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Containment by Design for Cytotoxic Manufacturing

By Erik Greb

The market for oncology drugs is growing as pharmaceutical companies increase efforts toward developing potent compounds. Innovative containment solutions aim to minimize workers' exposure to cytotoxic compounds and ensure these compounds are not contaminated.

Containment equipment vendors such as Howorth Air Technology (Louisville, KY) report growing client interest in containing development-scale equipment such as tablet presses. Manufacturers have traditionally opted to retrofit existing equipment for enclosure in an isolator, but this strategy can be problematic. Many tablet presses were not designed to be contained, and retrofitting them requires modifications that could compromise the presses' precision and integrity, according to Darren Garvey, vice-president of sales at Howorth. Retrofitting takes time and requires equipment to be taken out of service. "There's not an ideal [containment] solution for every tablet press that's out there," says Garvey.

To overcome these difficulties, equipment providers have begun to produce isolator-ready devices that can easily be retrofitted for containment. Contract developer Metrics (Greenville, NC) asked SMI (Lebanon, NJ) and Howorth to design a fully contained tablet press for its Greenville, North Carolina, cytotoxic facility in May 2008. The companies used their combined expertise to create the "Piccola-C" tablet press, which is enclosed in an isolator and provides approximately 30 ng/m ^{3} of containment, says Garvey. The unit will be on display at this March's INTERPHEX 2009 conference and exhibition in New York City.

The tablet press shares parts with Howorth's isolator and fits inside it seamlessly, according to Chris Zappa, a technical service representative at SMI. Its design has fewer components to clean, as well as fewer crevices that could entrap material than traditional tablet presses. Difficult-to-clean mechanical areas and controls are located outside the isolator to simplify cleaning, says Garvey.

Portability was one of Metrics's main requirements for the combined unit, according to Joe Cascone, the company's director of potent pharmaceutical development. SMI and Howorth chose a similar wheel configuration for the tablet press and isolator so that users can roll the integrated device into a facility, plug it in, and begin operation.

The combined tablet press and isolator take far less time to install than a retrofitted device would, says Zappa.

Another of Metrics's requirements for the tablet-press isolator was the room to house analytical instruments such as balances and friabilators inside the enclosure, says Cascone. The company wanted to eliminate the need to export tablets to determine their physical characteristics. To ensure their client's needs were being addressed, SMI and Howorth created a full-scale model of their design so that Metrics could evaluate the enclosure's ergonomics before receiving the final product. The integrated unit includes a work-surface area of 16 ft ^{2}, and the tablet press occupies about 2 ft ^{2}, thus leaving ample space for testing equipment.

To improve user control, Metrics's integrated tablet press–isolator is operated by an on-board programmable logic

control that displays all machine functions in one touch-screen interface. This configuration simplifies the operation of both devices and eliminates the need for communication between two separate control systems. The control interface is located outside the enclosure, which simplifies cleaning and reduces the opportunity for contaminating potent ingredients. In addition, Metrics could easily incorporate the isolated tablet press into a supervisory control and data acquisition system because the combined unit offers one point of integration, Zappa says.

A newly built, integrated unit also has benefits beyond immediate functional advantages. A retrofitted tablet press must be revalidated, for example, but “one integrated unit means one validation protocol, one maintenance schedule, and one standard operating procedure instead of two for a nonintegrated containment solution,” says Cascone. The end user can ensure that the integrated device meets its requirements by participating in the unit’s design from the outset, he adds.

Metrics uses its contained Piccola-C tablet press to produce preclinical, developmental, and Phase I–III supplies of potent and cytotoxic solid oral dosage forms. Although vendors have only designed development-scale tablet presses for containment so far, increased interest in cytotoxic manufacturing will likely spur vendors to pursue production-scale presses that are isolator-ready, Garvey says. Creating equipment with containment in mind also could make the production of cytotoxic drugs more efficient by bringing sophisticated design, improved ergonomics, streamlined control, and easy maintenance to commercial-scale machines.