MAY 2003 Volume 15 Number 5 www.ptemag.com

# Pharmaceutical Technology
EUROPE

21 CFR Part 11
## The new draft guidance

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# The New **Tabletting Facility**

**Modern tablet production facilities are faced with two increasingly important, yet contradictory, demands — being able to handle more potent drugs and, at the same time, reduce costs. Additionally, batch sizes must become smaller and production planning more flexible. Until recently, these issues could only be dealt with individually and not as a whole; however, the exchangeable functional module (EFM) may provide a solution to this problem, as this article describes.**

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Intense pressure from governments regarding health care costs, increasing competition from generics manufacturers, and escalating research and development (R&D) expenses are forcing pharmaceutical companies to review and significantly reduce their costs. Consequently, the industry is witnessing continuous merger and acquisition (M&A) activity,[1] aimed at consolidating the enormous R&D costs, and increasing efficiency in the manufacture and distribution of pharmaceutical products.

As part of corporate cost-cutting measures, some tabletting facilities have closed and tablet production is now concentrated at a limited number of plants. Striving for ultimate efficiency, these remaining facilities must be able to handle greater volumes of more varied and more potent products in smaller batch sizes; at the same time, stocks (products in production and finished goods) and lead time must decrease, whereas flexibility to market demands must increase. These issues can be grouped into three areas:

- total cost of ownership (TCO) of the production plant; that is, the total cost per produced unit
- flexibility, allowing quick reaction to external factors such as sudden market changes
- containment of potent drugs for maximum operator safety and environmental protection.

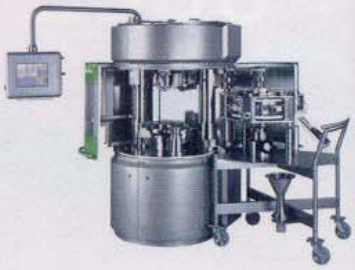
The TCO approach is being increasingly used by pharmaceutical manufacturers when selecting new equipment because it takes into account the real total cost of operating process equipment per unit of production. This total unit cost is the only true basis for comparison. Not only does it consider the capital investment of the equipment, but also

- its overall productivity, based on the downtime of the machine for cleaning, product changeover, maintenance and repair

**Figure 1** A Courtoy MODUL rotary tablet press.

**Figure 2** The ECM inside the tablet press.

**Figure 3** The ECM removed from the press.



- product losses
- the cost of spare parts and maintenance
- the space required for installation and operation
- the staff required to operate the equipment
- energy and utilities consumption.

The cost of equipment such as air conditioning, cleaning and clean rooms, is often underestimated and manufacturers should, therefore, consider fewer or smaller pieces of equipment.

## Exchangeable functional module

Considering each of the three issues listed previously; for minimal TCO, a machine with a high instantaneous output and minimal downtime (high reliability and quick cleaning) is required. To achieve maximum flexibility, a machine that can changeover from one product to another easily and quickly with minimal risk of cross-contamination is required. For maximum containment, a machine that is completely isolated and sealed, ensuring operator and environment safety, is required.

The concept of the exchangeable functional module (EFM) came to fruition after searching for a single solution to all three issues. An EFM can be described as part of a piece of process equipment that

- contains all product-specific format parts
- contains all parts in contact with the product
- can be isolated from the remainder of the equipment
- can be easily and quickly installed or removed.

Using multiple EFMs, it is possible to simultaneously achieve quick product changeover in a completely contained way. The use of product-dedicated EFMs even eliminates the risk of cross-contamination. Removing all product-contaminated parts from the equipment eliminates the cleaning operation, which can then be performed off-line without impacting on downtime in a dedicated area.

## EFM applied to a tablet press

The EFM concept has been developed and integrated into a rotary tablet press (Figure 1). This was relatively simple because on a rotary press all product-contact parts and product-format parts (upper and lower punches, and the dies) are situated around the central area of the machine; that is, the turret or die table.

In a turret, the punches and dies, powder feeder, scraper and ejection finger, dust extraction nozzles and tablet chute can all be integrated in one isolated box, called an exchangeable compression module (ECM). The ECM can be removed from the equipment as a complete, isolated unit in less then 15 min; installation also takes 15 min, resulting in a complete machine changeover time of 30 min. The entire ECM exchange procedure can be performed by one operator because most operations are performed by the machine's

**Figure 4** The tablet press in a grey zone with peripheral equipment duplicated in clean rooms.

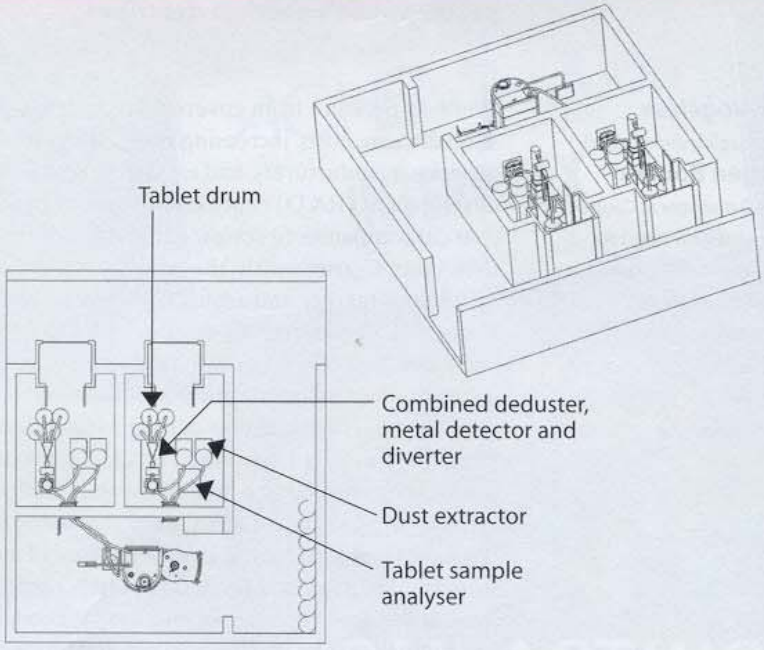
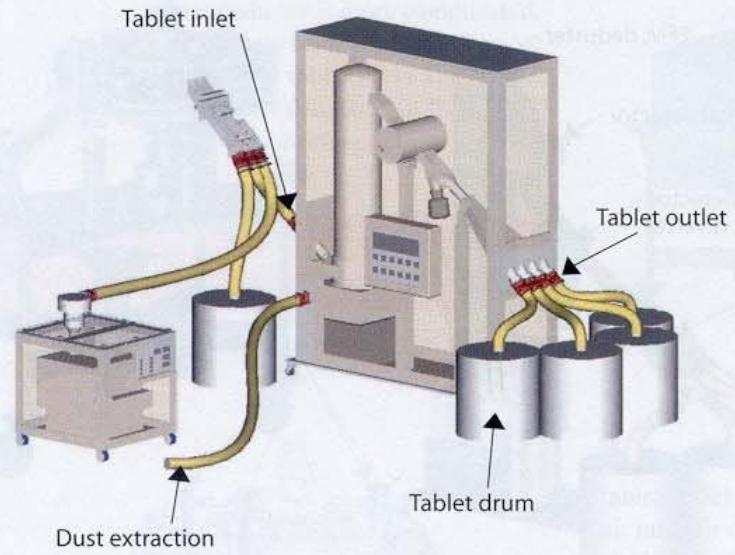


**Figure 5 Peripheral equipment integrated in an isolator.**




control system, minimizing human errors. Furthermore, using an isolated ECM eliminates the need for covers inside the machine to prevent dust from entering, thereby significantly improving visibility, accessibility and maintainability of the equipment (Figures 2 and 3).

## EFM and peripheral equipment

Applying EFM technology to a tablet press brings advantages to productivity, flexibility and containment. However, the full potential of EFM technology can only be appreciated when the peripheral equipment of the tablet press (such as tablet dedusters and metal detection systems), also has extremely fast changeover, flexibility and containment. As long as standard peripheral equipment is used, the time required to clean these peripherals, as well as the clean room, will still determine the total downtime. There are three alternative solutions to this problem:

**Alternative 1.** This method involves duplicating the peripherals in two separate clean rooms (Figure 4). Standard peripheral equipment is set up in two separate clean rooms and at product changeover, the ECM of the tablet press is disconnected from the tablet deduster, integrated with a metal checker, and, eventually, the tablet distribution system. It is then disconnected from the sampling unit for online tablet analysis and the dust extraction unit. Finally, it is removed from the press. The clean ECM is then installed and connected to the peripherals located in the adjacent room. The tabletting process can restart, after which the equipment in the first room can be cleaned. The tablet press can be located in a grey zone, allowing one (large) clean room to be replaced by two smaller ones.

**Alternative 2.** Integrating the peripheral equipment in an isolated box (Figure 5). Again, there are two sets of peripherals, but they are now integrated in a dust-tight transparent box. The isolation level of this box depends on the required level of containment, which can range from a dust-tight box up to a high containment isolator. Although the peripheral equipment becomes more complex, tabletting is now fully isolated, eliminating the need for a clean room. The complete tablet production operation can take place in a grey zone.

**Alternative 3.** Applying EFM to peripheral equipment (Figure 6). In this solution, only the EFM parts of the peripheral units need to be duplicated, saving space and equipment compared with the previous solutions. Moreover, the EFM concept is easily applicable to the metal detector and tablet diverter gate. With the metal detector, the product travels through a closed tube running through a magnetic field;

**Figure 6 The EFM concept applied to peripheral equipment.**

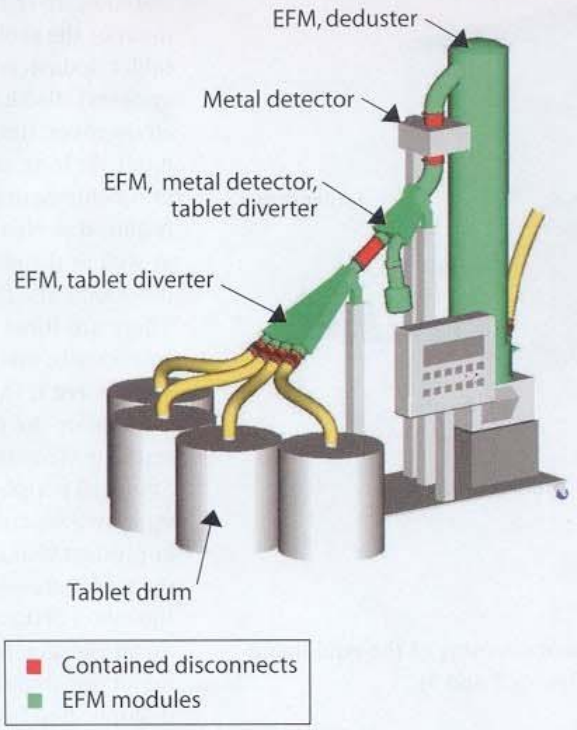



**Figure 7 The EFM on its trolley.**

removing and exchanging this tube in an isolated way is simple. Applying EFM technology to a tablet deduster is more complicated, but is simple compared with the ECM on the tablet press. The EFM of the tablet deduster has five external connections:

- tablet inlet
- tablet outlet
- air inlet for dedusting
- air/dust extraction outlet
- drive axis for vibratory action.

Only the drive axis is between the EFM and the machine base, making the interface and connect/disconnect design straightforward. Alternatives 2 and 3 allow tablets to be produced in grey zones, eliminating the need for clean rooms and representing a significant cost saving.

**Figure 8 The ECM equipped with spray nozzles and a drain for WIP.**

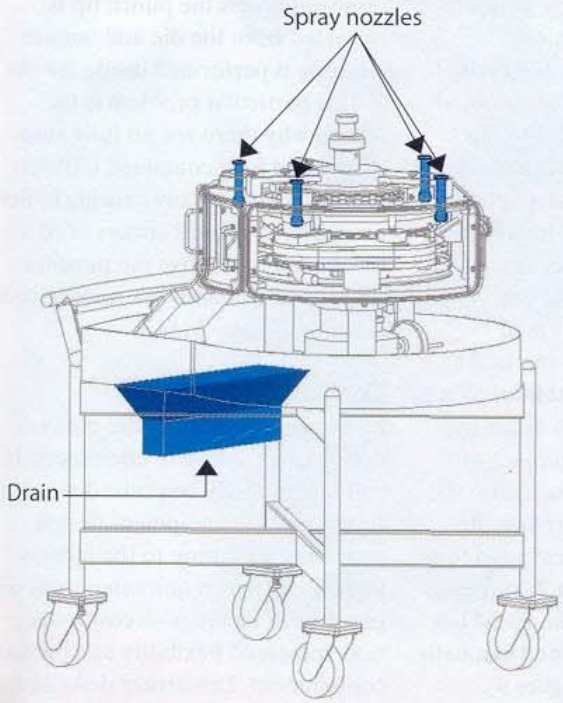



**Figure 9 The ECM integrated with an isolator and a docked washing booth.**

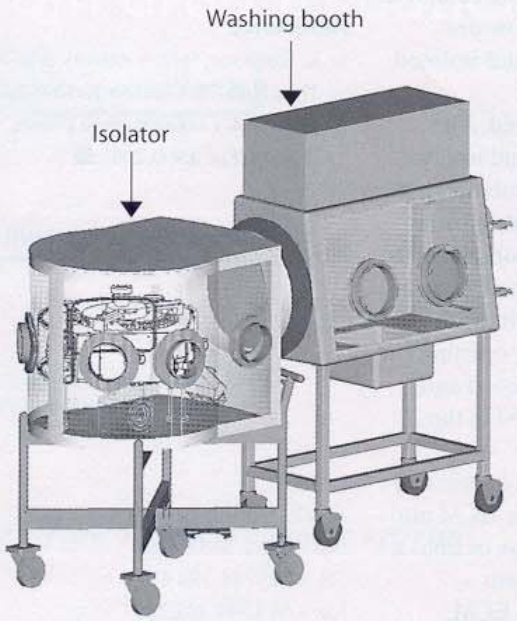
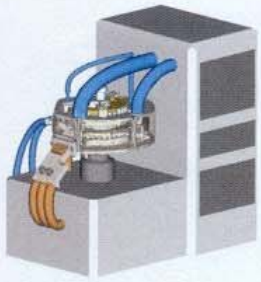



**Figure 10 The ECM submerged in a wash bath.**

**Figure 11 The ECM connected to a fully automatic wash system (patent pending).**



## Product containment

When using a variety of equipment simultaneously, each using EFM technology, an important issue is to guarantee product containment. A high level of containment is important for processing high-potency drugs and when working in a grey zone environment. Product containment must be maintained, not only during production but also when disconnecting and removing different EFMs. Currently, there are a number of solutions available that allow a contained disconnection; that is, a disconnection with minimal product loss.

**Split valve technology.** A split butterfly valve, split ball valve or split piston valve consists of two separate halves, each having a mating part. The two halves are connected together so the surfaces of the mating parts that would otherwise be open to the atmosphere are sealed, preventing the surfaces becoming contaminated by the product while the valve is open. The valve is opened by turning or sliding the connected mating parts; when the valve is closed again, the two mating parts can be disconnected, exposing the sealed non-contaminated surfaces to the environment.

**Rapid transfer or alpha-beta ports.** This system uses the same concept as the split valve, but is typically bigger. This type of valve is primarily used for the transfer of parts rather than product feed.

**Heat sealing and cutting.** When plastic tubing such as polyethylene or PVC is used, heat sealing with electrical resistance threads or RF welding can be used to close the tube. By cutting across the seal, or between two seals close to each other, a contained disconnection is possible.

**Strapping and cutting.** When flexible tubing is used, a variety of systems, such as plastic cable ties, steel bands, twisted wires or adhesive tape, can be used to close the tube. Cutting across the strap or between two straps close to each other allows contained disconnection. The optimal technology depends on the required level of containment.

A number of solutions do exist, but the solution of choice depends on the required level of containment. It should be clear that the effective operator exposure level (OEL) will also depend on the product characteristics and the standard operating procedures (SOPs).

## Cleaning the ECM

The EFM removes the cleaning stage, reducing the equipment's downtime and increasing its flexibility. Wash-in-place (WIP) or clean-in-place (CIP) processes are not recommended because it can take several hours to prerinse, wash,

dry and cool. There are a number of off-line cleaning alternatives, depending on the level of containment required.

**Manual cleaning.** Once the ECM is removed from the press and placed on its dedicated trolley (Figure 7), it can be moved to a washing area to be opened and cleaned manually. The fast changeover design of the ECM minimizes the time and resources needed for such manual cleaning, and the procedure can be performed in a downflow booth for limited operator protection.

**Manual cleaning after a WIP cycle.** To accelerate the cleaning process and reduce operator exposure to the product, a WIP system is available on the ECM, which can be equipped with internal spray nozzles and a water drain via the tablet chute (Figure 8). Final cleaning and changeover is still performed manually after opening the ECM.

**Manual cleaning in an isolator.** When processing high potency drugs, the ECM trolley can be equipped with an isolator, which is closed after the ECM is placed on the trolley; the isolated unit is then transferred to a dedicated cleaning area. A washing booth is connected to the ECM isolator and the ECM opened manually through glove ports (Figure 9). Removable parts such as punches and dies, the feeder, scrapers and dust extraction nozzles are transferred to the washing booth for cleaning.

A cleaning hose and drying air can be supplied from the washing booth into the ECM isolator. The complete cleaning procedure is now performed in a contained and isolated environment.

**Manual cleaning in a liquid.** An alternative to the WIP and isolator cleaning solutions is to submerge the ECM in a cleaning liquid, allowing the liquid to enter and completely fill the ECM (Figure 10). The ECM can then be either removed from the bath and drained before opening and cleaning, or it can be opened and cleaned whilst submerged in the liquid.

**Automatic CIP.** The most automated solution is to transfer the ECM into a closed washing machine or onto a CIP pallet. The first system completely encloses the ECM, automatically opens it and cleans both the internal and external surfaces. The second system requires spray nozzles and a drain to be integrated in the ECM, which are then connected to a CIP service pallet.

Both solutions must overcome the problem of retracting the lower punches from the dies for fully automatic washing because the gap between the punch tip and die wall is very small (a few hundredths of a millimetre). Powder trapped and compacted in that area can never be removed unless the punch tip is retracted from the die and intense cleaning is performed inside the die.

This particular problem is the reason why there are no fully automated and fully contained CIP systems available on any existing tablet press. The press will always need to be opened to remove the punches (or punch tips) and dies prior to final cleaning (Figure 11).

## Conclusion

EFM technology provides many options for a range of equipment. It will undoubtedly be utilized more in future process equipment design, providing a solution to the increasingly important requirements put on production facilities — cost reduction, increased flexibility and product containment. This article describes how an EFM has successfully been applied to a tablet press and can easily be applied to peripheral equipment. The preferred method for off-line cleaning depends on the specific product to be manufactured.

## Reference

1. K. Robinson, "M&A Activity at an All-Time High," in *Contract Services Europe* (2003) p 4, a supplement to *Pharm. Technol. Eur.* **15**(3), 2003. ■

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- To enhance the security of the operator against increasingly potent drugs

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The revolutionary new MODUL™ tablet press from Courtoy has an EXCHANGEABLE COMPRESSION MODULE, which allows **full change-over in less than 30 minutes**. All product contact parts are included in this ISOLATED DUST TIGHT MODULE, which is disconnected and removed in minutes. Another clean isolated module with the right tooling can now be installed and the machine is ready to produce the next batch.

## Immediate Results

- **Extremely short downtime** (compared to 4 to 8 hours for all other presses) resulting in very high overall productivity
- This highly flexible system enables you to run different batches/products with different tooling types **in one day**
- **Closed system:** no cleaning on the machine, no contamination of the room, maximum security for the operator, **designed to process high potent drugs**

***Now you will use a tablet press for what it is designed for - MAKING TABLETS!***

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