness

According to 21 CFR 860.7(e) (1), “[t]here is reasonable assurance that a device is effective when it can be determined, based upon valid scientific evidence, that in a significant portion of the target population, the use of the device for its intended uses and conditions of use, when accompanied by adequate directions for use and warnings against unsafe use, will provide clinically significant results.”

Risks to Health

For *in vitro* diagnostic devices, the majority of the risks to health are not direct risks of device use (e.g., needle sticks, burns, etc.) but are indirect risks. That is, the risk is generally related to the impact of the decisions made in treatment of a patient based on an undetected false positive (FP) or false negative (FN) test result. For example, the use of an isoniazid test strip does not introduce much risk through the collection of urine and use of the test device. However, if a FP isoniazid test is used to manage a patient’s treatment strategy, the patient may be managed differently than if the correct negative result were reported.

The literature is sparse regarding the prevalence of FP or FN results other than the citations in this summary. The impact of a FP or a FN isoniazid test result will vary by factors including the clinical situation, the reason for testing, and the additional clinical information being considered by the treating clinician.

For example, if isoniazid testing is being used to determine compliance to therapy, a FP could result in a missed opportunity for therapeutic intervention. Thorough patient follow up along with INH Test Strip labeling recommendations to adhere to good laboratory practices (storage of strips, quality control monitoring, etc.) may help to reduce any FP results that may occur.

A FN test could result in unnecessary additional testing or inappropriate intervention. FN results in patients who are tested too soon, or too late after taking their Isoniazid medication have been reported. Isoniazid is cleared more slowly than other anti-tuberculosis medications such as Rifampin, and optimal INH testing time is recommended to be between 8-36 hours post-dose. Some have suggested that certain racial groups clear INH more rapidly than other groups so optimal testing time should be 24 hours post-dose because testing beyond 36 hours may yield negative results. Direct observation of Isoniazid ingestion may mitigate the risk of FN results.

Potential causes of FP and FN results may include interferences, test design flaws, device malfunctions, contaminated or expired reagents, inadequate instructions for use, and pre-analytical errors (e.g., incorrect specimen collection or storage). Based on our literature search and the studies performed in k912888, it does not appear that smoking, chewing tobacco, or other commonly prescribed TB drugs show significant interference with the INH Test Strips. As with many visually interpreted colorimetric based urine assays, inter- and intra-rater variability, accurate timing, and color perception are limitations to accurate test results.

IX. Agency Review of *In Vitro* Diagnostic Devices

As described above, FDA regulation of medical devices is meant to help mitigate the potential risks of those devices. For example, general controls such as the requirement for Good Manufacturing Practices provides assurance that devices are designed under a Quality System and that device remains safe and effective when manufactured over time (e.g., maintain lot-to-lot consistency). Similarly, premarket review provides assurance that the characteristics of the device (including analytical and clinical performance) are appropriate for its intended use and that the labeling provides adequate instructions for use (including appropriate precautions, where necessary).

Special controls, often implemented for class II devices, provide even greater assurance that devices are as safe and effective as other similar devices. For example, a performance standard special control would assure that all devices meet a certain minimum standard necessary for safe use of that device. Though performance data and labeling claims for Class II *in vitro* diagnostic devices are generally reviewed by the Agency prior to marketing, manufacturers do have some flexibility in modifying these types of devices and their labeling once the devices are on the market without further FDA review.

Premarket approval provides the highest level of assurance that a device is safe and effective and remains safe and effective over time. Once a device is approved, manufacturers cannot make any changes to the Class III device or to the device labeling without notifying and receiving approval from FDA. (Refer to Appendix A for examples of Class I, II and III *in vitro* diagnostic devices)

Agency review of *in vitro* diagnostic devices assesses the following characteristics (where applicable) of an assay submitted for clearance:

- Indications for use
- Special Conditions for use
- Instrument requirements

- Device Description
- Substantial Equivalence information
- Standard/Guidance Documents Referenced
- Test principle
- Performance Characteristics:
 - Precision/reproducibility
 - Linearity/assay reportable range
 - Recovery
 - Traceability
 - Stability
 - Expected values,
 - Detection limits (LoB, LoD, LoQ)
 - Specificity/Cross reactivity
- Method Comparison studies
- Matrix comparison studies
- Labeling

Agency experience with INH test strips is limited to 1 pre-market notification, the DynaGen Mycodyn, Uritec Test Strips Isoniazid Test Strip device (k912888). The review for this device focused on indications for use, method comparison, stability, and specificity. Method comparisons between the INH Test Strips on samples collected from individuals known to be on INH therapy (unobserved), or were under direct observation for Isoniazid medication were conducted at several internal and external centers to the United States and compared to the pre-amendments device (N=74). Additionally, specificity studies were performed on individuals who smoked, chewed tobacco, or used drugs of abuse and no interference was observed. Based on the data, the DynaGen Mycodyn, Uritec Test Strips Isoniazid Test Strip was cleared for marketing.

As stated above, examples of potential causes of FP and FN isoniazid results include interferences, test design flaws, device malfunctions, contaminated or expired reagents, inadequate instructions for use, and pre-analytical errors. Premarket review of devices can help mitigate many of these issues, including interferences, test design flaws, and pre-analytical errors. In addition, as part of the review the Agency ensures that the labeling clearly communicates the information necessary for safe use of the device.

X. *Post-market surveillance, Medical Device Report query for the product code MIG, Strip Test, Isoniazid.*

The medical device industry and healthcare facilities submit mandatory medical device reports to FDA to help monitor the safety of medical devices. In addition, the Agency receives and reviews voluntary reports from the public. Medical device reports may include deaths, serious injuries, and product malfunctions. This information is used by FDA to learn about post-market performance for a device as well as to identify those devices that are not safe and effective for their intended use. Event reports are analyzed by healthcare clinicians, engineers, and scientists. Follow up actions include additional investigation, requesting information from the device manufacturer, conducting a manufacturer facility inspection, issuing a public health advisory/safety alert, among

other actions. Postmarket regulation helps to mitigate the risk of FP and FN isoniazid results due to problems such as device malfunctions and contaminated or expired reagents.

A query of the FDA Post-market Surveillance for a Medical Device Report database was conducted for the product code MIG (Strip Test, Isoniazid) from the inception of the database to the present. There were no deaths, major injuries, or adverse outcomes to patients or testing personnel found to be associated with the use of Isoniazid Test Strips.

XI. Summary and Conclusion

The use of INH test strips in the qualitative detection of Isoniazid is an established technology. The technology has been used from prior to 1976 to the present with few negative consequences as indicated by the literature review and search of the FDA post-market adverse event reporting database. The INH Test Strip assay has been used to supplement direct patient observation and self-reporting as confirmation of patient compliance with INH therapy.

The indications for use for Isoniazid Test Strips is similar to other previously classified devices used for therapeutic drug monitoring such as procainamide, quinidine, and lidocaine, in that the device is only used for individuals taking Isoniazid; however, unlike the aforementioned therapeutic drug tests, the INH Test Strips only provide qualitative results (presence or absence of INH metabolites) rather than quantitative results essential for monitoring appropriate drug dosages and cannot be used to determine therapeutic levels or toxicity. Technologically, INH Test Strips are more similar to Urinalysis reagent strips where colorimetric dry reagent pads are used for the detection of a substance or its metabolites in urine.

FDA believes that there is a reasonable assurance of safety and efficacy for the use of the INH Test Strip to qualitatively detect Isoniazid metabolites in human urine.

XII. Chemistry and Toxicology Devices Advisory Panel Discussion Questions for Isoniazid Test Systems.

Panel Discussion Questions

1. The Agency has provided a summary of some key risks to health due to potential false positive and false negative Isoniazid test results. Using your own knowledge and expertise, please identify any additional risk(s) to health you feel may have been omitted with regards to Isoniazid test systems and how they may be addressed and mitigated (e.g., labeling, additional studies, etc.).
2. Which classification, class I (general controls), class II (special controls), or class III (premarket approval), is most appropriate for Isoniazid test systems?
 - a. If Class I is recommended, please explain why you believe that there is sufficient information to determine that general controls alone are sufficient to provide reasonable assurance of safety and effectiveness of Isoniazid test systems. Should premarket notification be one of the general controls required for Isoniazid tests?

- b. If Class II is recommended, please explain why you believe that there is sufficient information to determine that general and special controls are sufficient to provide reasonable assurance of safety and effectiveness of Isoniazid test systems? What special controls would you recommend (e.g., performance standards, labeling, etc.)?
- c. If you believe the device should be classified into class III and made subject to Premarket Approval (PMA), discuss the important clinical and analytical study design features necessary to demonstrate that the device is safe and effective.

XIII. Appendices

Appendix A: Classification Table

	Class I*	Class II	Class III
Risk	<ul style="list-style-type: none"> ▪ Considered low risk ▪ Present minimal potential harm to a user. ▪ Devices for which general controls are sufficient to provide reasonable assurance of the safety and effectiveness of such devices. 	<ul style="list-style-type: none"> ▪ Considered Moderate risk ▪ General controls alone are not sufficient to mitigate the risks of harm to a user. ▪ There is sufficient information to establish special controls, existing methods specific to the device that can control the risks not controlled by the general controls. 	<ul style="list-style-type: none"> ▪ Considered high risk ▪ Risk may not be completely mitigated by general and special controls alone ▪ There is insufficient information to establish a reasonable assurance of safety and effectiveness. ▪ Typically life sustaining or life supporting. ▪ Of substantial importance in preventing impairment of human health, or present an unreasonable risk of illness or injury.
Controls	<p>General Controls:</p> <ul style="list-style-type: none"> ▪ Establishment registration and listing; ▪ 510(k) premarket notification*; ▪ Good Manufacturing Practices (GMPs); and ▪ Other regulatory controls, e.g., adverse event reporting 	<p>General Controls <u>Plus</u> <u>Special Controls, which may include:</u></p> <ul style="list-style-type: none"> ▪ Performance standards; ▪ Post-market surveillance; ▪ Patient registries; ▪ Design controls; and ▪ Other appropriate actions deemed necessary for mitigating the risks of the device 	<p>General Controls and Special Controls <u>Plus</u> <u>Premarket Approval:</u></p> <ul style="list-style-type: none"> ▪ Data from a well-controlled, statistically significant clinical study (valid scientific evidence) ▪ Manufacturers cannot make any changes to the Class III device or to the labeling without notifying and receiving approval from FDA.

Examples	<ul style="list-style-type: none"> ▪ Estradiol test system (21 CFR 862.1260) ▪ Follicle-stimulating hormone test system (21 CFR. 862.1300) ▪ Luteinizing hormone test system (21 CFR 862.1485) 	<ul style="list-style-type: none"> ▪ Sirolimus test system (21 CFR 862.3840) ▪ Cyclosporine test system (21 CFR 862.1235) ▪ Cocaine and cocaine metabolite test system (21 CFR 862.3250) 	<ul style="list-style-type: none"> ▪ Human Papillomavirus (HPV) tests ▪ Non-invasive glucose sensing devices for diabetes ▪ Her2/neu tests for predicting response to Herceptin therapy
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*Many of the Class I devices are exempt from 510(k) notification due to low risk

Appendix B : Systematic Literature Review: INH screening tests

(I.) Introduction

FDA conducted a systematic literature review to assess the safety and effectiveness of Isoniazid screening devices by searching and evaluating the existing clinical and *in vitro* literature. We sought to address the following questions:

1. What is the evidence for effectiveness of Isoniazid Test Strips to detect INH metabolites in human urine?
2. What are the reported adverse events associated with the use of Isoniazid Test Strips for the detection of INH metabolites in human urine and are they mitigated adequately for safe and effective use?

(II.) Methods

A literature search was conducted through PubMed in October, 2012, using the following search strings:

```
Topic =(isoniazid AND (treatment AND (adheren* OR complian*))) AND Topic=("urine test*" OR "lab* test*" OR assay*) AND Language=(English)
Timespan=All Years. Databases=SCI-EXPANDED.
Lemmatization=On
EMBASE
'isoniazid'/exp AND treatment AND (adheren* OR complian*) AND ((*lab* AND test*) OR (urine OR assay*) AND [humans]/lim AND [english]/lim AND ([embase]/lim OR [embase classic]/lim)
```

Using the search criteria listed above, 24 results were obtained.¹⁻²⁴ Titles and abstracts were reviewed for clinical or *in vitro* Isoniazid Test Strip devices or similar Isoniazid test methods. A total of 14 articles were excluded during the initial screening. These articles were excluded because the studies were: (1) not relevant to the Isoniazid Test Strip device per indication; (2)

not relevant to Isoniazid screening (includes outdated citations), and (3) non-clinical study (i.e., editorials, commentaries, discussions, or overviews).

References for background information on the derivation, clinical use, and pharmacology of Isoniazid were obtained through a general internet search.

(III.) Results

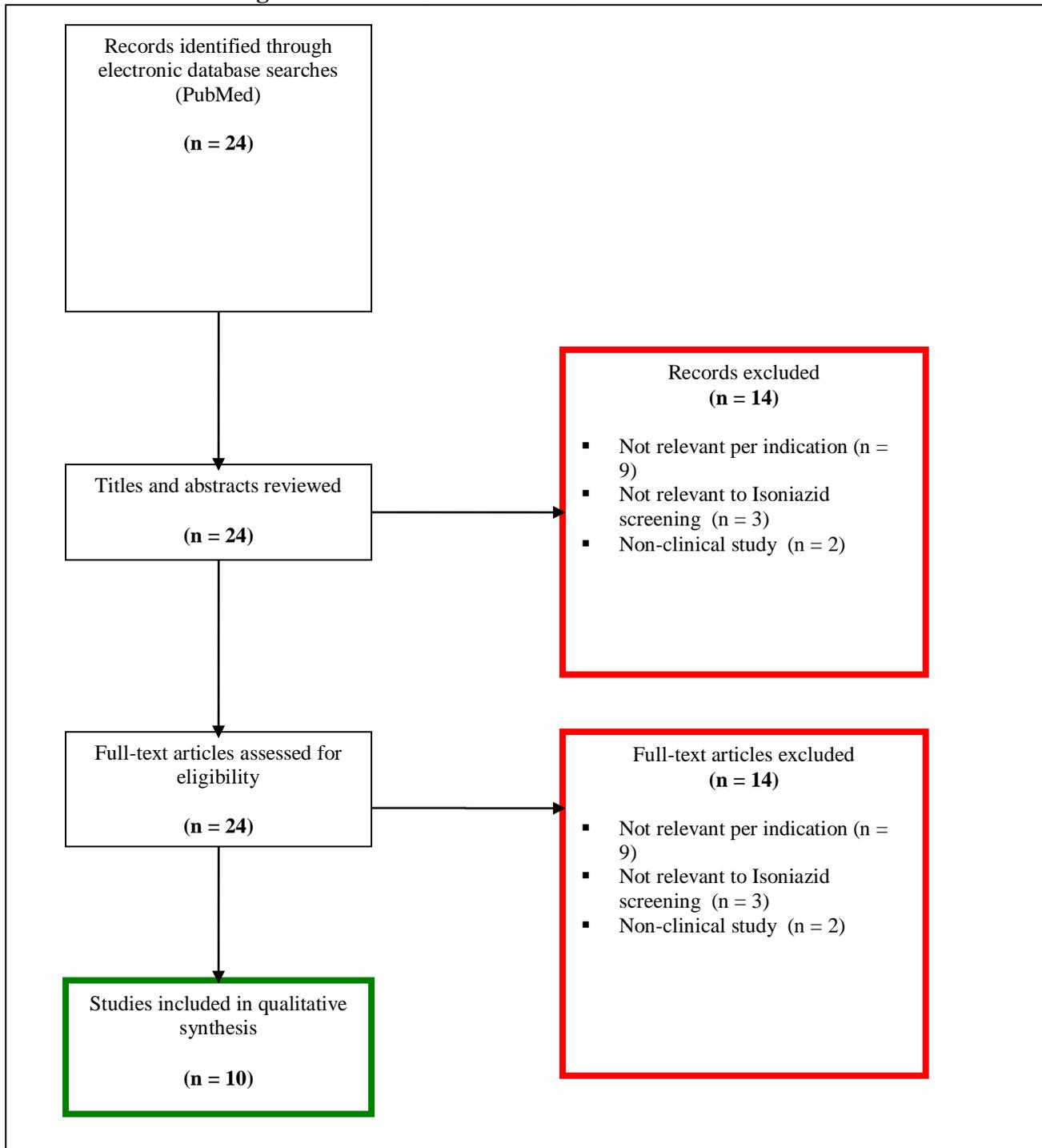
A total of 10 articles were included for systematic review. Additional information regarding the methodology for inclusion and exclusion criteria may be found in the Appendices below.

(IV.) Conclusions

There are relatively few articles that directly address the safety and effectiveness of FDA cleared INH Test Strip devices in patients. This may be due in part to the fact that the practice of using direct observation or self-reporting of patients to demonstrate compliance with INH ingestion. In conclusion, based on our systematic review of the literature, we find that colorimetric test strip testing for the qualitative measurement of Isoniazid in human urine samples appear to be safe and effective when FDA guidelines are followed.

Appendix C

Figure 1: Workflow of Article Selection



Appendix D: Cited Sources

1. Kraus, P. and E. Krausova (1965). "Paper Strip Urine Test for Checking the Intake of Isoniazid." *Tubercle* **46**(Copyright (C) 2012 U.S. National Library of Medicine.): 206-208.
2. Schraufnagel, D. E., R. Stoner, et al. (1990). "Testing for isoniazid. An evaluation of the Arkansas method." *Chest* **98**(2): 314-316.
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22. Meissner, P. E., P. Musoke, et al. (2002). "The value of urine testing for verifying adherence to anti-tuberculosis chemotherapy in children and adults in Uganda." *Int J Tuberc Lung Dis* **6**(Copyright (C) 2012 U.S. National Library of Medicine.): 903-908

Appendix E: PubMed References/Reviewed Articles

1. Barreto, R. C. and D. B. Mano (1963). "A New Paper Strip Test to Determine the Presence of PAS and Isoniazid in Urine." *Am Rev Respir Dis* **88**(Copyright (C) 2012 U.S. National Library of Medicine.): 556-557.
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20. Schraufnagel, D. E., R. Stoner, et al. (1990). "Testing for isoniazid. An evaluation of the Arkansas method." Chest **98**(2): 314-316.
21. Sirgel, F. A., J. S. Maritz, et al. (2006). "Monitoring the ingestion of anti-tuberculosis drugs by simple non-invasive methods." Int. J. Pharm. **307**(Copyright (C) 2012 American Chemical Society (ACS). All Rights Reserved.): 182-187.
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Appendix F: Status of Reviewed Articles

Author	Year	Title	Journal	Include or Exclude	Reason for Exclusion/Inclusion
Barreto, R. C., D. B. Mano	1963	"A New Paper Strip Test to Determine the Presence of PAS and Isoniazid in Urine."	Am Rev Respir Dis 88(Copyright (C) 2012 U.S. National Library of Medicine.): 556-557.	E	not relevant to Isoniazid screening (includes outdated citations)
Eidlitz-Markus, T., A. Zeharia, et al	2003	"Use of the urine color test to monitor compliance with isoniazid treatment of latent tuberculosis infection."	Chest 123(3): 736-739.	E	not relevant to the Isoniazid Test Strip device per indication
Ellard, G. A., P. J. Jenner, et al.	1980	"An evaluation of the potential use of isoniazid, acetylisoniazid and isonicotinic acid for monitoring the self-administration of drugs."	British Journal of Clinical Pharmacology 10(4): 369-381	E	not relevant to the Isoniazid Test Strip device per indication
Fallab-Stubi, C. L., J. P. Zellweger, et al.	1998	"Electronic monitoring of adherence to treatment in the preventive chemotherapy of tuberculosis."	Int J Tuberc Lung Dis 2(7): 525-530.	E	not relevant to the Isoniazid Test Strip device per indication
Flanagan, R. J., N. W. Brown, et al.	2008	"Therapeutic drug monitoring (TDM)."	Bulletin Clinical Biochemistry 9(1): 3-21.	E	not relevant to Isoniazid screening (includes outdated citations)
Guerra, R. L., M. B. Conde, et al.	2010	"Point-of-care Arkansas method for measuring adherence to treatment with isoniazid."	Respir Med 104(5): 754-757.	I	
Hanifa, Y., K. Mngadi, et al.	2007	"Evaluation of the Arkansas method of urine testing for isoniazid in South Africa."	Int J Tuberc Lung Dis 11(11): 1232-1236.	I	
Hollender, E. S., D. Ashkin,	2003	"Urine color test to monitor isoniazid	Chest 123(3): 668-670.	E	non-clinical study (i.e., editorials,

Author	Year	Title	Journal	Include or Exclude	Reason for Exclusion/Inclusion
et al.		compliance: "pissin' in the wind"?"			commentaries, discussions, or overviews)
Khalili, H., S. Dashti-Khavidaki, et al.	2008	"Assessment of adherence to tuberculosis drug regimen."	Daru-Journal of Faculty of Pharmacy 16(1): 47-50.	E	not relevant to the Isoniazid Test Strip device per indication
Kilburn, J. O., R. E. Beam, et al.	1972	"Reagent-impregnated paper strip for detection of metabolic products of isoniazid in urine."	Am Rev Respir Dis 106(Copyright (C) 2012 U.S. National Library of Medicine.): 923-924.	I	
Kraus, P. and E. Krausova	1965	"Paper Strip Urine Test for Checking the Intake of Isoniazid."	Tubercle 46(Copyright (C) 2012 U.S. National Library of Medicine.): 206-208.	I	
Meissner, P. E., P. Musoke, et al.	2002	"The value of urine testing for verifying adherence to anti-tuberculosis chemotherapy in children and adults in Uganda."	Int J Tuberc Lung Dis 6(Copyright (C) 2012 U.S. National Library of Medicine.): 903-908.	I	
Mqoqi, N. P., G.A. Churchyard, et al.	1997	"Attendance versus compliance with tuberculosis treatment in an occupational setting--a pilot study."	S Afr Med J 87(11): 1517-1521.	E	not relevant to the Isoniazid Test Strip device per indication
Nicolau, I., L. Tian, et al.	2012	"Point-of-Care Urine Tests for Smoking Status and Isoniazid Treatment Monitoring in Adult Patients."	PLoS One 7(9)	I	
Palanduz, A., D. Gultekin, et al.	2003	"Low level of compliance with tuberculosis treatment in children: monitoring by urine tests."	Annals of Tropical Paediatrics 23(1): 47-50.	E	not relevant to the Isoniazid Test Strip device per indication
Palanduz, A.,	2003	"Follow-up of	Pediatr Pulmonol	E	not relevant to the

Author	Year	Title	Journal	Include or Exclude	Reason for Exclusion/Inclusion
D. Gultekin, et al.		compliance with tuberculosis treatment in children: monitoring by urine tests."	36(1): 55-57		Isoniazid Test Strip device per indication
Perry, S., M. F. Hovell, et al.	2002	"Urine testing to monitor adherence to TB preventive therapy."	J Clin Epidemiol 55(3): 235-238.	E	not relevant to the Isoniazid Test Strip device per indication
Rothe, T. B. and W. Karrer	1996	"Short-course therapy of pulmonary tuberculosis: doctor's compliance."	Tuber Lung Dis 77(Copyright (C) 2012 U.S. National Library of Medicine.): 93-97.	E	not relevant to the Isoniazid Test Strip device per indication
Schmitz, K. E., M. F. Hovell, et al.	2010	"The reliability and practicality of the Arkansas method assay of isoniazid adherence."		I	
Schraufnagel, D. E., R. Stoner, et al.	1990	"Testing for isoniazid. An evaluation of the Arkansas method."	Chest 98(2): 314-316.	I	
Sirgel, F. A., J. S. Maritz, et al.	2006	"Monitoring the ingestion of anti-tuberculosis drugs by simple non-invasive methods."	Int. J. Pharm. 307(Copyright (C) 2012 American Chemical Society (ACS). All Rights Reserved.): 182-187.	I	
Szakacs, T. A., D. Wilson, et al.	2006	"Adherence with isoniazid for prevention of tuberculosis among HIV-infected adults in South Africa."	BMC Infect Dis 6: 97.	E	not relevant to Isoniazid screening (includes outdated citations)
van den Boogaard, J., R. A. Lyimo, et al.	2011	"Electronic monitoring of treatment adherence and validation of alternative adherence measures in tuberculosis patients: a pilot study."	Bull World Health Organ 89(9): 632-639.	E	non-clinical study (i.e., editorials, commentaries, discussions, or overviews)

Author	Year	Title	Journal	Include or Exclude	Reason for Exclusion/Inclusion
Whitfield, R. and G. F. Cope	2004	"Point-of-care test to monitor adherence to anti-tuberculous Treatment"	Annals of Clinical Biochemistry 41(5): 411-413	I	