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Europe Leads the Way in Continuous Manufacturing

The shift toward continuous manufacturing among European pharmaceutical manufacturers has not been accompanied by a similar strong increase in the use of automation and sensor-based on-line monitoring.
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Continuous manufacturing is increasing rapidly in Europe's pharmaceuticals sector after expanding only slowly for several years. In 2016, Europe had—at 35%—the largest share of world pharmaceuticals output through continuous processes, according to a report by Transparency Market Research (TMR), Albany, New York, on the global continuous manufacturing market, which it forecasts will grow by a compound annual growth rate of 8.8% in 2017–2025 (1).

Automation and digitization

TMR expects Europe to retain its leading position as it maintains an above average growth rate, mainly due to the availability of advanced technologies and the greater number of technology providers in the region, led by Siemens AG of Germany. The rise in the introduction of continuous manufacturing technologies, however, has not been accompanied by a similar strong increase in the use of automation, or in particular, the adoption of digitization through the application of sensor-based on-line monitoring. The industry in Europe appears to be holding back from introducing advanced digitalized measuring equipment, data analytics, and advanced automated controls to raise the efficiency of its manufacturing practices. There has, for example, only been cautious use of automated real-time release testing (RTRT) for on-line or in-line measuring and controlling of the quality and specifications of medicine components.

"A number of manufacturers have implemented use of instrumentation such as near infrared (NIR) or Raman spectroscopy for gathering information on processes, and in the case of active substance manufacture, for determining reaction end points," explains an official at Ireland's Health Products Regulatory Authority (HPRA), Dublin, in an interview with *Pharmaceutical Technology Europe*. "However, not many have implemented these as fully operating real-time release systems," he adds.

Regulatory hurdles hinder adoption of new technologies

Ireland is one of Europe's major centres for pharmaceuticals production with nine out of 10 of the world's leading drug companies having operations there. A priority in its current strategy from 2016–2020 is to encourage new technologies such as digitization and the Internet of Things (IoT). Despite initiatives by most regulatory agencies across Europe to encourage pharmaceutical companies to introduce continuous manufacturing and automation technologies, many producers are deterred by the need to obtain regulatory approvals for the installation of digital equipment and systems.

"The introduction of any in-process sensors as part of the control strategy will need to be appropriately supported and approved prior to implementation," says a spokesperson for the United Kingdom's Medicines and Healthcare products Regulatory Agency (MHRA). "It is also normal practice for, where relevant, submission-specific manufacturing site inspections to be carried out as part of the review process, [which] would involve both assessors and inspectors."

Pharmaceutical companies complain that in Europe, in particular where post-marketing changes or variations to processes are mainly approved at the national level, there are too many inconsistencies in the way authorization decisions on the changes are applied. The Parenteral Drug Association (PDA) announced in July 2017 that a survey of its members on the impact of national-level post-approval changes showed a 97% belief that the regulations on variations were hurting innovation and holding back technological progress (2).

"It is not so much that the European regulations on variations are prohibitive," Ursula Busse, a European-based quality regulations specialist and member of the PDA board of directors, told *Pharmaceutical Technology Europe*. "A lot depends on the way they are implemented."

PDA has been urging that more use be made of the concepts behind the pharmaceutical quality system (PQS) put forward by the Geneva-based International Council for Harmonization (ICH) to be applied throughout a product's lifecycle along with good manufacturing practice (GMP) requirements. In today's pharmaceuticals market, post-marketing changes to processes are inevitable, PDA contends, therefore, adherence to PQS principles should be used as a possible means to reduce the need for approval of variations.

Gaps in existing regulations

Another concern for drug companies is that fast advances in technologies, especially in automation and digitization areas, are leading to gaps in existing regulations. "There does not need to be new regulations but rather a reshaping of existing regulations and guidelines," Busse said.

Pharmaceutical companies are worried about the interpretation of regulations by the

regulators themselves; the regulations have failed to keep pace with the new technologies, especially those based on the collection of vast quantities of data from automated equipment and sensor systems.

“Ten years ago, only limited amounts of process control data could be captured, processed, and analyzed,” Peter Behner, leader of the pharma life sciences sector in Europe at the PwC consultancy Strategy&, told *Pharmaceutical Technology Europe*. “Now huge amounts of it can be stored and analyzed,” he continued. “Furthermore, it can be stored and updated in a permanent, automatic process. This needs to be reflected in guidelines.” Revisions of guidelines can, however, take several years after allowing for multiple drafts and public consultations. As a result, new versions of guidelines could be technologically out of date by the time they are finally published.

The basic concepts governing regulations and their implementation for quality controls and management in pharmaceutical manufacturing are laid down in three International Council for Harmonization (ICH) guidelines—Q8 and its revisions, Q9, and Q10 (3–5). ICH Q8 covers pharmaceutical development, Q9, quality risk management, and Q10, PQS. A fourth guideline, ICH Q11 (6), gives guidance on the production of drug substances in line with advice in Q8–10.

A major disadvantage of the ICH Q8–10 guidelines is that, although accepted by both industry and regulators as still being highly relevant to today’s manufacturing trends, they were drawn up more than five years ago before automation and digitization began to make inroads into life-science sectors such as pharmaceuticals. Also, the guidelines were mainly focused on the creation of quality controls during the development of processes, whereas the introduction of automation systems, particularly in continuous processing, is likely to take place after a product is commercialized.

ICH Q12 guideline

In line with the policy of regulators in Europe and North America to concentrate more attention on controls in the post-authorization period, ICH is currently creating a Q12 guideline (7) to deal with what it calls a "lack of a harmonized approach on technical and regulatory considerations for lifecyle management." ICH admits that "several gaps exist which limit full realization of intended benefits" of Q8–11, in which the main emphasis has been on the early stages of the lifecycle (7).

"Generally what is and what is not a variation with digitalization/automation is still a bit of a grey area given the early stage of many of the technologies and their adoption." said Marcus Ehrhardt, a life-sciences strategy advisor at Strategy&. "We hope that ICH Q12 expert working group will be much more specific in deciding how digitisation can be used in quality control strategies."

The expert group, including specialists from governments, regulators, and industry, was due to finalize Q12 in the second quarter of 2017, but now it is not likely to be finalized until the middle of 2018 (8). Meanwhile, professional organizations such as PDA and the International Society for Pharmaceutical Engineering (ISPE) have been putting forward their own guidance on automation.

An ISPE group headed by Christoph Herwig, professor of biochemical engineering at the Vienna University of Technology, Austria, published this year proposals (9) for a "holistic" production control strategy that would "address challenges from digitalization and big data management." It would aim to transform today's development-based controls system into one that would meet the quality needs of post-authorization commercial manufacturing.

"Regulatory prerequisites for the [holistic] approach are already in place," according to the ISPE group (9). The guidelines, however, need to be adapted to take into account current technological trends such as Industry 4.0, the fourth industrial revolution driven by automation, IoT, and cloud computing.

FDA and EMA jump onboard

Although European regulatory agencies, headed by the European Union's European Medicines Agency (EMA), have been active in promoting innovation, they have fallen behind initiatives in digitization taken by the United States Food and Drug Administration (FDA). Nonetheless, the two agencies are collaborating on automation and digitization matters. In April 2017, they published a report (10) on a five-year joint pilot programme for parallel assessments of applications containing quality-by-design (QbD) elements. The aim of the project, completed in 2016, was to facilitate consistent implementation by the two agencies of QbD concepts in ICH guidelines. The programme included assessment of RTRT methods and prediction models in continuous manufacturing processes and post-approval issues such as change management. The report concluded that on the basis of the parallel assessments in the pilot, "there is solid alignment between both agencies regarding the implementation of multiple ICH Q8, Q9, and Q10 concepts." As a result, both agencies are "currently exploring potential joint activities with specific focus on continuous manufacturing (and) additional emerging technologies."

"FDA has been more open and progressive about digitization than EMA," Behner said. "But FDA and EMA are working together and both take into account ICH thinking and guidelines. Ultimately, they will be aiming to achieve the same objectives with digitization."

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