



BEST PRACTICE GUIDE IN WATER EFFICIENCY

BIOMEDICAL MANUFACTURING SECTOR

VERSION 1

PREFACE

Singapore's water consumption stands at 430 million gallons a day, with the domestic sector accounting for 45% of total water use, while the remaining 55% comes from the non-domestic sector. By 2060, Singapore's water consumption is expected to double, with the non-domestic sector making up 70% of total water demand. Therefore, it is important that PUB's partners in the non-domestic sector join us in the move to conserve water, and reduce water demand. This will help Singapore in its water sustainability journey.

The aim of this **Best Practice Guide in Water Efficiency - Biomedical Manufacturing Sector** is to provide professional engineers, developers, plant owners and facilities operators involved in water management, with the basic knowledge of designing, maintaining and operating a water-efficient plant.

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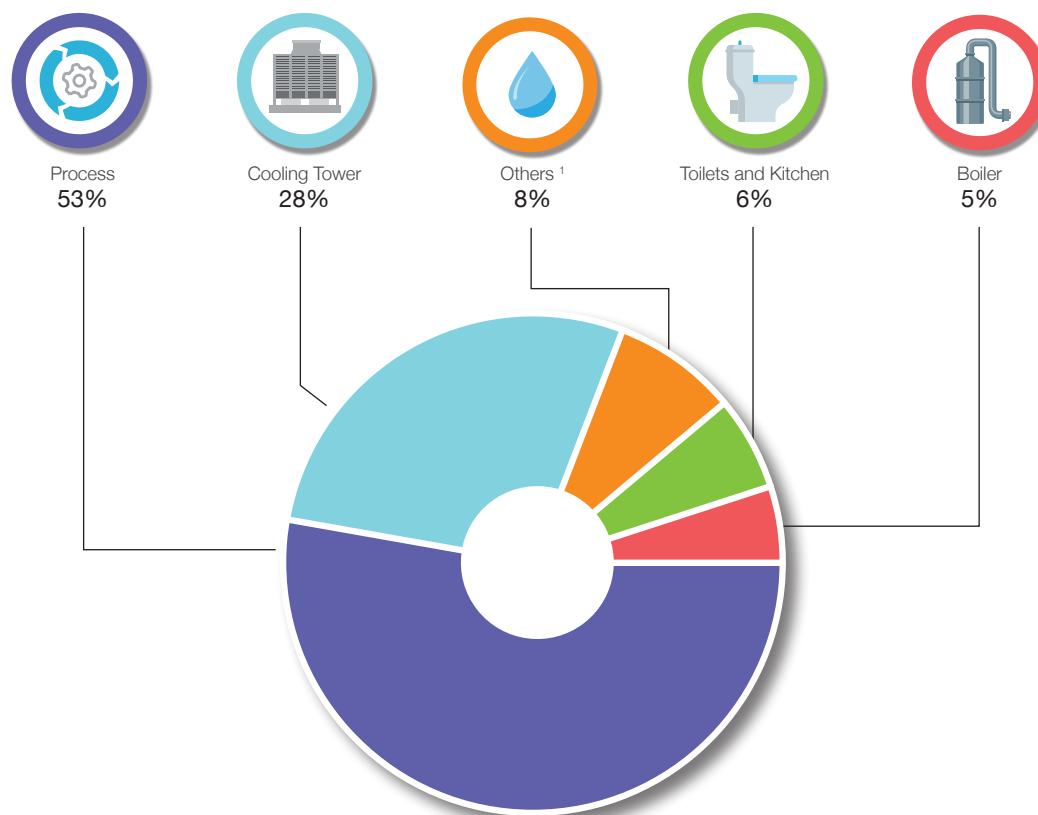
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The Biomedical Manufacturing sector is a key contributor to Singapore's manufacturing economy. Manufacturing plants in this sector are typically large water-consumers. The water usage breakdown of the sector is shown in Fig. 1.



► Fig. 1 Water Usage Breakdown for the Biomedical Manufacturing Sector

Others include scrubber, general washing, irrigation, fire protection etc.

The products produced in this sector can be broadly categorised into the following subsectors – active pharmaceutical ingredients (APIs), biologics, nutrition, medical equipment and technology etc. Nevertheless, the product(s) produced in each plant will differ from facility to facility, even within each subsector. Depending on the type of pharmaceutical use of the products produced, plants will require water of different grades of quality, such as Water-for-Injection (WFI), Highly Purified Water or Purified Water. Therefore, biomedical manufacturing is a highly heterogeneous sector with non-identical processes and/or reaction pathways being used in each facility to manufacture a wide range of products across the sector. Consequently, the water used for process as well as the wastewater produced can be of varying qualities.



Many biomedical manufacturing plants do incorporate some form of water reuse and recycling in their facilities, albeit to varying degrees. Due to the heterogeneous nature of the sector, opportunities for water efficiency



improvements can vary significantly and solutions should always be site-specific and tailored to the needs of the individual site.

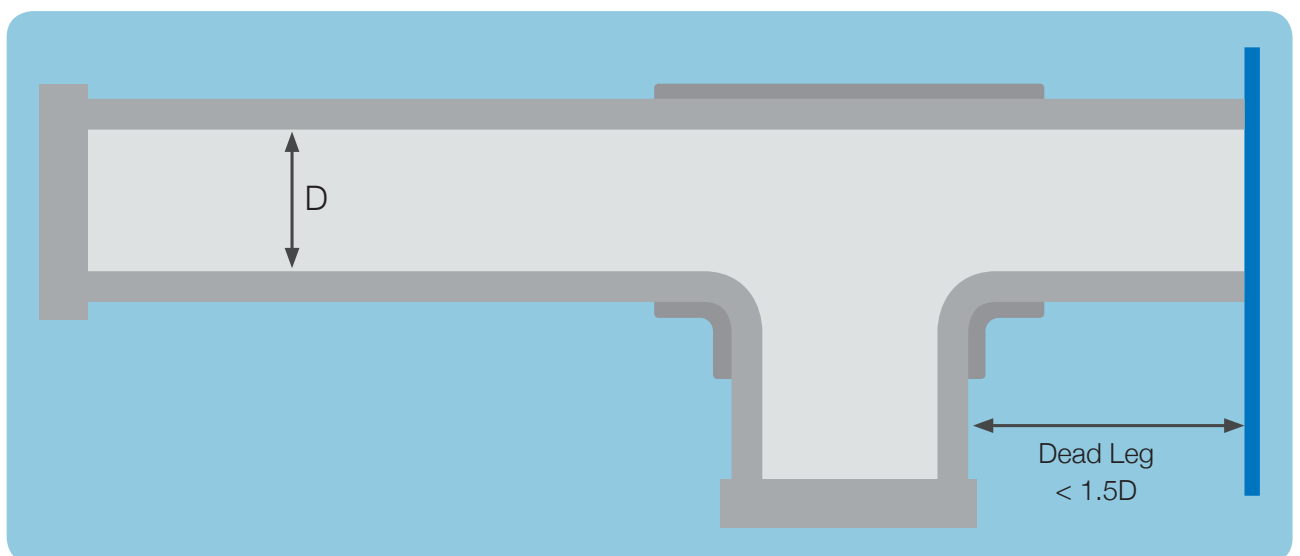
Nevertheless, this guide seeks to share with companies the water efficiency opportunities within the sector that may be implemented and to provide practical guidance for efficient water management in the biomedical manufacturing sector. It is not intended to be prescriptive nor does it set an industry standard.

Companies may wish to read this guide in conjunction with the following standards and references:

- ISO 46001:2019 Water Efficiency Management Systems
- Technical Reference for Water Conservation in Cooling Towers
- Pharmaceutical Inspection Convention/ Co-operation Scheme (PIC/S) Guide to Good Manufacturing Practice for Medicinal Products/ Active Pharmaceutical Ingredients

Uses	Recommended Best Practices
<p data-bbox="185 331 288 360">Process</p> 	<p data-bbox="373 331 564 360">Clean-in-Place</p> <p data-bbox="373 398 1402 568">Although the processes in each plant tend to vary across the sector, Clean-in-Place (CIP) is commonly used in many biomedical manufacturing plants to ensure high levels of sanitation and hygiene in the process lines. Depending on the plant and type of product manufactured, a significant proportion of water usage for process can be for CIP. Water savings in CIP systems may be achieved by:</p> <ul style="list-style-type: none"> <li data-bbox="373 607 1402 981"> <p>◆ Optimising the CIP process -</p> <ul style="list-style-type: none"> <li data-bbox="416 645 1402 779">• Customise the CIP process in accordance to the size of the plant and the type of soiling. Pre-rinse and post-rinse durations may not always be optimised for the plant and size of equipment. When in doubt, do consult a reputable supplier to carry out an audit of the CIP system. <li data-bbox="416 786 1402 875">• Monitor CIP system with the aid of software. Software systems are capable of providing real-time monitoring and charting of trends to help in the analysis of the performance of the system. <li data-bbox="416 882 1402 981">• For plants which produce more than one type of product, improve product scheduling such that similar products are processed sequentially, thereby reducing cleaning requirements. <li data-bbox="373 1025 1402 1093">◆ Using a recirculating system for CIP instead of a single-pass system, where possible. <li data-bbox="373 1128 1402 1196">◆ Removing residual product before cleaning to reduce the amount of water used for cleaning. Pigging and air-blowing techniques may be used. <div data-bbox="411 1234 1382 1823" style="background-color: #ffffcc; padding: 10px; border-radius: 10px;">  <p data-bbox="533 1294 735 1323">For New Plants</p> <ul style="list-style-type: none"> <li data-bbox="443 1361 1358 1480">◆ Ensure that “dead legs”, crevices or pockets in the piping are minimised as these are often difficult to clean, resulting in longer CIP rinse times and larger rinse volumes. Refer to Fig. 2 for a brief illustration of the recommended piping design. <li data-bbox="443 1518 1358 1800">◆ Where feasible, adopt single-use systems for processes in order to avoid the need for CIP. Single-use assemblies may consist of a combination of bags, tubing, connectors, filters, mixers, reactors etc. Pre-sterilisation of single-use components is typically via gamma-irradiation or autoclaving. These single-use components may be discarded after each production batch, thus eliminating the need for CIP. While the use of single-use systems may lead to water savings for the plant, careful consideration should also be given to the management and disposal of solid waste generated. </div>

Uses	Recommended Best Practices
<p>Cooling Tower</p> 	<ul style="list-style-type: none"> ◆ Improve Cycles of Concentration (COC) to minimum 7 and 10 for cooling towers using potable water and NEWater respectively. ◆ Install a side-stream filter. ◆ Install a makeup water or side-stream softening system when hardness is a limiting factor on COC. ◆ Install automated chemical feed and blowdown control systems on large cooling tower systems (more than 100 refrigeration tons). ◆ Routine maintenance to check for water leakage and ensure correct water balancing of connected cooling tower basins. ◆ Minimise cooling load by minimising waste heat generated and/or using waste heat for other purposes in the facility. ◆ Use alternative sources of water for cooling tower makeup. Alternative water sources include condensate from air handling units (AHUs), harvested rainwater, reverse osmosis (RO) reject streams etc. <p>More details can be found in the Technical Reference for Water Conservation in Cooling Towers.</p>
<p>Toilets/ Pantries/ Domestic Use</p> 	<ul style="list-style-type: none"> ◆ Install water-saving devices at basin, sink/kitchen, and shower taps/mixers to meet water-efficient flow rates designated by PUB or replace these water fittings with those labelled 2-ticks and above under the Mandatory Water Efficiency Labelling Scheme.



▲ Fig. 2. Recommended piping design to minimise dead leg

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WATER RECYCLING OPPORTUNITIES

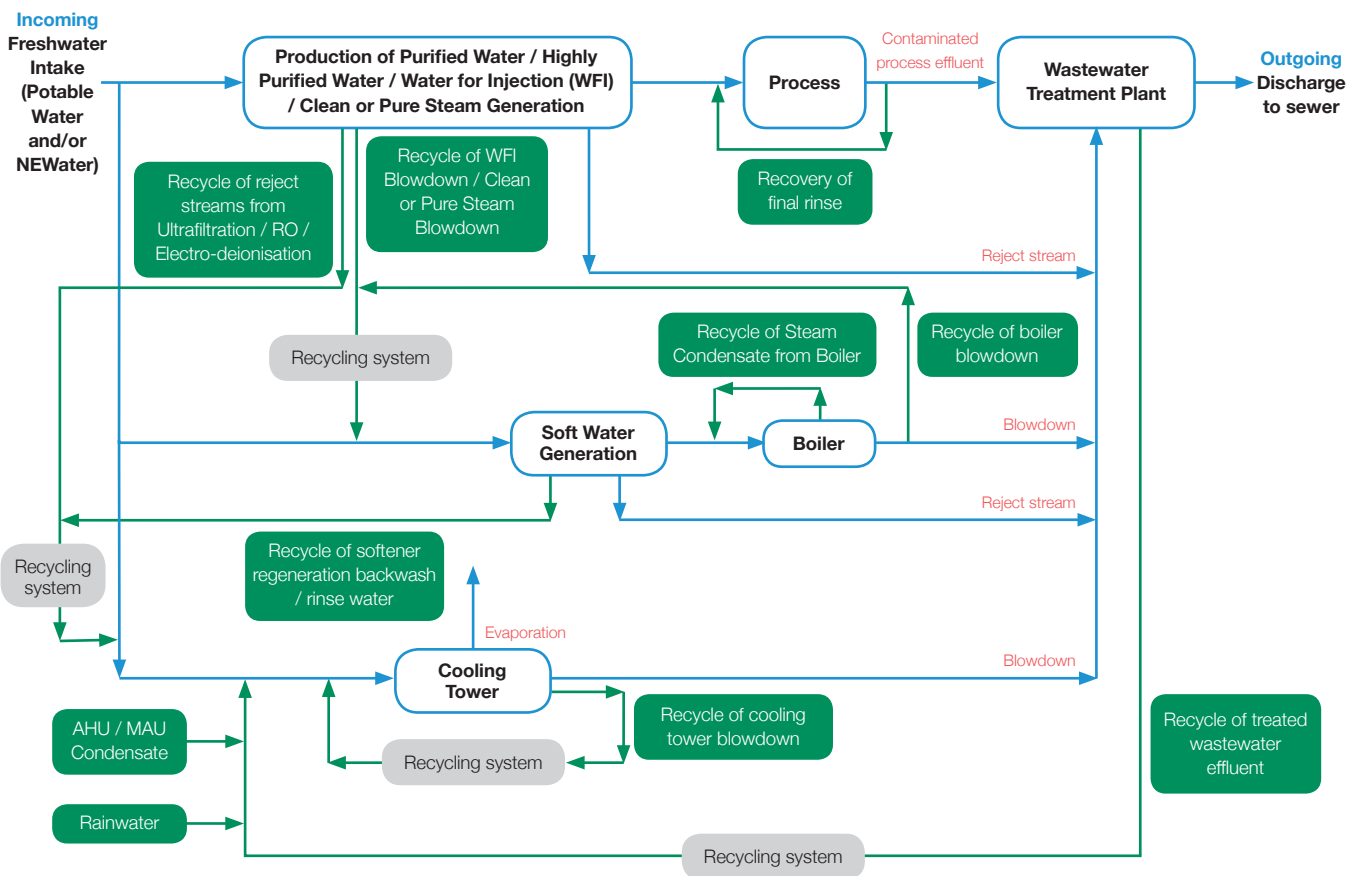
Based on the reported data, the plant recycling rate² of the biomedical manufacturing sector can vary considerably, ranging from 0% to 41%, with an industry average of 12%.

Manufacturing plants in the biomedical manufacturing sector can sometimes face constraints when it comes to reusing/ recycling water for process streams due to the need for water of exceptionally high quality and to meet the requirements for Good Manufacturing Practice (GMP) certification or relevant food safety standards (in the case of the Nutrition subsector). Notwithstanding, water can often be reused for non-potable uses or at non-contact processes – a common example of an area of reuse is the cooling towers which is a major water consumer in many plants. In fact, a majority of manufacturing plants from this sector have successfully implemented at least one type of water reuse/ recycling system. Plants are, therefore, strongly encouraged to reuse and recycle water wherever and

whenever possible. This will not only help companies to ensure water sustainability and to reduce reliance on external source of water but it could also potentially generate return on investment for the company in the form of cost savings.

Fig. 3 illustrates the possible reuse/ recycle streams in a biomedical manufacturing plant and the likely areas where these recycle streams can be suitably reused at. The reuse/ recycle streams are described in further details in this section.

Water quality requirements are subject to specific site conditions. Interested companies can approach independent consultants or PUB's in-house Industrial Water Solutions Project Unit team to review the feasibility of water efficiency improvements at process areas. A comprehensive water audit can also be conducted to identify and prioritise potential areas of water efficiency, reuse and recycle.



▲ Fig. 3. Water Recycling Opportunities in a Typical Biomedical Manufacturing Facility

² Recycling rate is calculated as follows: Total amount of water recycled / (Total amount of water recycled + Total supplied water)

Common Reuse/ Recycle Streams in Biomedical Manufacturing Facilities

Streams	Recommendations
AHU and Makeup Air Unit (MAU) Condensate	Condensate from AHUs and MAUs is suitable for reuse to cooling towers as it is generally cold with low dissolved mineral content. A typical condensate recovery and reuse system consists of drain pipes, pumping lines, a condensate water collection tank and pumps. Depending on condensate water quality and stipulated requirements, appropriate simple treatment systems can also be included.
RO Reject	RO membranes are often used by biomedical manufacturing facilities to produce the required grades of water for pharmaceutical applications, including Purified Water, WFI etc. RO reject water can typically be reused to cooling towers, toilet flushing and scrubbers with minimal treatment. Where appropriate and where water quality requirements permit, it can even be recycled to certain process applications - with or without further treatment before reuse.

Other Possible Reuse/ Recycle Streams

Streams	Recommendations
Rainwater	Rainwater can be harvested and reused with minimal treatment such as filtration. It can be reused at areas such as cooling towers, toilet flushing, landscape irrigation etc. The construction of rainwater collection systems for any purpose is regulated by Section 31 of the Sewerage and Drainage Act. An application must be submitted to obtain the approval of PUB prior to the installation of the rainwater collection system. Companies are advised to refer to the “Guidance Notes for the Application of Rainwater Collection Systems” published on PUB’s website ³ for more details on the requirements for the installation of a rainwater collection system.
Treated Wastewater Effluent	Wastewater from different process streams or usage areas may be combined together and reclaimed as the final effluent of the wastewater treatment plant. In general, treatment for reuse may be costlier as compared to the reuse of separate streams due to the relatively poor water quality of the combined wastewater effluent. Consequently, the reuse of wastewater effluent is less commonplace in the industry. Nevertheless, when successfully implemented, the reuse of wastewater effluent to areas such as cooling towers can help companies to achieve substantial water savings.
Ultrafiltration (UF) Reject / Electro-deionization (EDI) Reject	UF and EDI are often used, in conjunction with RO, to produce Purified Water / Highly Purified Water / WFI for use in biomedical manufacturing plants. Reject streams from UF and EDI can be reused to cooling towers either directly or with minimal treatment.

³ <https://www.pub.gov.sg/savewater/atwork/alternatesources>

Streams	Recommendations
WFI Blowdown / Clean or Pure Steam Blowdown	<p>Besides the use of membrane processes as treatment, WFI can also be produced using distillation. The biomedical manufacturing sector also uses clean or pure steam for the sterilisation of process lines and equipment. The blowdown streams from the distillation process and the generation of the clean or pure steam are high in temperature and may therefore, be suitable for reuse to the boilers.</p>
Cooling Tower Blowdown	<p>Cooling tower blowdown can be recycled back to the cooling tower, via a combination of microfiltration (MF) / UF and RO / Nanofiltration (NF) processes. However, care must be taken to ensure that the final treated effluent can still meet the trade effluent discharge limits due to the high level of Total Dissolved Solids (TDS) in the blowdown water and hence, the reject of the treated water.</p>
Boiler Blowdown	<p>Despite the high heat content, boiler blowdown can be an alternative source of water for the cooling towers as it is typically of reasonably good water quality. However, careful consideration may need to be given to the possibility of the interference of polymers and phosphates in boiler water with the cooling water chemistry. Boiler blowdown may also be reused as makeup water to the boilers due to the high heat content.</p>
Steam Condensate from Boiler	<p>As hot steam generated from the boilers cools down, condensate water is produced. The condensate water is usually free of contaminants, rendering it suitable to be recovered and reused as makeup water for the boilers. Further treatment of the recovered condensate may not be necessary before it is returned to the boiler. Since the temperature of the condensate is already quite high, less energy is required to increase it to steam temperature.</p>
Softener Regeneration Backwash / Rinse Water	<p>Backwash is used to remove any solids which have been caught on top of the resin bed before the exhausted resin bed is regenerated. As a result, backwash water may contain some suspended solids which can be removed via simple treatment such as sedimentation, filtration etc. before reuse. Water from the fast rinse, which is typically the final step of the regeneration process, can be of good quality (since most of the excess sodium and hardness brine should have been removed during the preceding slow rinse step) and may be suitable for reuse.</p>
Final Rinse from production including CIP	<p>In general, the final rinse water used in production for the CIP of equipment, containers etc. should be of the same quality of water as used in the manufacture of the API/ medicinal product. As such, the water used for final rinse is highly purified and meets strict quality standards. Following from the rinse process, final rinse water is only slightly contaminated and thus may be reused at the initial rinse stage as the initial rinse typically does not require water of purity as high as that of the final rinse water.</p>

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CASE STUDIES

Case Study 1: Wyeth Nutritionals (Singapore) Pte Ltd

Wyeth Nutritionals (Singapore) Pte Ltd is a manufacturer of milk powder, producing a full range of products to serve the nutrition needs of consumers, from expectant mothers to infants, children and adults. The plant was first commissioned in 2002, with further expansion completed in 2010. With strong

support from the management and the establishment of measurable targets to improve water efficiency, the company is committed to ensuring sustainable use of water and continuous improvement in water management within its premises.

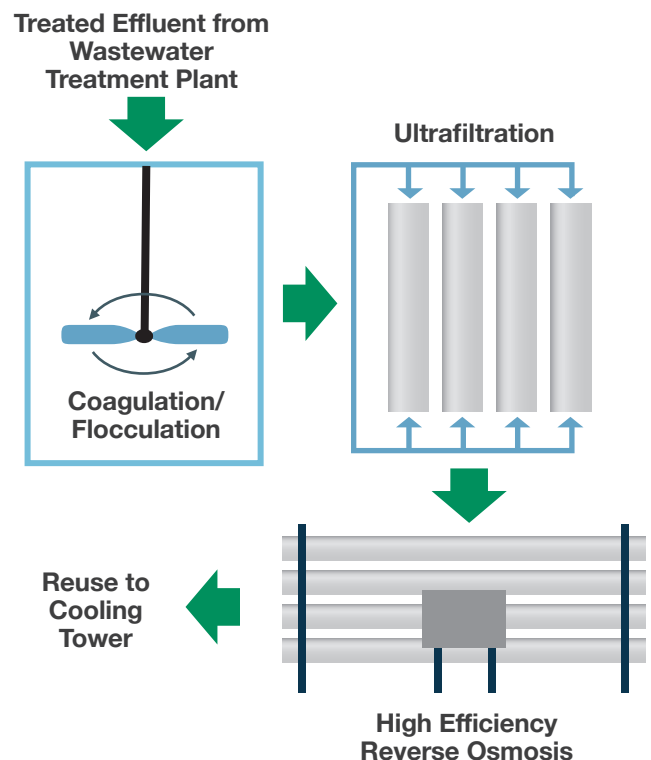


▲ Fig 4. Wyeth's manufacturing facility in Singapore

1. Recycling of Used Water from Wastewater Treatment Plant to Cooling Towers

Process used water is treated in the wastewater treatment plant using biological treatment with a Sequential Batch Reactor (SBR). Thereafter, the resulting effluent from the wastewater treatment plant undergoes further treatment before its subsequent reuse to cooling towers. Fig.5 illustrates the key treatment processes, including the use of High Efficiency Reverse Osmosis (HERO™) technology which allows for a high recovery rate of 90%. The treated water is of good quality and is comparable in terms of quality to potable water supplied by PUB.

Through the implementation of this recycling system, Wyeth can expect to significantly reduce the amount of freshwater make-up to cooling towers and achieve substantial water savings of 109,500 m³ each year, an amount approximately equivalent to the volume of 44 Olympic-sized swimming pools.



▲ Fig. 5. Process schematic for the treatment of effluent from wastewater treatment plant before reuse



▲ Fig. 6. Photo of RO membranes used in the treatment process

2. Reuse of Condensate from Air Handling Units (AHUs) to Cooling Towers

Wyeth has implemented a recovery system to collect condensate from the AHUs within their premises and reuse the collected condensate as make-up water to their cooling towers. As the condensate is of good quality, there is no need for further treatment before reuse. This recovery system was completed in two phases (in 2015 and 2017) and has resulted in annual water savings of approximately 13,000 m³.

The system is cost-effective with a relatively short payback period as it consists of simple retrofitting, such as the installation of localised collection points for each AHU. The collected condensate at each point is pumped to a main condensate water tank for subsequent reuse to the cooling towers.

3. Other Water Efficiency Improvement Opportunities

Wyeth is continuously looking for opportunities to improve water use efficiency within their premises. In addition to the implementation of above water reuse/recycle systems, the company is also putting much focus on the optimisation of their CIP process, in order to reduce water usage for this area. Some of the steps taken towards this include: reusing final rinse water in CIP process for initial rinse and reducing the rinse time for each CIP cycle.



▲ Fig. 7. Photo of AHU condensate collection system

Case Study 2: GlaxoSmithKline (GSK) Biologicals

GSK's premises at the Tuas Biomedical Park was opened in 2009 and is a state-of-the-art manufacturing facility producing vaccines. GSK is committed to continuously investing in its vaccine manufacturing facilities, improving processes and building partnerships to meet the growing global needs for high quality vaccines.

The plant is currently able to achieve a water recycling rate of 30% which is higher than the norm in the biomedical manufacturing industry. This can be attributed to the following recycling efforts that GSK has adopted over the years:

1. Recycling of Reverse Osmosis and Ultrafiltration Reject Streams to Cooling Towers

Purified water is used in the manufacturing process of vaccines due to the high standard of sanitation required. It is used for processes such as CIP, generation of WFI and clean steam. In order to generate purified water, potable water from PUB undergoes a water treatment system which includes UF and RO. Reject streams from the UF and RO treatment processes are channelled to and stored in a sump pit and recovery tank respectively before being reused as make-up water for the cooling towers.

No treatment of the reject streams is required before reuse as the streams are of relatively good quality. By recycling these waste streams that would otherwise have been discharged to the sewers, GSK is able to save an estimated volume of 20,000 m³ per year. The cost of the implementation of this recycling system was not high, resulting in an attractive payback period and the company was able to generate returns on investment in the form of cost savings within a short span of time.



▲ Fig 8. GSK's manufacturing facility at Tuas Biomedical Park



▲ Fig 9. Sump pit and recovery tank used to store reject streams from UF and RO before reuse

2. Reuse of Condensate from Air Handling Units (AHUs) and Makeup Air Units (MAUs) to Cooling Towers

GSK is also reusing condensate from their AHUs and MAUs as makeup water for their cooling towers. With this system in place, the company is able to generate water savings of approximately 30,000 m³ each year. Simple treatment, in the form of strainers, is used to remove particulate matter from the condensate before it is reused to the cooling towers.

Case Study 3: Roche Singapore Technical Operations Pte Ltd

Roche Singapore Technical Operations Pte Ltd (RSTO) is Roche's first biologics manufacturing site in the Asia Pacific region. It is also the first company in Singapore to use recombinant DNA technologies to produce licensed biotherapeutics. RSTO produces the drugs substances for age-related vision loss and oncology treatments.

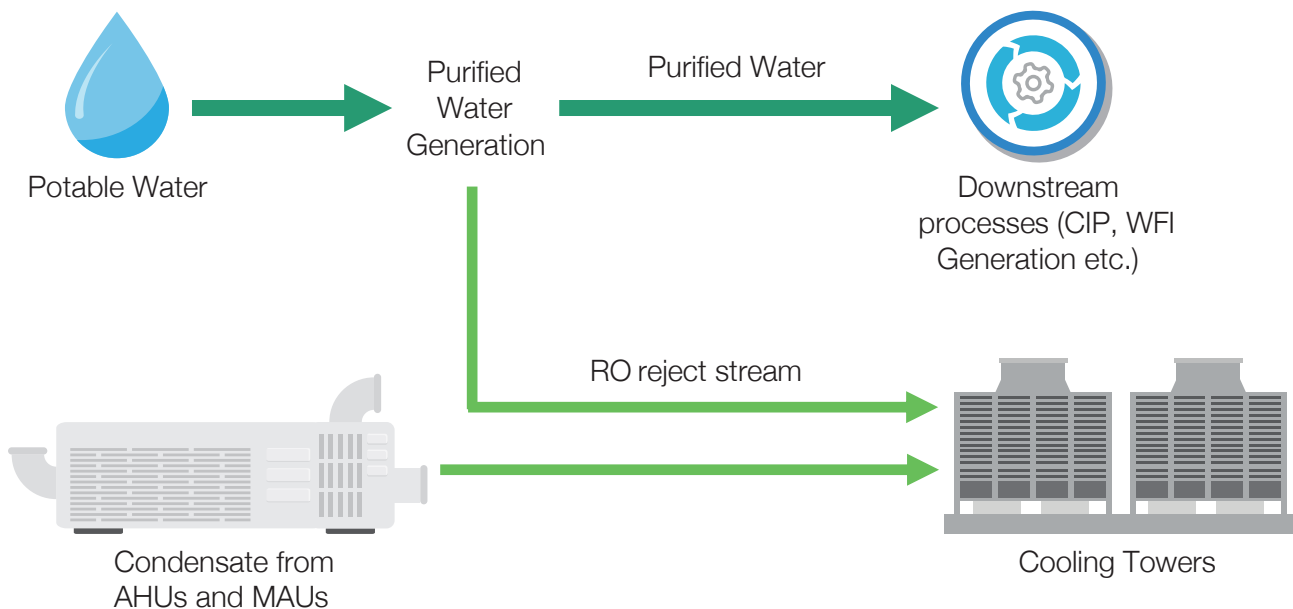
1. Recycle and Reuse Efforts to Reduce Water Used for Cooling Needs

RSTO has demonstrated its commitment to environmental sustainability from the outset. Even at the design stage, the company had ensured that systems were put in place so that possible water recycle and reuse efforts could be readily implemented. The plant is currently recycling a portion of the reject stream from the reverse osmosis (RO) treatment process used to generate purified water in the site's B10 building.

The reticulation system for this recycle stream was incorporated and built in right from the design and construction phase, thus no retrofitting was required in order for the company to undertake this initiative. Moreover, no further treatment of the water from the RO reject stream is needed before it is reused as make-up water for the cooling towers.

In addition to the above, RSTO also collects condensate water from the air handling units (AHUs) and makeup air units (MAUs) within the manufacturing site. The condensate is collected via gravity feed and reused at the cooling towers. The condensate collection and reuse system for the facility was similarly planned for at the design and construction stage. With little to no retrofitting required, the cost of implementing the above water saving initiatives could be minimised.

With the reject stream from the RO treatment process and condensate from AHUs and MAUs supplementing the NEWater supply to cooling towers, RSTO is able to achieve significant water savings with more than 50% reduction in total freshwater consumed for its cooling needs.



▲ Fig. 10. Reject stream from the RO treatment process and condensate water from AHUs and MAUs are recycled and reused as cooling towers make-up water

2. Reduction in Ambient Water-for-Injection (AWFI) Hot Water Sanitisation (HWS) Frequency

The AWFI distribution loop in the site's B1 building undergoes a periodic HWS process with a fixed schedule four times a week. During the HWS process, the system is heated up to a temperature of 85°C, flushed at each sampling drop before being cooled back down to 25°C once the HWS is completed. As part of RSTO's continued efforts to optimise and improve their operational processes to ensure greater environmental sustainability, the company initiated a project in 2018 to reduce the frequency of HWS to once a week instead of the original four times per week.

Performance Qualification was carried out over an extended period of time in order to validate the new HWS frequency cycle and to verify that the AWFI would still be able to meet the desired quality standards and requirements even with the reduced HWS frequency. More than 1,000 tests on quality of the AWFI were conducted over the extended period and all samples were able to successfully pass these quality checks. Through the reduction in HWS frequency and hence water loss through sampling flushing, RSTO is able to save approximately 2,200 m³ of water every year. In addition to water savings, a reduction in the site's energy consumption can also be expected with the implementation of this initiative.



Support and Resources

PUB provides funding and technical support as part of PUB's effort to encourage companies to explore ways to improve water efficiency.

For technical support, interested companies may contact PUB's in-house Industrial Water Solutions Project Unit team at PUB_One@pub.gov.sg.

For information on funding available from PUB including Water Efficiency Fund and Industrial Water Solutions Demonstration Fund, please refer to PUB's website at www.pub.gov.sg.



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