# Awash with ideas

The use of water in the manufacturing process is vital to the industry, yet its importance is rarely acknowledged. Ensuring water quality is essential to the quality of the final product and to making sure manufacturing processes are in line with regulations. **Dr John Hutcheson** explains the issues surrounding the use of water within pharmaceuticals, and offers some practical advice.

The use of water in virtually every manufacturing process is of key importance to the pharmaceutical industry; even processes that produce 'solid' products or use organic solvents still rely on water at some stage. Ensuring that a water system consistently and reliably meets the requirements of the pharmacopoeial specifications, the demands of the process and the expectations of regulatory inspectors, is never simple. Combining these demands with the commercial and financial constraints of the current economic environment only makes the task more difficult.

At the start of 2009 two mega-mergers and a takeover were announced. At the end of January, Pfizer announced the takeover of Wyeth, then six weeks later Merck & Co acquired Schering-Plough and Roche took full control of Genentech. Other deals announced included Solvay selling its pharma business to Abbott. The fallout from these changes began to become apparent towards the end of the year, with announcements of job losses. However, it was not just newly merged companies shedding jobs; Johnson & Johnson, Lilly, AstraZeneca and GlaxoSmithKline all announced job cuts. Further cost-cutting seems inevitable. Also, despite the pharmaceutical industry not feeling the full wrath of the global downturn, the crisis is bringing new pressures, which may also lead to cuts.

Another big trend for 2009 was an expansion in interest in emerging markets – particularly pharmaceutical companies setting up research sites in China. Novartis, Pfizer, Bayer Schering Pharma and Merck Serono are all setting up R&D facilities. The recession is also opening up a big gap in output performance between the chemical industries of the developed and developing worlds, which will continue to widen over the next few years. There is also a significant increase in the number of new facilities being built in countries such as India.

A further trend that will continue for the foreseeable future is an increasing focus on the carbon footprint of a product, process or entire facility. Linked with this is the concept of 'embedded water', that is, how much water is used in the complete manufacturing process of a product. This may not sound important but much of the growth in new manufacturing facilities is taking place in locations where there are also already considerable constraints on the availability of suitable water supplies.

Do these trends have any impact on pharmaceutical water systems? The answer to that question is, typically, 'no and yes'.

## Pharmaceutical water standards

Apart from the introduction of Highly Purified Water in the European Pharmacopoeia, the quality requirements for pharmaceutical grades of water have not really changed in more than 150 years. The way the standards are described and measured may have changed but the basic water quality that the standards define has not. For example, the USP Purified Water conductivity specification of 1.3 µS/cm at 25 °C was established based on rigorous calculations that showed that at this level of conductivity the limits of all the 'old wet chemistry' would be complied with. These old test limits had effectively remained unchanged since they were established in the 1800s. With the introduction of instrumental monitoring methods, the various pharmacopoeial standards are coming closer to harmonisation, and with modern system designs, achieving the required standard has become increasingly reliable.

Long before PAT became an acronym, and before the water quality standards were changed, process analytical technologies such as pressure, conductivity and flow measurement were used to monitor and control the operation of pharmaceutical water systems. For example, the specialist instrument supplier, Hach, supplies monitoring instrumentation from well-known brands such as Orbisphere and Anatel for monitoring and controlling pharmaceutical water systems.

## WFI production

There have been no significant changes to the design of Water for Injection (WFI) systems. Multi effect and Vapour Compression (or Thermo-compression) distillation equipment has continued to be developed and improved, but the basic design principles have not changed. In Europe, multiple-effect stills have been the preferred choice for WFI generation for perhaps 20 or more years, but there is an increasing use of vapour compression technology. This may be due to technical advances but if you consider the cost per litre of generated WFI in isolation, then thermo-compression may often be the lower-cost option, particularly in high-volume applications or when the WFI water is required to be cold. Depending on the various site-specific factors, you can get quite different costs per litre for the different generation methods. One interesting point to consider is the requirement for services and utilities; multi-effect distillations require higher pressure plant steam and typically a higher grade of feed water.

## Skid-mounted PW systems

Over the same period there has been a significant change in the design of Purified Water (PW) systems, both in generation and storage and distribution systems. Many PW systems being installed now are almost indistinguishable from WFI in respect of construction materials, the control and monitoring systems and the use of 'standard' factory-assembled skid systems. Almost every major, and many minor, equipment supplier has developed integrated, skid-mounted, PW generation systems. Because each design is not a one-off, the systems have become more reliable and the use of standard systems has reduced the design activities on each project and standardised validation packages. This has resulted in reduced costs and project timescales. It has also made it possible to make Factory Acceptance Testing (FAT) more extensive and effective. Most of the Installation Qualification (IQ) and Operational Qualification (OQ) protocols can be carried out in the factory prior to the equipment being shipped to site.

With the development of new Reverse Osmosis (RO) membranes and Continuous Electrodeionisation (CEDI) modules, the almost universally used combination of technologies is Pre-treatment, RO and CEDI. Sometimes a UV light is included, either before or after the CEDI unit and to produce Highly Purified Water either a second RO stage, or an Ultrafiltration (UF) stage is added after the CEDI unit. This second membrane stage is required to ensure that the endotoxin limit of 0.25 EU/ml can be guaranteed irrespective of levels in the potable water.

## CEDI developments

An interesting development described by Christ Water Technology is the Septron Bio-Safe unit. This combines the spiral wound SeptronCEDI module with an integrated membrane stage. The company claims that this bio-safe unit, combined with an upstream RO stage, will enable the production of Highly Purified water with no additional pipework, pump or energy requirement for the membrane stage.

Arguably, the market-leading CEDI unit is the Ionpure range manufactured and supplied by Siemens Water Technologies, with more than 1,000 units installed in validated pharmaceutical water systems. The first Ionpure CEDI unit was installed in a commercial system in 1989 and since then the technology has been extensively developed by Siemens and other water treatment companies. Initially, RO and CEDI systems had to be chemically sanitised, but product developments meant that both technologies could be hot-water sanitised. However, there were process restrictions, even following the development of hot water sanitisable units because it was important that the rate of temperature increases and decreases was controlled to within relatively strict limits because of the different rates of expansion and contraction of the materials used.

A recent development in the Ionpure product range is the new LX-HI module. With a guaranteed performance for 150 cycles, this unit does not need any temperature ramp up or down and can be sanitised at 85°C +/- 5°C.

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## PW system operation

Despite the good water conversion performance of the RO/CEDI combination of technologies, every supplier is seeking ways of improving the efficiency of the complete system. A characteristic of modern pharmaceutical water systems is that the generation system is operated continuously to minimise the possibility of bacterial growth, but this can waste water and energy. Different companies take different approaches to reduce this.

If a purification system were operated in a 'stop-start' manner, water and energy would only be used when Purified Water was being produced however, that could increase the risk of microbiological excursions. Siemens Water Technologies has reported a process based on using the capabilities of the LX-Hi CEDI module described above. Its S3 system technology operates by shutting down the make-up water system during periods of non-use. When there is a call for water the system undergoes a rapid, 20- 30 minute heat sanitisation before resuming normal operation. During long periods of non-use the system can automatically sanitise, then return to a dormant state.

A published example of the savings that this design approach can achieve was based on a system installed at a major healthcare products manufacturer. Table 1, below, shows the data published by Siemens for this system. The savings amounted to 16.4 million gallons a year.

## Storage and distribution

Possibly the next step in integration is to integrate the generation and distribution systems into one unit. For example, Elga Process Water offers the Triton packaged integrated system, which can supply up to 350 litres/hour of Purified or Highly Purified Water for

**Table 1: Description of cost savings from S3 system**

| | Annual savings | 10-year savings projection |
|---|---|---|
| Rain water & filters | $77,105 | $1,177,989 |
| Electricity | $28,789 | $417,062 |
| Water softener | $2,469 | $35,799 |
| 53 operational cost | $(13,838) | $(200,473) |
| Total savings | $94,525 | $1,370,377 |

Source: Siemens Water Technologies

applications such as the production of clinical trial material and for scale-up studies. However, this approach is still not common for production scale systems.

Standardising the control and reporting system for pharmaceutical water systems using a software package, which also meets the requirements of 21 CFR Part 11, has been considered, with Christ Water Technology Group offering the Aqu@View system. This system allows remote data acquisition and evaluation, remote plant operation and data export to packages such as MS Excel. However, despite all the developments in the monitoring and control systems and the generation systems, there have been no significant developments of the basic designs of distribution loop systems.

That has recently been changed by the introduction of the HydroGienic system by the Honeyman Group. All water distribution systems have been based on the points of use being connected in series, either using one loop or sometimes two or three conventional loops operating in parallel. While this design works well, there are a number of potential limitations. The HydroGienic system is the world's first parallel distribution system. The system features small-bore PTFE hoses and a unique reverse-flow principle for hydraulic balancing.

A HydroGienic system has been installed at Dales Pharmaceuticals in the UK. Managing director Mike Annice said: "The nature of our business is such that we need to be able to alter production schedules quickly and efficiently to meet changing client requirements. Fundamental to this are facilities that can be easily adapted, and with its ease of modification HydroGienic allows us to do exactly that."

## Reclaim/reuse

A final area where savings may be possible is water reclaim. This can be defined as the treatment of a waste stream to produce high-quality water that can be fed to another operation within the pharmaceutical site. Although reclaiming water can reduce or even eliminate waste disposal costs, unfortunately, the water can only be reused as a feed water supply if the waste stream is of better quality than the original.

## Final thoughts

Some suppliers describe themselves as 'vertically integrated' manufacturers so that they can integrate various aspects of their complete range of products and services to meet the requirements of pharmaceutical manufacturers. For example, GE Infrastructure offers a range of water and process technologies for the pharmaceutical industry, including Betz treatment chemistries, Osmonics membrane systems and pre-engineered RO and deionization systems.

It will be interesting to see developments in new technologies and the business models adopted by suppliers over the next decade to meet requirements of pharmaceutical R&D and production operations. Regulatory focus on water systems remains high and users now better understand the importance of routine monitoring, maintenance and pro-active intervention when operating parameters change.

However, possibly the largest change has been the development of standard, skid-mounted PW generation systems, which can operate consistently and reliably while allowing the user to implement the control and sanitisation procedures they prefer. Suppliers are now also working hard to further improve these systems to minimise their environmental impact and reduce operating costs. ■

*Note: For full list of acknowledgements please contact the editor.*