Integration is a challenge for the industry. Many equipment manufacturers have only one piece of the jigsaw but for continuous manufacturing you need to have all the pieces not just fitting together but talking to each other.

Tablet manufacturing provides quite a good example and is also the process where many pharmaceutical companies are choosing to pilot continuous manufacturing. In a traditional batch approach, tablet manufacturing is really a series of disconnected single unit operations, installed in separate rooms, with product waiting to be released to the next process step in another room. The equipment is isolated and the automation solutions are often so-called Islands of Automation.

With continuous manufacturing of tablets, an in-line/on-line quality measurement by means of a process analytical technology (PAT) tool would control the critical process parameters determining the quality attributes that allows automatic release for the product to move from one process step to the next. It is important that the equipment is completely interconnected hardware-wise, but also that there is one user software interface to operate the hardware as one line. As a single operator would be able to operate the line, a uniform look and feel, uniform alarming concepts, and central recipe management, among others, are a must.

But many equipment manufacturers sometimes focus on only one aspect of the process. They might, for example, have a solution for continuous coating or for tablet pressing, but they don’t design it in a way that integrates with the equipment that precedes it and the one that comes next in the line. They depend on the HMI to operate and control the single-unit operation, independent from predecessor or successor equipment in a continuous manufacturing line topology.

The separate devices need to be integrated and the interdependencies and data flows between them understood and controlled. Siemens’ SIPAT and SCADA (supervisory control and data acquisition) systems provide an integrated and data-driven control platform that can cover all of the requirements for continuous manufacturing. The SIPAT data management platform integrates all the PAT tools that are necessary for continuous manufacturing into one overall platform. This allows companies to orchestrate feed-forward,
feed-backward controls over the different unit operations in the whole line.

In addition, as well as the SIPAT software, Siemens can provide much of the on-the-line automation hardware and integrate this into the Siemens SCADA system to track the material mass flows over the complete manufacturing line.

Siemens has developed considerable experience of utilising these systems in a variety of continuous manufacturing development environments and with different pharmaceutical and OEM partners. According to one pharmaceutical partner, a project like this takes a lot of trust in their partners. But because of this, the technology has improved tremendously within the last three years, and today, has been the most integrated solution on the market.

The prize for companies is considerable. Small, fully enclosed processes, with a high level of automation and reduced manual intervention will enable companies to reduce variability, deliver high yields, increase profitability and lower operating, inventory and capital costs. Facilities are less costly to build and 100% of capacity is utilized when they are in operation. A major part of the savings come from not having to take batches to the laboratory for analysis, which can shrink the time taken getting the product to the patient from a few months to something in the order of less than 10 days.

**Increasing Sustainability**

Apart from saving time and costs, continuous manufacturing can dramatically reduce building, energy and carbon footprints. For instance, an oral solid dose continuous manufacturing unit developed by Siemens with a leading pharmaceutical company occupies a space that is just a tenth of what is needed for traditional batch process equipment. The continuous tablet making unit can be easily fitted into a regular room.

These considerations, together with less waste and more recovery, mean that continuous manufacturing offers companies the opportunity to increase their sustainability by delivering more energy-efficient operations and reducing their carbon footprint.

**Transforming Drug Manufacturing**

In 2009, the British Technology Strategy Board-funded initiative called SPRINT (Secondary Process Intensification) was formed, aimed at improving the performance and quality in pharmaceutical drug manufacturing through continuous processes. The project involved GlaxoSmithKline (GSK); GEA Pharma Systems, as a supplier of pharmaceutical process technology and integrated manufacturing systems for material handling, granulation, drying, and compression; Siemens, as a supplier of process automation and information technology; the Warwick University as the provider of the facility layout; and the Newcastle University as a contributor to process optimization and modelling.

Secondary manufacturing processes typically suffer from low equipment utilization, are labour-intensive, and are based on a process setup that requires extensive release procedures. This is particularly true of oral solids dosage (OSD) manufacturing, which is characterized by high inventory requirements, long changeover times, disconnected processes, high process losses, and low asset
utilization. Additionally, the product quality is ascertained in postproduction analysis, which means that it can take as long as two months for a batch to be released.

Accepting the challenge, the partners provided a proof of feasibility (PoF) for a continuous manufacturing unit with real-time-release capability. A key factor in it was a suitable Process Analytical Technology (PAT) and automation solution, which Siemens provided through its SIPAT.

The test plant that was set up for the PoF consists of equipment for granulation, drying, milling, blending, and compression. The automation solution consisted of two Simatic S7-300 controllers. One CPU controlled the granulation, drying, mill, and blending processes; while the tablet press from GEA Courtoy was controlled by the second S7-300. The signals in the field were collected via Simatic ET 200 systems, while the Simatic WinCC was used as the line visualization system.

Siemens’ SIPAT software collected and evaluated quality- and performance-related process parameters in the process steps, such as loss on drying or particle size distribution. These parameters were transmitted to the Simatic IT manufacturing execution system (MES) for real-time-release reporting. The real-time-release reports were generated via the Simatic IT Report Manager and provided drill-down functionality down to individual parameters.

The PoF started in August 2009 and was completed in February 2010, with the GEA test plant in Wommelgem producing tablets reliably, continuously, and with excellent quality.

One of the noticeable benefit of the plant is its much smaller footprint (10 times less than conventional batch units), which minimizes investment in clean-room space and saves tremendous amounts of energy in maintaining clean conditions.

According to the partners, the results exceeded their expectations, and that they were able to prove that continuous manufacturing can reduce the process development time tremendously. For instance, it only took less than two weeks for them to develop a process for a new tablet. They also said that the real-time release enabled by in-process quality control alone makes a strong case.

By introducing continuous manufacturing capabilities in drug manufacturing, experts said the pharmaceutical industry can significantly improve its processes. Among the main benefits are increased equipment efficiency; savings in space, construction, and energy; scalability improvement in time-based process; better process understanding; reduction of raw material and energy usage; reduction of scrap, waste, and rework; and reduction of human interference – which would also result in lower costs of operations and improved safety.

Based on the above results, GSK brought the new technology into its real-world manufacturing, investing £10 million into a new production line which is now up and running.

In recognition of their efforts in radically changing the manufacturing of pharmaceuticals, GlaxoSmithKline, alongside project partners GEA, Siemens, Sagentia and the Universities of Newcastle, Warwick and Surrey, won the Outstanding Achievement in Chemical Engineering Award as well as the Chemical Engineering Project of the Year Award at the IChemE 2012 Awards – a testament to the benefits of continuous manufacturing. PA

Ivo Backx is Siemens’ manager of business and project development for the pharmaceutical industry.