



Strip Test, Isoniazid

Classification Panel Meeting

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Executive Summary of Isoniazid Test Strip

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 - Introduction
 - Regulatory history
 - Device description
- **Indications for Use**
- **Overview of Isoniazid (INH)**
 - Device Description Medical History and Use of Isoniazid
 - Side effects
- **Discussion of Safety and Effectiveness**
- **Summary and Conclusions**
- **Closing Remarks**

Introduction

- **Purpose:** To determine the appropriate regulatory classification for Isoniazid (INH) Test Strips. The devices were considered pre-amendments devices (before May 28, 1976).

Regulatory History

- **Prior to 1976:** the Difco Bacto INH Strip and Controls.
- **After 1976:** One device has been submitted and found to be substantially equivalent to the pre-amendment device:
Mycodyn Uritec Test Strips FDA cleared in 1992 (k912888).
- Isoniazid Test Strips are **unclassified** devices.

General Device Description of INH Test Strips

- Isoniazid Test Strips are a qualitative, colorimetric, chemical assay for detecting isonicotinic acid and its metabolites in urine.
- Chemical reaction based on work by Kilburn¹ et al. to monitor patients on Isoniazid therapy without relying on self-reporting or direct observation of Isoniazid ingestion.
 - Reagent impregnated filter paper
 - Colorimetric reaction between reagents and isoniazid metabolites in urine, isonicotinic acid and isonicotinoyl glycine.
 - Color development occurs in 15-30 minutes.
 - Technology is similar to urinalysis reagent strips for detection of pH, bilirubin, blood, etc.

¹. Kilburn, J. O., R. E. Beam, et al. (1972). Am Rev Respir Dis **106**: 923-924.

Indications For Use (IFU)

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

Medical Use of Isoniazid

- Isoniazid (Laniazid, Nydrazid), also known as isonicotinyldrazine (INH), is an organic compound that is the first-line medication in prevention and treatment of tuberculosis.
- Isoniazid is prescribed for patients with **active or latent** tuberculosis (TB).
 - It may be combined with other anti-TB medications.
 - Treatment covers many months. Patient compliance for taking their INH is problematic and of concern.
 - Individuals may stop taking INH, thereby increasing the possibility of developing INH resistant TB.

Isoniazid Metabolism

- Isoniazid can be recovered in serum, cerebrospinal fluid, and within caseous granulomas.
- It is metabolized in the liver via acetylation.
- Two forms of enzymes 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.

Isoniazid Side Effects

- Adverse reactions may include:
 - Rash
 - Abnormal liver function tests, hepatitis
 - Sideroblastic anemia
 - High anion gap metabolic acidosis
 - Peripheral neuropathy, mild central nervous system (CNS) effects—due to Vit B6 depletion
 - Drug interactions resulting in increased phenytoin (Dilantin) or disulfiram (Antabuse) levels
 - Intractable seizures (status epilepticus)
 - Drug-induced lupus erythematosus

Monitoring Isoniazid Compliance

- **Monitoring compliance with INH therapy may be accomplished by:**
- Direct observation of the patient taking the medication
 - Patient self-reporting
 - Performing a post-dosage assay in serum by HPLC
 - ❖ requires a blood draw—may be problematic for pediatric patients
 - ❖ provides quantitative values
 - ❖ results are not available during clinic visit.
 - Measuring INH metabolites in the urine by test strip.
 - ❖ requires urine sample within ~ 24 hrs of medication
 - ❖ provides only qualitative results (negative/positive)
 - ❖ results are available during clinic visits

Risk and Mitigation

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

- The persons for whose use the device is represented or intended;
- 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;
- The probable benefit to health from the use of the device weighed against any probable injury or illness from such use; and
- The reliability of the device.

Risks to Health

➤ **Impact of False Positive Results:**

- Missed opportunity for therapeutic intervention.
- Possibility of developing a drug resistant form of TB.

➤ **Mitigations:**

- Isoniazid Test Strip labeling (instructions for use, correct timing, limitations, color interpretation, storage conditions)
- Adherence to good laboratory practices (strip storage, quality control monitoring, monitoring expiration dating),
- Current patient history and follow-up.

Risks to Health (cont.)

➤ **Impact of False Negative Results:**

- Inappropriate intervention
- Unnecessary additional testing

➤ **Mitigations:**

- Test strip labeling (instructions for use, correct timing, limitations, color interpretation, storage conditions)
- Direct patient observation

Literature Search for Evidence of the Assurance of Safety and Effectiveness

- Isoniazid metabolites seem to be stable in the urine when stored from about -20° C to RT.
- No significant interference from other TB medications
- No significant interference from other urine nicotine metabolites.
- Point-of-care.
- The use of INH qualitative testing did seem to monitor compliance, however, there was no in-depth discussion in some of the literature regarding false positive or false negative results.

FDA Experience with Isoniazid Test Strips

➤ Premarket

- Indications for use, precision in the hands of the intended user, cutoff between negative and positive results (sensitivity), method comparison, and interferences.

➤ Postmarket

- No deaths, injuries, or adverse outcomes to patients or testing personnel reported from the inception of the MDR database to present.

Summary and Conclusions

- The use of INH test strips in the qualitative detection of Isoniazid is an established technology—in use prior to 1976.
- Although the literature is sparse, there were no reported deaths or serious consequences to patients due to FP or FN results.

Closing Remarks

- The Chemistry Devices Advisory Panel is asked to discuss the key risks associated with Isoniazid Test Strip systems (false positive and false negative results) and identify any additional risk(s) that may have been omitted. The Panel should also discuss these risks in the context of their potential impact on public health.
- How the risks may be addressed and mitigated (e.g., labeling, additional studies, etc.)
- Whether the evidence allows for Isoniazid test systems to be classified as Class I, II or III in accordance with the medical device regulations.



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Isoniazid Test Systems Panel Discussion Questions

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Panel Discussion

Question 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.).

Panel Discussion

Question 2

Which classification, class I (general controls), class II (special controls), or class III (premarket approval), is most appropriate for Isoniazid test systems?

Panel Discussion

Question 2(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?

Panel Discussion

Question 2(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.)?

Panel Discussion

Question 2(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.