Marking Pharmaceutical Ingredients for Solid Dosage Security

As these case studies show, Molecular Recognition Marker technology offers an effective, FDA-approved means of forensic drug authentication.

By Jim Rittenburg, Ph.D., Vice President, Pharmaceuticals, Authentix, Inc.

In-product authentication is a crucial element of pharmaceutical security because it allows manufacturers to quickly and easily authenticate their products.

Often, the dosage form is repackaged as the drugs travel from the point of manufacture through the supply chain. In-product authentication features ensure that the dosage itself can be authenticated both in the field and in a lab setting. Follow-up forensic examination can ensure that results are valid and legally defensible.

Molecular Recognition Marker technology is the most effective way to deliver in-product authentication security features. It is a technique that is currently being used to protect billions of dollars worth of pharmaceuticals.

The Molecular Recognition Marker approach utilizes pharmaceutical excipients and inactive ingredients in a proprietary process to create trace markers and a matching recognition molecule. The marker and recognition molecule create a highly specific binding pair that enables sensitive and specific detection of the marker.

The following case studies illustrate the challenges faced by two different pharmaceutical manufacturers, the specific in-product authentication solution they used, and the outcomes.

Case 1. Marker Insertion via Tablet Film Coating Solution

**Issue:** A well-known pharmaceutical tablet with global distribution was being manufactured in several Asian countries in violation of patents. The rightful manufacturer sought a method to identify not only authentic drug, but also the manufacturing site where the tablet was produced

**Solution:**
- Marker selection—FDA, generally regarded as safe (GRAS) status compounds were included in the new drug application (NDA)
- Accelerated stability data were generated with registration batches
- A marker was added to film coating suspension during manufacture
- Multiple marker concentrations were used to identify manufacturing sites
- Marker stability was confirmed at over three years real time
- Lab method for authentication: Immunoaffinity-based quantitative method
**Outcome**
- The company received unequivocal product authentication
- Manufacturing sites were easily identified
- The solution has been in continual use for over 7 years

**Case 2. Marker Insertion via Active Ingredient**

**Issue:** A patented active ingredient is sold to third party formulators for inclusion in tablets and capsules. Formulators and distributors were violating supply agreements and patents by using active pharmaceutical ingredients (API) from unauthorized sources.

**Solution**
- The company used a proprietary trace marker in the API.
- The marker selected was an FDA Center for Drug Evaluation and Research (CDER) accepted substance.
- Short-term stability data were generated to support use of the marker.
- A rational sampling program was instituted.
- A routine monitoring program was implemented.

**Outcome**
- All formulated product using the patent owners active ingredient now contains a proprietary marker and can be easily authenticated.
- The brand owner is able to monitor and control the manufacturing and distribution chain.
- Infringers can be identified and confronted. Substantial revenue recovery has been realized.

**How markers are inserted**

Insertion of the molecular-recognition markers into tablets and capsules can be accomplished in several ways. The marker can be applied to the dosage through:

- Film coatings applied to tablets
- Inks imprinted on tablets or capsules
- Gelatin melts used for capsule manufacture
- Blending with the active ingredient

Long-term real-time studies have shown excellent marker stability for more than three years. The presence of the marker has no effect on tablet appearance or disintegration characteristics over the same periods of time. Since the markers are used at part-per-billion concentrations and are selected from recognized inactive ingredients, they have no impact on the performance, stability, or safety of the drug product.

**Safety**

Molecular Recognition Marker technology has been employed commercially in tablets and capsules since 1998. The technology has been vetted through the FDA’s regulatory process as a component of specific NDAs.
The Molecular Recognition Marker technology relies on compounds that are already approved for use in pharmaceutical products. These compounds include pharmaceutical inactive ingredients, excipients and substances classified as GRAS (generally recognized as safe). The compounds, when utilized as trace proprietary chemical markers, comply with regulatory requirements of the FDA, and other key regulatory bodies in Europe and Asia.

In 2003, FDA issued Guidance for Industry that specifically addresses the incorporation of proprietary markers into new drug products. The following is an excerpt from FDA’s Guidance Document:

“Trace amounts of harmless substances added solely as tracers or markers for individual product should be included in the composition statement and the batch formula.” . . . Tracers and markers need not be disclosed in the drug product labeling except for those used in parenteral drug products.”

What operators must know and do

The person conducting the testing in the field needs to follow a simple set of instructions to run the test. The field test is similar to a home pregnancy test and can be performed with very little training.

The big advantage of the Molecular Recognition Marker technology is that the test detects an intentionally added proprietary ingredient that will only be present if the product is authentic. Therefore the test is definitive and 100% accurate. Unlike various fingerprinting technologies, the results of the Molecular Recognition Marker test are not statistical results that can vary over time.

The future of Molecular Recognition Markers

Molecular Recognition Marker technology can also address problems related to product diversion or product quality. For example, different concentrations or combinations of markers can be used to identify specific manufacturing sites. This can be helpful in identifying products that are diverted from one region into another. It can also be useful in identifying the site of manufacture in cases where a product defect may show up after distribution.

About the Author

Jim Rittenburg, Ph.D., is Vice President, Pharmaceuticals for Dallas-based Authentix. His company provides authentication solutions for pharmaceuticals, consumer goods, industrial goods, petroleum and spirits. Authentix has patents on the Molecular Recognition Marker technology for product authentication applications.