



Near-Infrared Inspection Complements Other QC Systems

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For pharmaceutical manufacturers, making sure the right product is put in the right package is imperative. Mistakes can be life threatening or worse for patients, and recalls not only are costly in terms of time, money, and manpower, but also are damaging to a company's image and product reputation.

Pharmaceutical manufacturers use a variety of techniques to prevent such errors, including visual inspection, machine-vision inspection, scanning and matching of bar codes on labeling materials, and strict adherence to GMP cleaning and validation protocols. Despite these precautions, mistakes still happen.

The final line of defense

A quality control technology, new to the pharmaceutical industry but well established in other fields, could provide the final defense. The solution,

near-infrared (NIR) analysis, could be applied at several points in the course of pharmaceutical processing and packaging.

NIR inspection systems, now appearing on the market, prevent product errors by providing 100% in-line, nondestructive, noncontact screening by means of a spectrometer, which measures the reflectance, transmittance, and transreflectance of infrared light to identify the chemical signature of its target. As a result, the analyzer can detect incorrect product composition, empty capsules, and variations in composition, humidity rate, or product water content. These assessments offer an additional level of security beyond current quality control capabilities. Of course, efforts still must be made to ensure that package labeling and contents match.

Because the NIR unit analyzes the chemical signature, or fingerprint, of a substance, it can detect a stray solid dose even if the stray's appear-

ance is similar to what should be present. This feature is particularly useful for clinical trials in which the placebos and active doses generally are manufactured to look identical. NIR inspection also can help ensure the proper packaging of products that require a titrated dosage regimen or that consist of a sequence of tablets (e.g., oral contraceptives). Because a NIR system checks the chemical identity of the target itself, it also can detect problem batches or contaminated product and confirm that the packaging material being used has the correct structure. Target color has no effect on the unit's performance.

Currently, at least two companies are developing NIR analyzers that are designed to be mounted on blister packaging machines (VisioNIR, Uhlmann Packaging Systems LP, Towaco, NJ and QualitySpec TI, Analytical Spectral Devices, Inc., Boulder, CO).

A prototype shown at Pack Expo 2000 and more recently at Interphex 2001 checks blister packs in a 2×4 format and accommodates cycle rates of ≤ 90 packs/min. As many as 200 tablets can be checked each cycle, resulting in a potential operating rate of 18,000 tablets/min.

The NIR analyzer mounts over the conveyor on a blister machine and can accommodate as many as four fiber-optic heads, each capable of checking as many as 12 tablets at a time in a 0.1-s scan. Inside each head, a fiber-optic bundle provides a discrete probe for each blister pocket and detects a spectral range of 350–2500 nm with a wavelength accuracy of ± 0.08 nm and wavelength repeatability of ± 0.02 nm. In operation, white light from the probe bounces off the tablet or capsule and reflects the signature of the compound, which is compared with a known reference and is accepted or rejected by means of a shift register-controlled ejection station. A photometric range of 5 absorbance units (AU) and noise of $60 \mu\text{AU}$ make the unit highly sensitive and precise. If changeover requires a different blister format, the unit is flipped up on a pivot, a metal plate with holes matching the new tablet-capsule positions in the blister is substituted for the one in the ma-

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chine, and probes are rearranged accordingly. A learn mode simplifies setup.

The monitor for the analyzer can be combined with the operator interface of the blister machine or mounted in a separate cabinet. Production models may mount heads and monitors on a

wheeled base so the NIR analyzer can be moved from line to line.

Putting NIR to work

The first NIR analyzer for blister package quality control will be installed at Sanofi-Synthelabo Research (Malvern, PA) on a low-volume machine used to package product for clinical trials (EAS unit-dose machine, Klöckner Medipak, Clearwater, FL). "When the cost of a Phase III trial is \$20 million or \$30 million, you want to make sure everything is correct," explains Dick Winokur, director of clinical trials supplies at Sanofi-Synthelabo. "This new technology will aid in increasing quality levels on the line and save time versus some of the standard analytical methods used today," he adds.

Additional time savings also may be achieved by combining production runs. "If there's three dosage forms for a clinical trial, there's usually three blister runs," Winokur says. With an NIR analyzer checking each blister pocket, runs for a study involving a placebo and multiple dosage levels can be accomplished simultaneously. The analyzer's 100% inspection capability ensures that each blister pocket contains the correct product. Compressing development time can positively affect the schedule for filing a new drug application and result in a product that reaches the market and generates revenue sooner.

The potential time saved by ganging production runs and eliminating the need for some off-line quality control testing translates into a compelling return on investment projection and helped convince Sanofi management to go forward with the project. "If you want to be the first to serve the market, you have to be able to find unique methods to reduce cycle time," says Winokur.

The NIR analyzer has been validated on the benchtop to show it can differentiate between placebo and 1-, 2-, 5-, and 25-mg doses. Winokur also is working with Sanofi-Synthelabo's quality control department to analyze capsules as they are received so the resulting fingerprint can be used to set up equipment and release product.

Work with the capsules has revealed one problem, however. Some commonly used coatings, including iron oxide and titanium dioxide, prevent NIR waves from

penetrating the capsule and identifying its contents. Fortunately, uncoated capsules of any color are readily available from capsule suppliers.

Sanofi-Synthelabo's next step is to put together a validation package and install the NIR analyzer on the small blister machine. Validation testing is expected to involve approximately 200,000 doses and is tentatively scheduled to begin in Decem-

ber. "The actual schedule will depend on the production workload at the time," says Winokur. "We may end up doing some validation runs on the weekend," he adds.

Once the NIR analyzer is validated on the small blister machine, Winokur plans to install a second NIR unit on a larger thermoform-fill-seal machine (CP-3, Klöckner Medipak). This blister packager also will be equipped with a black-and-

white video camera system to verify product integrity. "NIR will detect an empty pocket but cannot tell if a solid dose is chipped," explains Winokur, noting that the systems are quite complementary because the camera can detect physical damage but can't determine whether the right formulation is present.

Other potential applications for NIR analyzers in the pharmaceutical industry include confirming the structure and weight of the packaging film being used on a blister packaging machine and identifying incoming bulk products or ingredients without opening the container or bag. Because the agchem industry already uses NIR systems to identify incoming material on rail cars before receipt, Winokur believes the technology could make the transition to the pharmaceutical industry for this type of task. "It would enable much quicker sampling," he points out. Sampling in situ also allows packages to remain sealed until just before use, eliminating chances of spills and contamination.

Although existing quality control measures have reduced the number of incidents in which the product inside the package is different from what the label indicates, this problem remains a common cause of recalls. The use of NIR technology appears to be an effective way to avoid recall-initiating errors and the associated expense and brand-damaging negative publicity as well as potentially dire consequences for the consumer. **PT**

FYI

Call for abstracts

The Drug Information Association (DIA, Fort Washington, PA) has announced a call for abstracts for its workshop Optimizing Clinical Development to be held 25–26 July 2002 in Baltimore, Maryland.

Submitted abstracts are limited to 300 words or one page and must include a cover sheet with title, complete contact information, and a brief summary. Abstracts must be sent electronically by 1 February 2002.

For more information, contact DIA, 501 Office Center Dr., Suite 450, Fort Washington, PA 19034-3211, tel. 215.628.2288, fax 215.641.1229, dia@diahome.org, www.diahome.org.