WHAT’S NEXT?

FETTE COMPACTING MAGAZINE 1/2015

UPGRADE YOUR EFFICIENCY

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The pharmaceutical industry has been turning highly potent active ingredients into drugs for more than 70 years. During this time, containment has become a key issue for production and forms the focal point of this issue of What’s Next. The timeline below shows you how containment technology has developed and how Fette Compacting has contributed to milestones.

1943
US researchers develop the first industrial containment unit (biosafety cabinet) for military purposes.

1960
The industrial processing of toxic substances begins with oral cytostatic drugs. Hormonal preparations such as the contraceptive pill also help to advance containment technology.

1961
The US physicist Dr. Willis Whitfield from Sandia National Laboratories lays the foundations for modern clean-room technology with his laminar-flow ventilation system.

1968
Nuclear researchers in France develop the first RTP (rapid transfer port) system for linking production stages safely. By doing so, they pave the way for uninterrupted containment.

1970
The first fast-running tablet press from Fette Compacting means that drugs can now be produced in large batches.

1985
Fette Compacting launches the first computer-controlled tablet press with in-process control onto the market.

1992
The USA stipulates compulsory criteria and classes for clean rooms with Federal Standard 209E.

1994
Hot-melt extrusion offers a safe means of using new, high-potency active pharmaceutical ingredients to make powders and granulates for tablets.

1999
ISO standard 14644-1 defines international operator protection regulations for clean-room production.

2000
Fette Compacting develops the first washable double rotary press for maximum operator safety in large-scale series production.

2004
Fette Compacting becomes the first manufacturer of tabling machines to offer complete high-containment solutions up to OEB Level 5.

2005
ISPE issues SMEPAC (Standardized Measurement of Particulate Airborne Concentration) – an international guideline on gauging particulate contamination.

2015
Expanded regulations in the EU GMP Guideline up the requirements for protection against contamination (toxicological assessment, prevention of cross-contamination).

The key issue for production and forms the focal point of this issue of What’s Next. The timeline below shows you how containment technology has developed and how Fette Compacting has contributed to milestones.
CONTAINMENT IN 2025

Trends in the manufacturing and processing of high-potency active pharmaceutical ingredients

Containment technologies have progressed in leaps and bounds over the last few decades. At the same time, operator protection requirements have risen due to new, highly potent and highly hazardous active ingredients.

Richard Denk analyzed what that means for future technological developments as part of an expert group set up by the International Society for Pharmaceutical Engineering (ISPE). A look at the future of containment.

**By Richard Denk**

I have been passionate about containment for almost 20 years. I first came across the subject at an ISPE conference in the USA in 1996. Some time later, I became an active member of the US ISPE Containment Group, which I subsequently co-chaired for several years. During this time, a number of fundamental ISPE guidelines were initiated, such as the Standardized Measurement Of Equipment Particulate Containment (SMEPAC) covering maximum levels for containment systems. In 2008, the time was right to set up a regional ISPE containment group for Germany, Austria and Switzerland. I have been chairing this expert group ever since – something I love doing.

**Three major containment trends**

Containment technologies have developed more and more over the last 20 years. New technologies for safe and efficient pharmaceutical production have constantly emerged. But will the last 20 years of such low limits.

1. **Process-integrated containment** will replace adapted containment. The production process will merge with containment. This will enable optimum containment production with the smallest possible footprint. As a consequence, there will be fewer contaminated surfaces, resulting in considerable advantages for cleaning and refitting. Should it become possible to create a small, self-enclosed clean room inside the containment area, the GMP environment for this process could also be simplified. There have already been several initial developments along these lines – for example in the packaging of tablets and capsules.

2. **Single-use systems** will be another focal point over the next ten years. Disposable technologies have a major advantage in that the manufacturing process can be adapted quickly and easily to containment requirements. These systems offer the greatest advantages for relatively small production quantities and the field of research and development. Single-use technologies are also worth considering if the product being manufactured changes frequently or highly flexible process management is needed. Examples of such systems include disposable liners and single-use isolators for transportation and pharmaceutical processing of highly potent substances. The biotech industry is also increasingly replacing stainless steel systems with single-use technologies.

3. **Continuous manufacturing** will play an important role for the production of high-potency or highly hazardous active pharmaceutical ingredients. Continuous manufacturing has a number of advantages over batch production: the process equipment is more compact, meaning it has a smaller surface to be cleaned. The processes are also linked with one another or several process stages are completed by a single machine. This makes for fewer containment interfaces.

We will continue to examine these trends in depth within the ISPE Containment Expert Group over the coming years.

**Food for thought: containment pyramid and handbook**

When I developed the containment pyramid about 15 years ago (see diagram), it had five levels with corresponding limits. Now, some of the substances in use are so highly potent or highly hazardous that we have added a sixth tier. This category is for products with a maximum particulate contamination level of less than 200 nanograms per cubic meter. Even more efficient containment systems will be needed in the future to comply with such low limits.

We compiled our latest containment findings in the ISPE group and used them to develop a containment handbook specifically for pharmaceutical production. The book will be available from ISPE from late September 2015. It is designed to serve as a guideline and reference work for users in the pharmaceutical industry on all containment issues – from the basics to system life cycles.

Personally, I have no doubt that there are many more changes to come in the field of containment over the next 10 years. It will be interesting to see how things develop.

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**The production process will merge with containment. This will enable optimum containment production with the smallest possible footprint.**

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**Richard Denk**

Chair of the ISPE Containment Expert Group (Germany, Austria, Switzerland), Containment Sales Manager at SKAN AG, author at Maas & Pfletter GMP-Verlag

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**THE CONTAINMENT PYRAMID**

<table>
<thead>
<tr>
<th>OEL</th>
<th>Occupational exposure limit (maximum particulate contamination in the air operators breathe in the production room, measured in µg/m³)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>extremely toxic</td>
</tr>
<tr>
<td>5</td>
<td>highly toxic</td>
</tr>
<tr>
<td>4</td>
<td>toxic</td>
</tr>
<tr>
<td>3</td>
<td>slightly toxic</td>
</tr>
<tr>
<td>2</td>
<td>practically nontoxic</td>
</tr>
<tr>
<td>1</td>
<td>nontoxic</td>
</tr>
<tr>
<td>1,000–5,000</td>
<td>Level of active pharmaceutical ingredients (maximum amount of API per day, measured in mg/day)</td>
</tr>
<tr>
<td>54</td>
<td></td>
</tr>
</tbody>
</table>

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**OEB | Occupational exposure band (hazard class based on the toxicology of the pure active ingredient)**

| 6 | extremely toxic |
| 5 | highly toxic |
| 4 | toxic |
| 3 | slightly toxic |
| 2 | practically nontoxic |
| 1 | nontoxic |
| 1,000–5,000 | Level of active pharmaceutical ingredients (maximum amount of API per day, measured in mg/day) |

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THE KEY TO THE RECEPTOR
The effects and processing of highly potent substances

It is hoped that highly potent substances will make it possible to develop new therapies. Countless scientists are currently researching such high-potency active pharmaceutical ingredients (HPAPIs). In this interview, expert Prof. Dr. Karl G. Wagner explains the potential that these minute particles hold and the challenges faced by researchers.

Prof. Dr. Wagner, what makes an API highly potent?
Two aspects need to be considered when answering that question. One is the desired effect of a drug within the body. In this respect, a substance is considered highly potent if it is biologically effective at a dose of no more than 150 micrograms per kilo of body weight. The other aspect is operator exposure during pharmaceutical processing, which is defined in the OEL figures. In this context, APIs with a workplace concentration of 10 micrograms per cubic meter of air or less are rated as highly potent.

Which therapies are highly potent substances used for?
There are substances that are effective at extremely low doses in every therapeutic area. However, key application areas include highly toxic cytostatic drugs for cancer therapies and hormones for contraception, HRT, and numerous other uses.

What is the significance of HPAPIs for new drugs?
Due to their genesis, new API molecules are becoming more and more selective and active. This is also necessary, so that manufacturers can develop drugs that offer an advantage over the existing standard therapy, which is crucial for them to be approved.

Which fields of research are driving the development of high-dose drugs?
As the biochemical processes in the body are very well understood, we now know where most receptors – the targets for drug therapy – are located. The high-potency approach came about because we are increasingly able to design the right molecule keys for the receptors with the help of computer-aided simulations. After all, there is a key for each receptor which fits that particular lock perfectly. A picklock might work too, but this is more of a rough and ready approach which won’t operate the lock mechanism so smoothly. In the field of solids, however, we still often face the problem of low bioavailability when high-potency substances are administered orally.

What causes this low bioavailability?
Due to their high receptor affinity, most new chemical entities (NCEs) have low water solubility, which limits their absorption in the gastrointestinal tract. In this case, suitable formulation concepts need to be found. New biological entities (NBEs) suffer from another problem: our bodies are programmed to break down proteins and peptides as food. Outwitting this program is very complicated.

How can this problem be solved in solids production for biopharmaceuticals?
Personally, I think it might be possible to protect the protein by encasing it. Simply coating a tablet is not enough though. The substance needs to be made of into extremely fine particles – just a few micrometers or even nanometers. These then have to be used to generate miniparticles, which need to be encapsulated to protect them from enzymes and stomach acid. The casing also has to have an affinity with the mucous membrane in the intestine so that the particle can embed itself there in a targeted fashion and the active ingredient can penetrate the wall of the intestine. Scientists are already able to produce such particles. The challenge lies in finding the right shell. It is particularly difficult to subsequently put the particles in a solid form that enables them to disperse again as effective individual particles following administration. A lot of research still needs to be done here in the coming years and decades.

How is knowledge shared with pharmaceutical manufacturers?
There’s still a huge gap here. In my view, it would be constructive for pharmaceutical manufacturers to set up a cross-industry initiative to statistically analyze toxicological data with safety factors, OELs, and data from occupational health investigations. This would enable researchers and users to interact much better and tackle current challenges more effectively.

Main areas of research:
- availability-optimized dosage form, the influence of individual substances’ and mixtures’ compression properties on granulate and tablet properties (including customized tabletting systems), simulating processes for tabletting and extrusion

Receptors on the cell membrane trigger specific reactions inside the cell. High-potency APIs are designed to fit the relevant receptor precisely and achieve the desired effect.
EFFICIENT IN CONTAINMENT

Tablet presses for processing toxic substances

The trend towards high-potency APIs in drug manufacturing is having a knock-on effect on the tableting process. There is growing demand for containment systems to guarantee high safety standards for operators and products alike. So what are the associated requirements and which system is best suited to what type of production?

More and more tablets contain highly potent APIs. Modern processes such as hot-melt extrusion can be used to bind the substances to form powders or granulates and press them into tablets. Following administration, the formulations release a precise dose of active ingredients in the body. Two trends are emerging: one towards orodispersible tablets, which dissolve in the mouth, and the other towards delayed-release preparations that deliver active ingredients into the gastrointestinal tract.

“High-potency drugs make the greatest demands on the tableting process,” explains Jörg Gierds, Head of Product Management at Fette Compacting. “A tablet press has to compress powders and granulates safely and efficiently. We have therefore defined the following objectives for the associated containment components: no release of dust during production or preparations for cleaning, no contact with toxic products, a waterproof and dust-tight compression chamber, and maximum operator safety throughout the entire production process.”

Integrated containment from filling to washing

To achieve these objectives, containment solutions need to be integrated into the process and not concentrated on individual machines. Every technical interface needs to be designed to ensure that all the connections from end to end are sealed. For example, the docking system used for powder or granulate filling should be fitted with double-flap valves so that no dust can escape. The compression chamber itself must also be completely sealed. Fette Compacting has developed an enclosed compression chamber with inflatable seals for this purpose, which prevents even the tiniest dust particles from being released.

The tableting process should be as fully automated as possible. Ideally, there should be no intermediate manual steps – and therefore no break in the containment – between the filling of the machine and the removal of the tablets. However, in the case of machine stoppage, operators must have manual access from every side of the tablet press without breaking the containment. Glove ports in the window flaps are the most important means of ensuring this.

Even after production, containment tablet presses pose special challenges for both operators and technology. In the case of enclosed facilities, all of the components must be individually logged and washed using a program. With WiP and containment tablet presses from Fette Compacting, washing programs can be configured and saved for specific products. An automated washing process and easy handling of the machine components can save tablet manufacturers a lot of time.

Operator protection from conventional tablet presses to high-containment units

The class of containment tablet presses caters for three levels of toxicity. Single rotary tablet presses can be used to safely compress substances with a low level of toxicity up to OEB Level 3. WiP/containment tablet presses with standard process equipment are needed for toxins up to OEB Level 4. Highly toxic substances up to OEB Level 5 have to be processed using a WiP/containment tablet press with complete containment and integrated process equipment. You can find information about the different machine specifications on the opposite page.

FE55 NOW AVAILABLE WITH OPTIONAL CONTAINMENT PACKAGE

Users can mass-produce more than 90 percent of all products with the FE55 high-performance rotary tablet press. From now on, that also includes all toxic APIs with particulate contamination levels of 10 to 100 µg/m³ because Fette Compacting is offering the FE55 with optional containment components such as RTP access, glove ports, and simple parameter control via the machine terminal.

Toxicity level: slightly poisonous poisonous highly poisonous

<table>
<thead>
<tr>
<th>And maximum active material level (AML)</th>
<th>Painkillers, hormones</th>
<th>Painkillers, hormones</th>
<th>Cytostatic agents, hormones</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maximum dust contamination (OEL)</td>
<td>10 - 100 µg/m³</td>
<td>1 - 10 µg/m³</td>
<td>&lt; 1 µg/m³</td>
</tr>
<tr>
<td>Maximum active material</td>
<td>1 - 10 mg/day</td>
<td>0.1 - 1 mg/day</td>
<td>&lt; 1 mg/day</td>
</tr>
<tr>
<td>Machine type</td>
<td>WIP tablet press, washable, and FE55 with containment package for conventional cleaning</td>
<td>WIP/containment tablet press and standard process equipment</td>
<td>WIP/containment tablet press with complete containment and integrated process equipment</td>
</tr>
<tr>
<td>Machine equipment</td>
<td>For WIP presses:</td>
<td>For FE55 with containment package:</td>
<td>For FE55 with containment package:</td>
</tr>
<tr>
<td></td>
<td>- washable tablet press</td>
<td>- butterfly valve for secure product feeding</td>
<td>- washable tablet press</td>
</tr>
<tr>
<td></td>
<td>- changeover of the die table package</td>
<td>- hermetically sealed and lockable window flaps</td>
<td>- changeover of the die table package</td>
</tr>
<tr>
<td></td>
<td>- automatic emptying of the filling equipment</td>
<td>- RTP accesses for removal of components or tablet samples</td>
<td>- automatic emptying of the filling equipment</td>
</tr>
<tr>
<td></td>
<td>- no internal coverings</td>
<td>- dust-tight tablet outlet</td>
<td>- no internal coverings</td>
</tr>
<tr>
<td></td>
<td>- encapsulated system</td>
<td>- H13 HEPA filter</td>
<td>- encapsulated system with gloveports for operations on the tablet press</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- no contamination with toxic products</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- high safety during cleaning</td>
</tr>
<tr>
<td></td>
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<td></td>
<td>- access to the compression compartment via a rapid transfer port system (RTP)</td>
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<td></td>
<td></td>
<td></td>
<td>- high safety during cleaning</td>
</tr>
</tbody>
</table>

Available tablet presses

| 2090i WIP | 2090i WIP/containment | 2090i WIP/containment |
| 3090i WIP | 3090i WIP/containment | 3090i WIP/containment |
| FE55 with containment package | FE55 with containment package | FE55 with containment package |
TOTALLY SEALED

Containment components for tablet presses

All the components of a plant must be matched to one another in order to reliably press highly active materials, and the transfer points must be totally sealed. The following examples illustrate which containment solutions have proven themselves in the tableting sector.

SPLIT BUTTERFLY FLAP
A split-flap system allows a safe supply of material and filling of the tablets. Operators can attach material containers and remove them later without causing contamination. The contaminated side of the flap is supplied with water and fully cleaned by the WiP center.

RAPID TRANSFER PORT (RTP)
A quick transport-connection system is the basis of fast, repeating transfers. The RTP allows, for example, operators to bring tableting tools reliably into the tablet press and exchange them. A hollow section seal between the RTP and the window flap ensures that the containment is maintained.

GLOVEPORTS
Manual access from every side of the tablet press must be possible without compromising the containment. Gloveports in the window flaps are essential for this purpose. Automatic monitoring protects the operators here, and stops the tablet press whenever it is accessed. Thanks to the double seals, it is also possible to replace the gloves without contamination.

WIP-CENTER
The WIP center supplies the tablet press and the process equipment with water, cleaning agent and with air for drying. Up to 5 systems of a containment installation can be cleaned simultaneously. A combination of membrane valves and orbitally welded supply lines guarantees a hygienic cleaning process.

WINDOW FLAP SEALING
The tablet press must be completely sealed as from OEB Level 3 upwards. Fette Compacting has developed an encapsulated compression compartment with inflatable seals that prevent the release of the tiniest particles for this purpose. Automatic monitoring of the locks provides additional safety.

ISOLATOR
An isolator guarantees maximum safety for the operating personnel. The full implementation of the isolator comprises three modules: a Checkmaster for the in-process monitoring, an upwards deduster for GMP-conform dedusting, and a metal detector for removing tablets with metal contamination. Operators can supervise all of the process equipment through the machine terminal.

AIR MANAGEMENT
A software-controlled air management system is needed for optimum air cleaning in containment installations. Air Management from Fette Compacting has a vacuum emergency system for the event of a malfunction in the production equipment. Even if the controller fails, the system prevents the production room from being contaminated.

AUTOMATED WASHING
In an encapsulated plant, machine components that have come into contact with the product must be cleaned by a washing program. The WIP and Containment tablet presses from Fette Compacting can be configured – and the configuration saved – for specific products. This special rotating spray nozzle design makes sure that the cleaning agent reaches into all parts of the pressing cell.
Sexual hormones control complex biochemical processes in the body. They are used as highly active materials in a large number of medicines. The pharmaceutical processing of the hormones raises serious challenges for the protection of operatives. The pharmaceutical manufacturer DR. KADE is using a 1090i WiP Containment tablet press from Fette Compacting for maximum process safety. An inside view of production illustrates what is important to pharmaceutical manufacturers.

Christian Franke, Production Manager at DR. KADE

In Constance, set up exclusively for processing hormones under containment conditions. „In Constance we are focusing on customized containment”, explains Christian Franke, Production Manager at DR. KADE. „With the right equipment we can meet statutory safety requirements, give our staff all-round protection, produce efficiently and react flexibly to changes in product demand.”

From the contraceptive pill to hormone replacement therapy

Occupational safety has top priority when processing sexual hormones. Franke explains the safety regulations and technical requirements that apply to the work at DR. KADE: Our tablets contain estrogen and progestagen. The lowest dose is 30 micrograms per tablet. In our own risk assessment, the workplace limit values for the female sexual hormones that we use were defined as being from 0.04 up to 5.21 micrograms per cubic meter of air. That means we are working in the range from OEB 4 to OEB 5. This means that a classic clean-room solution is no longer adequate. On top of this, we need an isolated installation with consistent containment.”

In 2010, DR. KADE purchased a single rotary press of the 1090i WiP/Containment type from Fette Compacting for the manufacture of solid products. „Since then, the tablet press has been used exclusively for processing estrogen and progestagen into prescription-only medications,” said Franke. „The active materials are mainly used for contraception. In addition to this, we use the Fette Compacting equipment for hormone replacement therapy preparations for the menopause. These tablets contain estrogen and progestagen, which alleviate menopausal symptoms.”

Contraception is one of the most important applications for solid medications with sexual hormones.
Safe tabletting and fast product changeover
For safe production up to OEB Level 5 the tablet press at DR. KADE is fitted with Wash-in-Place (WiP) technology, air management and process equipment in the isolator. A system with split valves makes it possible to feed in material without contamination, and reduces the risk of cross-contamination. Operatives can access the compression compartment through integrated gloveports and RTPs (Rapid Transfer Ports) in order to change tools without breaking the containment. In addition, a combination of exchangeable segments and automated cleaning mean that the tablet press facilitates fast product changeover.

Franke emphasizes that, „Since we operate a number of product lines on the machine, fast refitting is an important criterion for us“. „Fitting up the equipment is always associated with prior cleaning in our procedures. A start is made with the preliminary and main cleaning in the closed containment zone. Only then do we open up the tablet press, do any additional manual cleaning that might be needed, and dismantle the parts that are no longer required. After passive drying, we re-fit the plant, disinfect those parts that come into contact with the product, and re-establish the containment.”

Sustained quality management
DR. KADE also makes use of the service and training options from Fette Compacting in pursuit of sustained quality assurance. Franke then gave this explanation: „From our point of view, the containment plant makes complete commercial sense. To profit from this for as long as possible, we regularly make use of Fette Compacting’s services for maintenance, operative training and consultation on plant optimization. We are very happy with this total package.”

In total the active refitting calls for about six hours. For a high-containment operation, we are therefore very efficient.

Christian Franke, Production Manager at DR. KADE

Functional Design Specification: The requirements specification describes the concrete steps required to implement the customer’s requirements. It is the response to the requirements previously defined in the User Requirements Specification (URS).

Factory Acceptance Test: In the case of a factory acceptance test, specialists inspect and document, amongst other things, the scope of supply, the safety functions of the tableting/containment system and conformity with GMP guidelines.

Site Acceptance Test: The components are matched to one another one more time during acceptance at the installation site. The service technicians adjust the measuring locations and check all the documentation.

Installation Qualification: Every detail of the hardware and software is on the test bench during installation. In the case of highly complex control processes, the validation of the computer software is documented separately (Computer System Validation, CSV).

Operational Qualification: Following installation, the inspection of qualified operation verifies that the system operates properly within predetermined limits, and that the FDA requirements and the Code of Federal Regulations 21CFR Part 11 are fully satisfied.

Performance Qualification: After the IQ and the OQ, specialists in cooperation with the customer check the product-relevant function in the course of tests with the customer’s product. In this way they show that the process is under control, and finally that the quality of tablets coming from the machine is always the same.
Continuous manufacturing has for long been standard in sectors such as the petrochemical and the food industries. Drugmakers are now also increasingly moving away from batch production and going over to continuous manufacturing. A comparison of the two approaches shows the potential to be found in the continuous manufacture of medications.

Batch-oriented versus continuous production

The challenge: pharmaceutical manufacturers need to say goodbye to established processes on the path to continuous production. Until now their work has been almost exclusively batch-oriented. This involves the starting material being brought in at the beginning of each partial process, and the respective product removed at the end. In continuous production, on the other hand, the supply of starting material and product removal occur simultaneously. A change of this sort requires new approval processes as well as the increased application of automation and analytical techniques. Some users feel that the associated investment is at present still too high. „However,” explains Dr. Steffen Wehlte, Sales Director Global Accounts & EMEA at Fette Compacting, „the advantages far outweigh the problems. The experience of international customers has shown that production times with continuously operating plant can be shortened enormously. One advantage, for example, is that manufacturers can use one and the same plant for development and for production. This means that scale-up can achieved up to ten times more quickly than in the past. Plant availability rises, and producers can react more flexibly to changes in the demand for medications. “

In continuous production, on the other hand, the tablet press is integrated into the total process. In the continuous sector, the trend is moving towards our smaller tablet presses, which can be refitted flexibly and can be integrated in to the plant optimally. It might even be the case that in future the tablet press cannot be recognized as such straightaway – it will be optimally integrated.”

CONTINUOUS MANUFACTURING

Example of continuous tableting

Perfectly integrated: the tablet press in the continuous process

Many manufacturers in the tableting sector are converting their processes to continuous medication production. They are integrating the classic, individual batch processes bit by bit into one total process. „What we often find in practice is that we are dealing with hybrid forms, somewhere between pure batch processing and pure continuous tableting,” explains Dr. Wehlte. „Users are moving in the direction of combining the stages of granulating, compacting, pressing, coating and packaging. As leading global specialists in tableting, it is our job to offer an effective technology and a comprehensive service for this part of the process. “

As Dr. Wehlte explains, the new understanding of the process also has an effect on the role of the tabletting technology: In most production facilities for solid dosages, it is still the case that the tabletting press represents the technical heart. Other parts of the plant are arranged around it. In continuous production, on the other hand, the tablet press is integrated into the total process. In the continuous sector, the trend is moving towards our smaller tablet presses, which can be refitted flexibly and can be integrated in to the plant optimally. It might even be the case that in future the tablet press cannot be recognized as such straightaway – it will be optimally integrated.”

Related processes: Continuous and containment

Continuous production is also suitable of processing highly active substances. In continuous production and content production alike, materials are processed in compact, closed units. The interfaces that connect the productive sections to form an integrated total process are crucial in both cases. What the pharmaceutical industry must still work on in the future is a comprehensive monitoring strategy for secure continuous production. In addition to classic parameters such as in-process control, it is of primary importance to consider the flow of material within the processes. According to the FDA recommendation, users should also consider the effect of possible instabilities within individual partial processes on the process as a whole. In the end it is important to be able to answer a clear „yes” to the question, „Is my process in a controlled state?”

Continuous manufacturing is blazing a trail in the pharmaceutical industry. This was made clear recently in the spring of 2015 by the „Pharma 2025” expert conference held by the International Society for Pharmaceutical Engineering (ISPE). One insight from the meeting is that continuous production of solid pharmaceuticals has broken away from just research and planning, and is finding its way into production facilities. The first pharmaceutical manufacturers have already grouped process steps together that previously had been carried out in separate batches.

The innovators have been encouraged by the Food and Drug Administration (FDA) amongst others. The authority sees significant advantages to process safety, product quality and cost efficiency in continuous production of pharmaceuticals.

Global Accounts & EMEA at Fette Compacting, “the advantages might even be the case that in future the tablet press cannot be recognized as such straightaway – it will be optimally integrated.”

The science and the pharmaceutical engineering are, in the view of the FDA, sufficiently mature to implement continuous production.
**NEW OPENING**

Fette Compacting opened a new service center in Basel on 1 May 2015. Customers in Switzerland and in south Germany can therefore count on fast, uncomplicated assistance with any questions related to tableting. The services range from commissioning and calibration one through to inspection and repair.

**NEW SERVICE CENTRE IN SWITZERLAND**

Lars Plüschau, Manager of Global Customer Support at Fette Compacting explained that, “With the new service company, we are fulfilling a long-cherished customer wish. This is something important to us, because projects with Swiss pharmaceutical companies have increased over recent years. The increased demand extends through to highly complex installations with WIP and high-containment equipment.”

**GLOBAL EXCHANGE: SYMPOSIA WITH EXCELLENCE UNITED**

Fette Compacting and four other specialist machine and installation manufacturers have, since 2011, formed the Excellence United Alliance. Starting in 2012, Excellence United has offered symposia round the world at which it transmits its many years of experience in the value-creation chain of medical products and pharmaceutical production. The Alliance recently met with its customers in South Africa.

37 experts from Excellence United met in Johannesburg on 26 March. The governing theme of the symposium was the “Installation and Modernization of Local Production Facilities according to the Latest GMP Standards”. In between the individual presentations from speakers from Excellence United, participants had an opportunity to compare notes with one another about their experiences on the challenges faced in practice. The next symposium will take place between 2 July and 3 July in Mexico. Further symposia are planned in Turkey and India for the second half of the year. You will find up-to-date information at www.excellence-united.com. We would be pleased to receive your suggestions by email at info@excellence-united.com.

**A NEW MEMBER OF THE P SERIES**

The latest member of the P series made its first appearance in the world in May 2015 at the China International Pharmaceutical Machinery (CIPM). The P1010 tablet press has been fully redesigned from the bottom up, and is specially aimed at the production of small batches.

Fette Compacting has completed its successful P series with the P1010. The single rotary press can produce a maximum of 234,000 tablets per hour, passing a new milestone in the development of Fette Compacting’s international network. The new tablet press was developed jointly by a German-Chinese team. Like the other machines of the P Series, the P1010 satisfies all the GMP requirements. The company has to date installed several hundred type P2020 and P3030 machines around the world, almost 70 percent of them in China.

**FOUNDING OF THE LMT GROUP ACADEMY IN CHINA**

In March 2015 the LMT Group Academy at Nanjing opened its doors to employees and customers in China. Specialists from Fette Compacting and LMT Tools, together with external trainers, convey up-to-date knowledge of techniques and processes. This new branch further expands the LMT Group’s range of training courses, seminars and conferences in the Asian region. The LMT Group plans to develop an academy in India as the next step.