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Packaging & Packaging Solutions

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Vial making maintains healthy pace

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Being an innovator has its ups and downs. At the Orlando, FL, operation of fast-growing Nephron Pharmaceuticals Corp., the ups are in full swing. The company's ever-expanding respiratory therapy solutions production plant in Orlando is now packaging single, unit-of-use, sterile, low-density polyethylene vials containing 0.5-percent sterile albuterol sulfate inhalation solution. The Nephron product is the first drug in a unit-of-use container to be approved by the U.S. Food and Drug Administration.

Extrusion/blow-molded in a modified process using transparent LDPE that allows viewing of the liquid content in a shatter-resistant yet easy-to-twist-open container, the 1/2-mL unit-of-use vial of nonpreserved albuterol sulfate inhalation solution should let consumers breathe a bit easier. The premeasured vial is individually packaged in a foil-laminated pouch. Until now, the product was available only in larger quantities in multi-dose bottles containing 10, 20 or 30 mL that had to be measured using a calibrated dropper. Nephron's innovative new vial package containing the 0.5-percent, 0.5-mL premeasured medication allows patients to open a single, sterile, disposable container that eliminates the measuring dropper and provides a specific quantity of the drug every time.

Nephron has produced the drug since '97 in other package formats. However, the unit-of-use vial package, ready to mix with other oral inhalation drugs, saline or other diluents, for dispersion from a nebulizer, is a breakthrough that took about four years to earn the FDA's approval. The 0.5-percent version of the drug in this container completed validation in July, and has been available in the clear LDPE single 0.5-mL vial since August 1.

Steve Simmons, Nephron's president, told PD during a recent plant visit that the unit-of-use vial pack represents a significant advance in innovative packaging for such a drug product. "This is a whole new [version of the] product, one we've been working on with the Food and Drug Administration for a number of years. It's the first sterile drug product for oral inhalation packaged in this manner."

To accommodate demand for the new product and unit-of-use vial package, Nephron is in the midst of installing new packaging equipment, which, when installation is complete, will total an equipment investment of $3 million. The equipment improves upon similar vial lines installed in the plant during the last six years. Already in place is a group of vertical f/f/s single-vial pouching machines from Japan's Tokyo Automatic Machinery Works (TAM), provided exclusively in the Americas by Duma Package Machinery, that packages the vials individually but generates the pouches in continuous, perforated strips of 10 pouches per strip.

One million vials/week

Running the vials on a 24/7 basis, with a shutdown for maintenance and cleanup every five days, the ever-expanding 72,000-sq-ft Orlando plant began its first production-level runs of the unit-of-use vial packs in July on a 12-cavity aseptic blow/fill/seal system at a rate of 12 interconnected, flexible vials per "card," four cycles/min, or 48 vials/min.

In addition to bringing in the new pouching machines, the plant, as of presstime, was about to ramp up capacity on the vial with the installation of a 40-cavity vial-molding system along with vial card-trimming and finishing equipment from Weiler Eng. (formerly Automatic Liquid Packaging, which supplied the 12-cavity ALP blow/fill/seal system). Also to be added is a Nikka Densok high-voltage leak-detection system and new conveyors from Westlund Eng. The upgrades will come in handy, as Nephron expects to boost production volumes to an astounding 1 million vials every five days.

"We can't seem to keep our warehouses full," Simmons says. "We're marketing and selling more product all the time. In order to meet full demand for production

quantities for this particular vial, we needed to have a larger-capacity blow/fill/seal system." Replacing the 12-cavity unit is Weiler's customized and modified Model 640 40-cavity Asep-Teche aseptic extrusion/blow/fill/seal system modified to accommodate Nephron's needs that produces, fills and seals the vials in multiples of 40 per cycle, or two sets of 20 vials. A vial set produced on the 40-cavity machine will include five interconnected vials per "card," four cards to a set, which will be molded at speeds of 160 vials/min. Once the 640 is running, the existing 12-cavity machine will remain at the plant for pilot projects.

"Right now, the line is sort of like a mosaic of pieces we're putting together," Simmons says. "The 40-cavity equipment and the machines that will trim and feed the vials to the pouchers aren't here yet, but should arrive in a few weeks. They will allow us to go from producing about 80,000 units a day to 200,000 units a day."

After being sent through the Duma/TAM vf/f/s machines, the continuous, perforated strips of 10 pouches are loaded in groups of three strips into 30-count SBS tuck-top/automatic-bottom folding cartons and shipped to hospitals, drug wholesalers and pharmacies nationwide.

The unit-of-use vial line makes the fourth vial-packaging line in place at the plant. Two other lines are currently being upgraded with improved packaging equipment, Simmons tells PD. "One challenge we've experienced with this new vial and pouch format was how to get a single vial into a single pouch without human intervention," he says. "We have to have a pouch that protects the solution against light and air and meets all of the regulations, but we typically pack multiple vials into pouches, not single vials." Last year, Duma installed a single-head pouch machine for Nephron to test on a trial basis and in October '00, Nephron purchased the Model 301 single-tube production-volume machine and one of the two Model 771 twin-tube machines. A few months later, the company added the second twin-tube system to complete its test-batch runs of the new product.

Straight forward machine design

The vial-pouching machines bring speed, simplicity and stability to the operation. "They are compact, can keep up with our volumes, and for the price, they were the right machines for the job," says Simmons. "Wayne Barr from Wei-Pak suggested the Duma machines," he says, adding that Barr found other equipment solutions for Nephron and was instrumental in its equipment selections for the entire unit-of-use vial line.

The TAM TWR 771 and TWR 301 strip-pouching machines are capable of packaging vials at speeds of 240 and 120/min, respectively, which will mesh with Nephron's vial blow/fill/seal speeds, which will soon average 160 vials/min. Duma integrated a

Markem SmartDate2C thermal-transfer coder inside each pouching machine to imprint lot numbers and expiration dates on the pouchstock so that they appear on the pouch's front panel. A sensor in the forming tube on each machine ensures that an individual vial goes into every pouch made. Each print impression in the pouchstock is also encoded and scanned in the pouching machines to verify that the pouch material for the run is the correct one for the product being pouched.

Accurate and stable feeding of the pouchstock and pouch sealing are carried out by the servo controls of the vf/f/s systems, which feature easy-to-operate touchscreen control panels and MMI and LCD displays for input of commands. The machines' vacuum "U" control chambers maintain even pouch film tension and edge alignment as the chambers eliminate the need for tension rollers. The controls also allow Nephron to run assorted film thicknesses without wrinkling.

Nephron appreciates the straightforward design and performance of the vf/f/s pouching machines, which didn't require extensive training to operate. The machines' film conveyors have few rollers, so film tracks easily, and overflows are eliminated. Pouchstock is controlled by a servo motor that allows precise setting of quantity and speed, achieving constant web feed and print registration. Film splicing can be done in-register, and roll changes can be done on-the-fly, a nice benefit, according to Nephron. Other bonuses include large, clear doors and an easy-access maintenance door that pivots out of the way to provide ample visibility to the interior components of the machine.

Able to output pouches ranging from 2.5 to about 7.8 in. W and 1.9 to 11.81 in. L, the machines in Nephron's case afford fin-sealed pouches measuring 6 in. L x 2.25 in. W to hold the single vials of 0.5-mL, 0.5-percent albuterol sulfate inhalation solution. Flexicon provides the two-color-printed foil/nylon/LDPE pouchstock, which is supplied on 430-mm-dia (16.9-in.) rolls.

Modified blow/fill/seal

Ahead of pouching, upstream production of the vials themselves is equally noteworthy and will become more so when the Asep-Tech 40-cavity modified blow/fill/seal vial machine arrives. The sets of vials are produced, filled and sealed in a sterile, operator-less environment in one of several clean rooms Nephron has separated from the rest of the packaging functions.

The 12-cavity vial machine running during PD's visit was a short walk from the main packaging and vial-production area. The system extrudes raw pellets of medical-grade 20-6064 virgin LDPE resin from DuPont before it molds, fills and seals the teardrop-shaped vials, their twist-off seals, bottom tabs and other interconnected plastic material. Never touched by human hands, the solution is pumped to the filler from 316L stainless-steel jacketed tanks. Traveling through a previously sterilized

path, the nonsterile fluid first hits dual sterilization filters upon processing, sterilizing it prior to filling.

During PD's visit, the aseptically filled and sealed cards of 12 vials exited the HEPA-filtered clean room by conveyor and were deflashed by hand. Next, they were further separated into individual vials and sent through a leak-detector built in-house. Loaded by hand into gaylords, the vials were transferred to the pouching machines on the main packaging floor.

Also at the time, a Class 10,000 clean room was being readied for the modified 40-cavity Asep-Tech 640 aseptic blow/fill/seal equipment which, when in place, will generate vial sets in the same five steps as does the 12-cavity machine, except, instead of 12 vials at a time, eight sets, or 40 vials will be produced at a time.

Both the 12-cavity and 40-cavity systems operate thusly: The LDPE resin is extruded into parison heads, eight of which are being equipped on the 40-cavity machine. As the mold closes, the parison is cut. The bottom of each parison is pinched closed, and the top is held in place. The mold then conveys to a forming/filling nozzle within the machine, as the blow/fill nozzle lowers to the parison until it aligns with the neck of the mold.

According to Simmons, Nehpron's machines have been modified to ensure validation by use of a vacuum to draw the wall of the vial out, instead of the usual way, in which sterile, filtered, compressed air is blown into the parison and expands it against the wall of the integrally cooled mold cavity. Afterwards, the sterile product is metered into the vial through the nozzle, which then retracts.

Separate sealing molds then close to form the vial tops and to hermetically seal the containers. The mold splits the vial sets into two, 20-vial sets. When the mold opens, the molded, filled and sealed vial sets emerge and exit the clean room, upright, on a patented bird's foot conveyor to the first of two automatic trimming systems. The first microprocessor-controlled system deflashes the sets into separate cards, incorporating five interconnected vials. When the additional equipment arrives, the cards will then be oriented horizontally and fed into the new Model HDI-1S nondestructive electronic leak/pinhole-detection system from Nikka Densok. The HDI system checks the twist-off seals and necks of just-made vials using a high-frequency, high-voltage spark test that detects secondary contamination of the product. Especially designed to work with blow/fill/seal containers, the inspection unit ensures that the vials are sealed by identifying small pinholes, cracks and other seal imperfections or leakage. Any rejects will be pushed off of the main conveyor into a rejection bucket for further evaluation, while "good" cards will progress to the second of the Weiler-built stations, a conveyorized stripper system that will separate the cards into single vials.

For the time being, the vials are individually hand-fed onto belts leading to the hopper of each of the TAM vf/f/s strip-pouching machines. Simmons indicates that the manual vial-feeding process leading to each of the pouching machine infeeds will be replaced by a five-lane "wheel spoke" conveyor system that will appear like a hand with five fingers, elevating the vials in single file.

Vial pouching

The pouching systems operate in intermittent motion as the foil-based rollstock, which contains enough material to produce about 2,600 pouches, unwinds through a set of rollers that tension the material as it nears the forming shoulder. Each pouch has a bar code, read by a scanner that verifies that the pouch material for the run is the correct one for the product being pouched. Just before pouch forming begins, the web of material is encoded by the SmartDate2C with the lot number, expiration date and machine number.

Next, the web passes a sensor positioned in the forming tube that ensures a vial has dropped into the pouch before it will finish sealing. The servo-controlled machine also automatically measures out the length of each pouch to perforate it and cuts a strip of 10 pouches. The vials meanwhile drop through the hopper chute in the pouch-forming section as the web encloses the forming tube and collar, and a vertical fin seal is made, the vacuum chamber maintaining film tension and alignment all the while.

The top seal is then made on the leading bag, and a bottom seal is made to the trailing bag. A tear-nick applicator built into the seal bar makes a small, easy-open notch in the top seal before a combination perforating/cutting knife makes a perforation between individual pouches and a full cut between strips of 10 pouches. The filled, sealed vial packs emerge from the machine in continuous strips onto an incline conveyor, are inspected and are then taken to a nearby packoff area.

Manual cartoning...for now

There, operators inspect the pouches, accordion-fold the continuous strips of 10 pouches and load them by threes into the 30-count SBS folding cartons from Malnove, insert product literature, and then case-pack 10 of the cartons into a master shipping case. Cartons are inspected for proper pouch count, contents and pertinent information and are hand-stamped with lot code and expiration date. Cartoning and casing will continue to be performed manually for the near future, Simmons says, but the cartons will soon be automatically checkweighed

For now, operators weigh the filled, sealed cartons on calibrated scales. "We plan to add checkweighing soon, but the cartoning and case packing functions aren't likely to be automated for a while, because we have to figure out a way to automatically handle the strip-packs of 10 pouches once they come out of the bagging machines."

The prognosis looks good for Nephron's new product and packaging operation in Orlando, which is about to increase in size by 50 percent, as another portion of the building is being acquired for production, Simmons says with enthusiasm. "We expect to install six more production lines within a year, and Nephron will be introducing additional products in bar-coded single-vial pouches. One is a patented, two-chamber vial for segregated, sterile solutions. Another is a cost-saving diagnostic product for hospital use. As hospitals increase their use of bar-coded products to cut costs, we see this as only the beginning of unit-of-use packaging." For users of pulmonary drug products, that could be a healthy breath of fresh air.

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