



An Alternative Purified Water Generation Plant

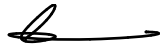
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BEng Mechanical and
Manufacturing Engineering
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Declaration of Authenticity

This thesis is the result of the author's original research. It has been composed by the author and has not been previously submitted for examination which has led to the award of a degree.

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List of Abbreviations

ABS - Acrylonitrile Butadiene Styrene

AI – Artificial Intelligence

BMS – Building Management System

BTG – British Technology Group

BS – British Standard

BWS – Borehole Water System

cGMP – current Good Manufacturing Practice

CEDI – Continuous Electro Deionisation

CFR – Code of Federal Regulations

DWI - Drinking Water Inspectorate

DNA - Deoxyribonucleic Acid

DC – Direct Current

DOL – Direct On Line

EPS - Extracellular Polymeric Substance

FAT – Factory Acceptance Test

FDA – Food and Drug Administration

GAMP - Good Automated Manufacturing Practice

GMP – Good Manufacturing Practice

GRP – Glass Reinforced Plastic

HMI – Human Machine Interface

HWS – Hot Water Sanitisation

ISO – International Organisation for Standardisation

ISPE – International Standard for Pharmaceutical Engineering

JP – Japanese Pharmacopoeia

LAL – Lumulus Amoebocyte Lysate

LCD – Liquid Crystal Display

MCB – Miniature Circuit Breaker

MHRA - Medicines and Healthcare products Regulatory Agency

MWS – Multiple effect Water Still

Ph.EUR - European Pharmacopoeia

PW – Purified Water

PLC – Programmable Logic Controller

QP – Qualified Person

RO – Reverse Osmosis

SS – Stainless Steel

TAMC - Total Aerobic Microbial Count

TOC – Total Organic Carbon

uPVC - Unplasticized Polyvinyl Chloride

UF – Ultrafiltration

US – United States

USP – United States Pharmacopoeia

UV – Ultraviolet

VSD – Variable Speed Drive

VWT – Veolia Water Technologies

WFI – Water for Injection

WHO – World Health Organisation

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Abstract

The aim of this project was to procure an alternative Purified Water (PW) generation plant to replace the current system at British Technology Group (BTG), called the Quattro 2000. This was to ensure that site operations were not restricted by the obsolescence and insufficient output of the Quattro.

Three different PW technologies were researched for this project before settling on a system supplied by Veolia Water Technologies (VWT) called the Orion. VWT were BTG's preferred supplier, following a longstanding relationship service agreement.

The Orion is a fully integrated PW generation plant, capable of producing 4m³/h of PW, is manufactured from 316/316L stainless steel (SS) that can be configured to perform thermal sanitisations on a weekly basis. An investment of £430,000 was required to implement the installation and commissioning of the Orion over a six-week period.

Since BTG is authorised and licensed to manufacture medicines by the Food and Drug Administration (FDA) and the Medicines and Healthcare products Regulatory Agency (MHRA) the Orion needed to meet the United States Pharmacopeia (USP), and European Pharmacopoeia (Ph. EUR) specification for PW. Therefore a robust qualification plan based on the standards and quality of water from the International Society for Pharmaceutical Engineering guidelines and current Good Manufacturing Practices (cGMP) saw that the Orion was validated to meet the PW specification for continued medicinal manufacture.

Although there were delays, which resulted in the timing plan being amended, the key milestones were achieved and the project implementation went according to plan and continues to supply BTG with the water necessary to continue manufacturing lifesaving medicines.

Chapter 1: Introduction

1.1 Company Background

BTG develops, manufactures and commercialises rescue medicines typically used in emergency rooms and intensive care units to treat patients with limited treatment options (BTG spec pharma, 2020). At the BTG manufacturing facility in Wales, the process focuses on polyclonal antibody development and manufacturing of three products: *CroFab*, *DigiFab*, and *Voraxaze* (Gethin Phillips, 2017).

CroFab and *DigiFab* are sterile, lyophilised immunoglobulin fragments. These are derived from sheep that have been immunised with a digoxin derivative, or small doses of snake venom after which the serum is collected, processed, and transported to the United States (US) market. Figure 1 shows the logistic operation of this process.

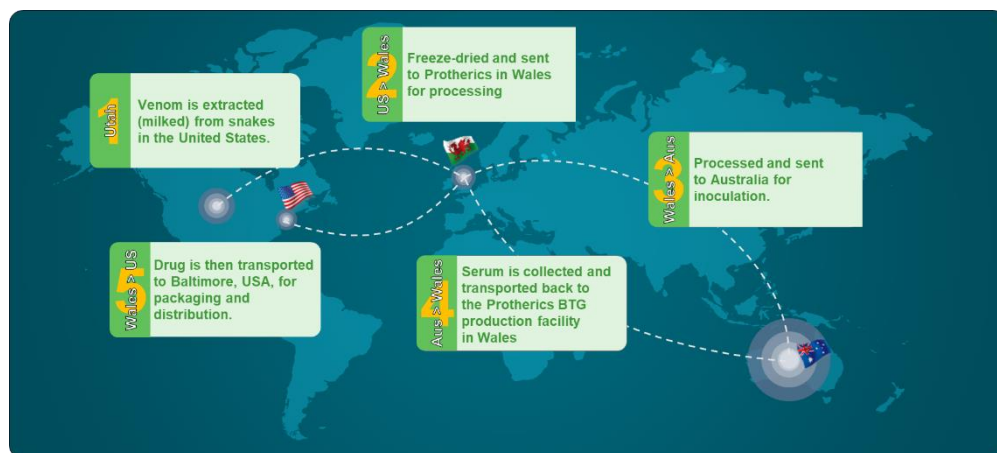


Figure 1 Global Operation of CroFab and DigiFab Manufacture

CroFab is the only Food and Drug Association (FDA) approved product derived exclusively from US snakes and approved to treat all North American pit viper envenomations in adult and paediatric patients (*CroFab* - BTG a SERB company, 2023)

Digoxin is used to treat heart failure and to slow heart rate in some cardiac disturbances. *DigiFab* is a treatment for patients with life-threatening or potentially life-threatening digoxin toxicity or overdose and is clinically proven to effectively clear it from the body (*DigiFab* - BTG a SERB company, 2023).

Voraxaze treats toxic effects caused by high dose methotrexate which is generally used as a chemotherapy regimen for a range of adult and childhood cancers.

Patients with impaired renal function may suffer toxic effects of delayed methotrexate

clearance. Voraxaze breaks down methotrexate into its inactive metabolites and removes it from circulation via non-renal pathways (Voraxaze - BTG a SERB company, 2023). Figure 2 shows the three trademark products manufactured in Wales.

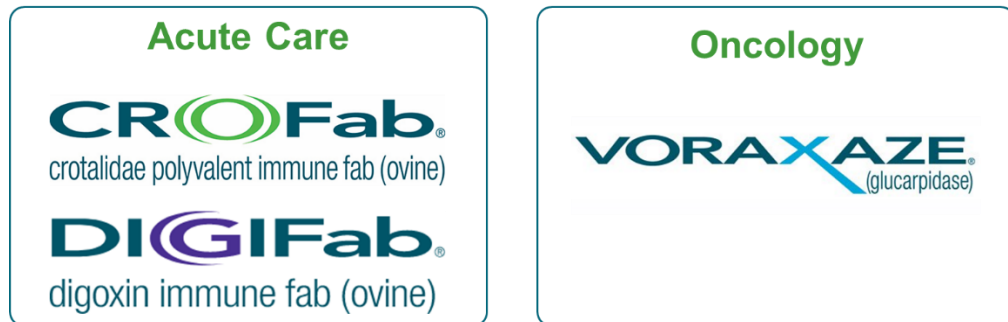


Figure 2 Products Manufactured in Wales

Purified water is essential to the manufacture of all three products in Figure 2.

1.2 Project Background

The current purified water generation system at BTG (referred to as the Quattro throughout this report, see Figure 3), has served the Wales site for 16 years but due to wear and tear, diminishing availability of spares and its low output it is no longer fit for purpose. Also, due to its obsolescence, when available the cost of spares is at a premium.



Figure 3 Quattro - Purified Water Generation Plant

The Quattro has an output of 2,000 litres per hour which is limiting site operations. Recent investment in critical utilities and an increase in production has compounded the problem as the requirement for Purified Water (PW) to sustain output has increased.

1.3 Problem Statement

At present there is not enough PW being generated by the Quattro to meet the demands of production.

Table 1 illustrates the demand for PW prior to investment which occurred in 2022. Although the Quattro was narrowly meeting demand, any additional demand would have put strain on the system posing a risk to the business.

In contrast Table 2 shows the demand for purified water post investment. Clearly, demand is greater than the output. As a result of this shortfall, water usage was balanced by rotating critical utilities. But this was an unsustainable solution due to the serious contamination issues it caused. Each contamination resulted in prolonged delays, heavy fines and posed an environmental health and safety risk due to the chemicals required to sanitise the systems.

Utility	PW usage (litres/hour)	Output
Water for Injection (WFI)	500	420 l/h
Pure Steam Generator	270	250 kg/h
Clean in Place	350	500 l/h
Points of Use	850	1,000 l/h
Quattro output		~2,000l/h
Purified Water usage		~1,970l/h @ max demand

Table 1 Purified water demand pre-2022.

Utility	PW usage (litres/hour)	Output
Water for Injection (WFI)	1,023	900 l/h
Pure Steam Generator	270	250 kg/h
Clean in Place	500	500 l/h
Points of Use	1,500	1,500 l/h
Quattro output		~2,000l/h
Purified Water usage		~3,293l/h @ max demand

Table 2 Purified water demand post-2022.

How much purified water do we need?

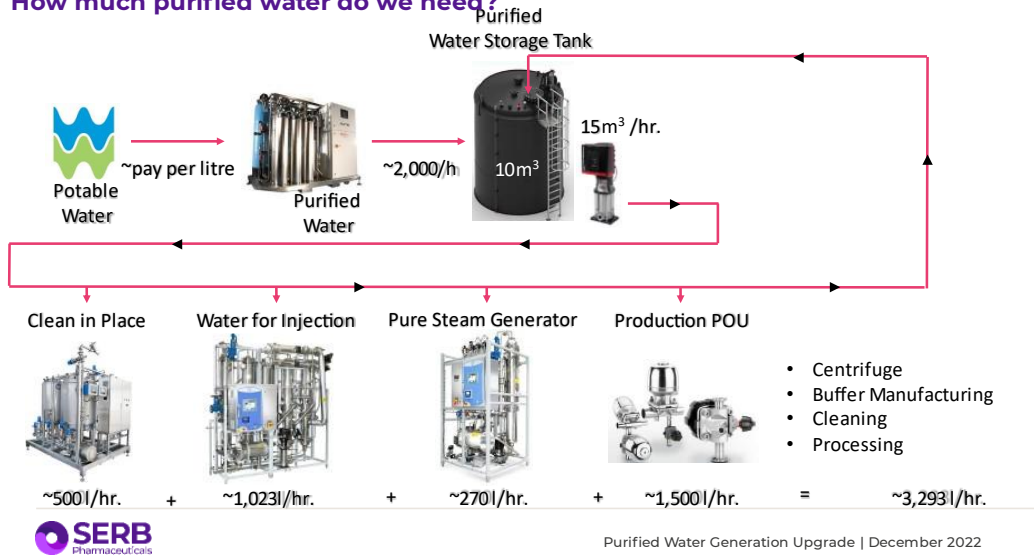


Figure 4 Flow schematic of purified water usage

Figure 4 further illustrates the shortfall of the output due to the condition and obsolescence of the Quattro. BTG were unable to meet the demand which restricted any plans for further expansion.

This project seeks to describe the work undertaken to upgrade the purified water generation plant.

This new PW generation plant will ensure that the system is capable of meeting current and peak demands as well as future proofing the system for new products, research, and development.

Chapter 2: Aims and Objectives

2.1 Aim

The aim of this project is to supply sufficient PW to all critical utilities and allow manufacturing to run at maximum capacity simultaneously so that no water level monitoring is required. Additionally, it will ensure there is no hinderance to investment in new utilities and new product development caused by insufficient PW.

Furthermore, the project will assess whether reducing and recycling wastewater produced by the PW system could further improve efficiency. Finally, it aims to provide a solution that will move away from the aggressive nature of chemically sanitising the system and reduce the significant disruption to the manufacturing operation this causes.

2.2 Objective

A *S.M.A.R.T* (Specific, Measurable, Achievable, Relevant, Time constrained) strategy was used to set the objectives of the project (Adobe Communications Team, 2022).

2.2.1 Specific

The objective of the project explores the option of replacing the current Quattro with a new PW generation plant. To do this, consideration was given to upgrade the infrastructure to support the replacement of the Quattro, which included ground penetration and preparation work, a bespoke glass reinforced fibre (GRP) enclosure, an upgrade to the electrical, chilled water, compressed air supply and the fire and security systems.

2.2.2 Measurable

Success of the project will be measured by the output of the new PW system and whether this allows for continued and additional manufacturing use without concern of water level monitoring. Additionally, the move away from chemically sanitising the system, which is both harmful to the environment and costly should prevent three days downtime each time costing BTG approximately £50,000 per day of overhead costs.

2.2.3 Achievable

The project was thought to be achievable based on the investment strategy used to determine the project budget as discussed later. It was thought to be achievable within the allotted timeframe. Also, given the expertise of the project team, the stakeholders thought there was adequate experience to carry out the project.

Following the installation of the PW generation plant a Validation Summary Report (VSR) was generated to ensure all deliverables were achieved, including the design, fabrication, assembly, testing, delivery, installation, commissioning, and qualification of the PW plant at BTG, Wales. This assured the stakeholders that the designed system will consistently meet purified water specification, detailed in Table 4 and will not impair product safety, quality, effectiveness, or efficacy.

2.2.4 Relevant

According to British Standard International Organisation for Standardisation 22519-2019 Purified water and Water for Injection (WFI) pre-treatment and production systems, (BS, 2019)

“All components in the PW/WFI production system shall be manufactured from Stainless Steel (SS) 316/316L. All PW/WFI contact parts to be fabricated from SS 316L, including piping/tubing, tanks, pumps, heat exchangers, valves, instruments, and other accessories”.

Due to the age of the Quattro, it was manufactured from a combination of SS, Acrylonitrile Butadiene Styrene (ABS) and Unplasticized Polyvinyl Chloride (uPVC). It is therefore no longer compliant to BS ISO 22519-2019 neither does it allow for any other form of sanitisation to take place other than chemical.

2.2.5 Time Constrained

A maintenance window was developed for this project, where the entire manufacturing operation was paused. The stakeholders agreed a maintenance window of 52 days after which, if the PW met the specification, the water could be released under a risk assessment to recommence manufacturing.

To achieve this maintenance window, collaboration was required from all contractors involved to meet the project deadlines, this involved weekend and night working. Owing to the time constraint, and to minimise the downtime, preliminary work on

utilities and infrastructure began before the project start date. Further consideration of the timeline is documented in the next chapter.

Chapter 3: Timing Plan

3.1 Introduction

This chapter will present the timing plan of the project and discuss the milestones achieved and the difficulties that caused a second revision of the plan to be implemented, causing a planned delay.

The Gantt chart in Figure 5 outlined the plan between the 06th of September 2022 – 28th of October 2022. However, due to difficulties outlined below, the plan required moving to the 31st of January 2023, and again to the 07th of February 2023 – 31st of March 2023 (Figure 6 Gantt chart). See Gantt chart revision 1 and 2 in Appendix 1.

3.2 Difficulties

Whilst preparing for the project the following hurdles were encountered:

- Supply of electrical components delayed the Factory Acceptance Test (FAT).
- Critical batch required urgent processing.
- Key members of staff leaving Veolia.

According to Siemens, there has been a global shortage of microchips caused by an initial surge of working from home during the COVID-19 pandemic as well as a perfect storm of chip upgrades driven by new technologies and expanding cloud and artificial intelligence AI services (Sank, 2022). Additionally, because of labour shortages and even draughts that directly impacted the water supply chain in Taiwan the semiconductor industry snowballed into global shortages (Barbiroglio, 2021).

Issues related to sourcing these parts meant that the plan was delayed by 3 months. However, this delay was used to strengthen the communication with contractors, and to finalise the sample and validation plan to ensure each department was aligned with the USP guidance, stating that, “the testing of water samples from a water system is critical to the ongoing control of the system and assessment of the quality of the water being used” (USP, 2021).

Furthermore, the project was again delayed by 1 week on the 30th of January, due to a critical batch requiring urgent processing for the development of a new ricin

antidote. This was very difficult to contend with a day before project start and required significant communication with all contractors who were already on high alert about a potential delay. The project plan was revised to accommodate this delay, see Figure 6, Gantt chart revision 3. Consequently, several principal contractors required additional payment for inconvenience. This is a historical issue at BTG and to combat the cost implication, a 2.5% adjustment was included in the project budget, dedicated to potential delays and rework.

Moreover, two key members of VWT overseeing the project left the business. One, left after the FAT in December 2022, and the other, the senior project manager left in February 2023. Although this did not cause any delay in the project it disrupted the line of communication. Provision was put in place by Veolia to handover the project to another senior project manager who worked through the transition and continued to consult with BTG on the project.

Finally, during the leadup to the FAT, VWT merged with a company called Suez and were moving all their manufacturing facilities from the Stoke-on-Trent, where the FAT took place, to Madrid, Spain (Brachlianoff, 2022). This caused issues during the FAT since the building and utilities were owned by Suez who were operating with a skeleton staff work force and limited utilities. This caused friction between Suez and VWT employees on site making the FAT difficult to complete. However, with support from higher management the FAT was completed successfully and on time, which given the circumstances was a major success.

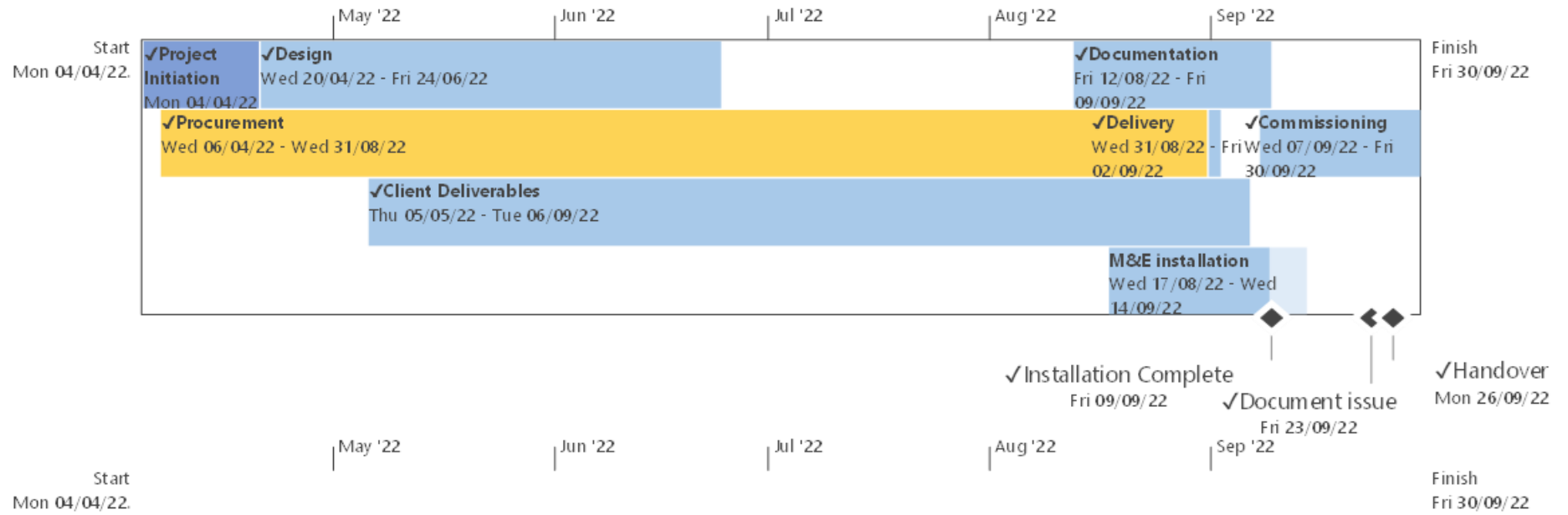


Figure 5 Gantt chart revision 1

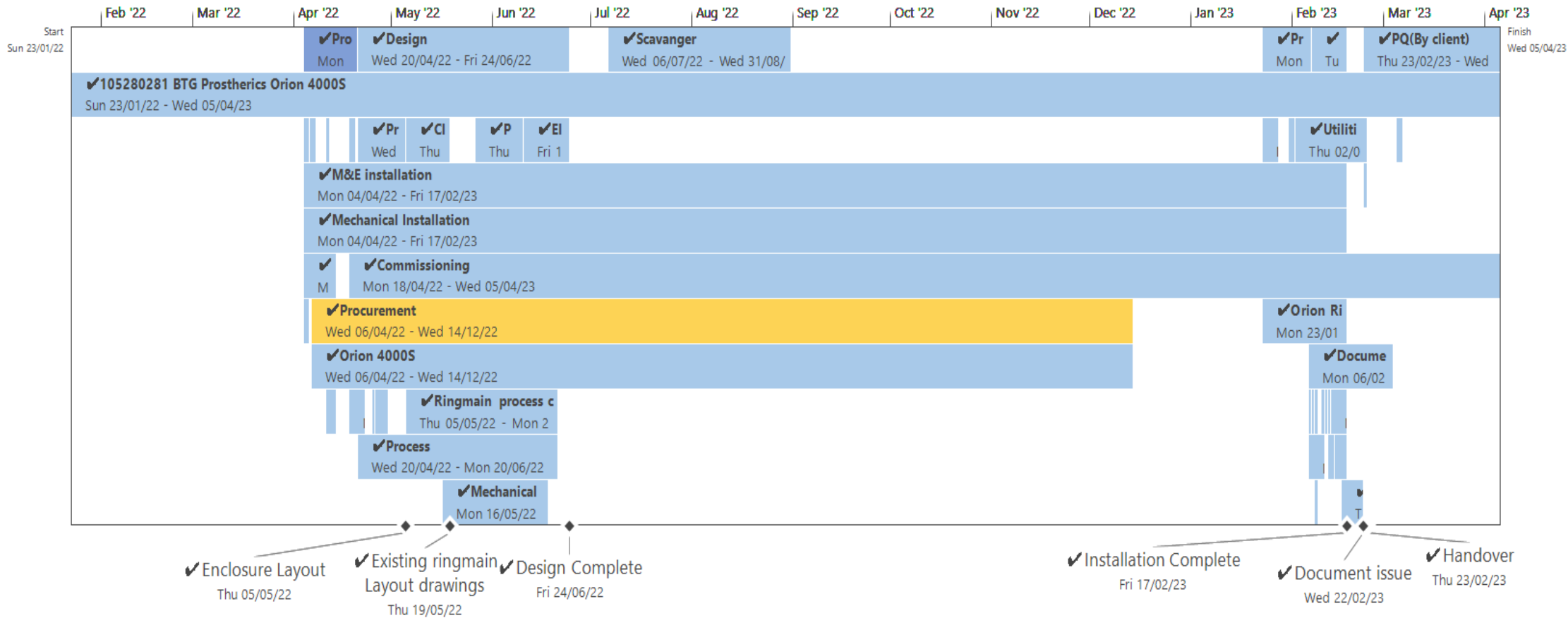


Figure 6 Gantt chart revision 2

3.3 Milestones

3.3.1 Procurement

To guarantee the project was not delayed, a formal procurement process was fast tracked to ensure the PW generation plant could be installed during the maintenance window.

Due to global material price increase and shortages in electronics, VWT could not guarantee a quote for 30 days, only guaranteeing the price for 7 days after which a revised quotation would be necessary. This proved exceptionally difficult and required several Director level meetings to expedite the process, eventually settling on a legally binding *letter of intent* in March 2022 agreeing to the purchase the PW plant from VWT at the agreed price, while terms and conditions of the project were still being finalised. This was only possible because of a longstanding relationship with VWT, who understood the nature of BTG's manufacturing operations and guaranteed a build slot to ensure the project was on track for September 2022.

The procurement stage was a significant achievement given the challenges presented by the pandemic, a skeleton workforce, worldwide shortages of labour and materials. To successfully sign-off procurement with a Factory Acceptance Test (FAT) in August 2022 before shipment was a major milestone.

3.3.2 Validation Plan

According to the Food and Drug Administration (FDA) the validation plan defines the documented programme, providing a high degree of assurance that the PW generation system consistently meets predetermined process specifications and would not impair product safety, quality, effectiveness, or efficacy (Food and Drug Administration, 2022).

The validation plan seeks to demonstrate compliance with Good Manufacturing Practice (GMP) and predetermined BTG specifications detailed within the scope of works and supplier proposal package; see appendix 2 for validation plan.

Document / Deliverable	System Owner (Engineering)	Validation	Quality Assurance	IT	Quality Control	Supplier (VEOLIA)
Design Qualification	A	A	A	NA	NA	O
Factory Acceptance Test – Wrap	O	A	A	NA	NA	O
Factory Acceptance Test – Supplier	A	A	A	NA	NA	O
Supplier Site Acceptance Test	A	A	A	NA	NA	O
Site Acceptance Test	O	A	A	NA	NA	NA
Supplier Installation and Operation Qualification	A	A	A	A	A	O
BTG Combined Installation and Operation Qualification	O	A	A	A	A	NA
Performance Qualification	O	A	A	A	A	NA
Interim Validation Summary Report – release for Concurrent Performance Qualification	O	A	A	A	A	NA
Validation Summary Report	O	A	A	A	A	NA
Vendor deviations	A	A	A	IR	IR	O
BTG/ internal Deviations	O	A	A	IR	IR	NA

Table 3 Document Responsibilities

O = Originator A = Approver N/A = Not Applicable (Not Required) IR = If required

Table 3 'Document/Deliverables' demonstrates the scope of documents required for the project validation which required drafting, reviewing and pre-approval prior to beginning the project.

This involved a cross-discipline team writing and agreeing a proposed method of documenting the project. Pre-approving these documents was a major milestone achieved and allowed progression of the installation phase of the project to begin without any procedural or documentation delays.

3.3.3 Sampling Plan

According to the USP and the World Health Organisation (WHO) a sampling plan is required for the qualification of any change to a PW system to verify the performance of the system while under routine challenge, and to ensure that the water produced by the change is still compliant and consistent with the PW specification in Table 4 (USP, 2021) (World Health Organisation, 2014).

A key milestone in this project was writing a Performance Qualification (PQ) for the release of the PW for routine manufacturing that was later implemented using a three staged approach, summarised below.

Stage one was performed prior to release of PW for routine manufacturing and included:

Two weeks of intensified monitoring of water produced by the PW plant including:

- Sampling the incoming feedwater daily to verify its quality.
- Sampling each stage of the PW generation process.
- Sampling each point-of-use valve within the manufacturing facility.

When all data was within specification, the PW was released for equipment cleaning only and not for routine medicinal manufacture. This was approved by BTG's Qualified Person (QP) who developed a risk assessment detailing stage one release.

Stage two involved further intensified monitoring to support the release of the PW for medicinal manufacture. This included a two week testing programme from the output of the PW generation plant and each point-of-use valve within the manufacturing facility. Once again, a second risk assessment was signed off by the QP to support stage two of the release of PW for GMP use.

Stage three which is currently ongoing, requires continuous monitoring for an extended 12-month period to allow for observation of any seasonal variance. The water produced by the PW generation plant will still be used for GMP manufacture and a review of the 12-month data will be captured and summarised within the final Validation Summary Report (VSR).

Achieving and developing the sample plan was a first in BTG's experience and marked a key milestone in the initial stages of the project. Its clarity and success means it will be used to further support any future projects of this scale.

3.3.4 The first week

The Figure 6 Gantt chart highlights the importance of the 07th – 15th of February since a significant amount of work was required to prepare and install the new PW generation plant and any delay incurred during this period would have impacted the entire project timeline.

A day-by-day account of this period was necessary and no slack in this period was allowed due to the timeline rigidity. Good planning and positive rapport with a variety of different contractors meant the goal of installation was achieved to the highest degree and on time. A detailed outline in chapter five documents the step-by-step account of this period. Given the volume of work that was undertaken whilst managing multiple scenarios, any delay would have affected the timeline; however good planning ensured the first week was a success. This was another milestone achieved.

Chapter 4: Research and Literature Review

4.1 Introduction

This section will address the importance of water to the pharmaceutical industry and the three different ways that PW can be produced. This section describes the pre-treatment stages that are necessary for purification, where PW comes from and how it is manufactured and monitored.

4.2 Water for pharmaceutical use

According to the Ph EUR and the USP there are three grades of water all of which are used in BTG during pharmaceutical production: potable water otherwise known as domestic water, Purified Water (PW), and Water for Injection (WFI) .

Water is a major commodity in the pharmaceutical sector and is a key ingredient for raw material or a starting material in the production, processing, formulation, cleaning, and manufacture of pharmaceutical products (Choudhary, 2008). Water, due to its polarity and hydrogen bonds, has unique chemical properties rendering it useful (Smarter, 2023). It can dissolve, absorb, adsorb, or suspend several components (Smarter, 2023). However, this also becomes a potential issue if the water contains contaminants that could present a risk themselves or react with the product causing a risk to patient safety (World Health Organisation, 2014). Therefore, it is necessary and a legal requirement to ensure the production, storage and distribution of PW is designed, installed, commissioned, and qualified correctly to guarantee consistent water quality (Medicines Agency, 2020).

4.3 What is Purified Water?

According to the Ph EUR monograph 0008, purified water is water for the preparation of medicines other than those that are required to be both sterile and apyrogenic, unless otherwise justified and authorised (Frestedt, 2020).

Purified water is prepared by distillation, ultrafiltration (UF), Reverse Osmosis (RO) or by any other suitable method from water that complies with the regulations on water intended for human consumption laid down by the competent authority (Dwi, 2022).

Broadly speaking PW is used for:

- Production of non-parenteral preparations or formulations.
- Cleaning of certain equipment used in non-parenteral product preparation.
- Cleaning of non-parenteral product contact components.
- All testing and assay.
- Preparation of bulk chemicals.
- Feedwater supply for Water for Injection.

There are different specifications for PW, WFI and Potable Water which are included in Tables 4-6 below.

Purified water shall conform to the requirements as detailed below:

Test	Test Method	Specification
Total Organic Carbon (TOC)	Current USP and latest supplement unless indicated.	Alert: > 150 ppb Action: > 500 ppb
Conductivity		< 1.1 $\mu\text{S}/\text{cm}$ @ 20°C
Nitrates	Current Ph Eur and latest supplement unless indicated.	≤ 0.2 ppm
Heavy Metals		≤ 0.1 ppm
Endotoxin (LAL)	Internal Procedure WAL-SP-13.132	Alert: > 0.10 EU/mL Action: > 0.25 EU/mL
Microbial limit (Total aerobic microbial count)	Internal Procedure WAL-SP-13.014	Alert: > 100 cfu / 10 mL Action: > 350 cfu / 10 mL

Table 4 Purified Water Specification

Water for Injection shall conform to the requirements as detailed below:

Test	Test Method	Specification
Total Organic Carbon (TOC)	Current USP and latest supplement unless indicated.	Alert: > 150 ppb Action: > 500 ppb
Conductivity		< 2.7 $\mu\text{S}/\text{cm}$ @ 80°C
Nitrates	Current Ph Eur and latest supplement unless indicated	≤ 0.2 ppm
Endotoxin (LAL)	Internal Procedure WAL-SP-13.132	Alert: > 0.10 EU/mL Action: > 0.25 EU/mL
Microbial limit (Total aerobic microbial count)	Internal Procedure WAL-SP-13.014	Alert: > 5 cfu / 250 mL Action: > 25 cfu / 250 mL

Table 5 Water for Injection Specification

Potable water shall conform to the requirements as detailed below:

Test	Specification
Total Organic Carbon (TOC)	Alert limit 150ppb, alarm limit <500ppb
Total Aerobic Microbial Count (TAMC)	< 500 cfu/mL Note: 'Out of Specification' report generated upon more than 3 consecutive specification breaches
Microbial Limit Test (sanitary analysis) Total Coliforms & Total <i>Enterococcus</i> spp.	< 1 cfu / 100mL

Table 6 Potable water specification

4.4 Where does PW come from?

According to the British Standard ISO 22519:2019 “Purified water and water for injection pre-treatment and production systems” (BS, 2019) incoming feed water must meet local standards or WHO standards for potable water (BS, 2019). If this is not the case, additional systems should be installed to improve the water feed parameters before the PW/WFI pre-treatment and production.

Purified water is manufactured from source or feed water, normally potable, which in the case of BTG is sourced from Welsh Water. However, there is an alternative source used in emergencies.

Source water can come from multiple supplies such as streams, reservoirs, sea water, aquifers, public or private distributors or a combination of these. Given this is the case, it maybe that source water is not potable (Ezedike, 2016). Therefore, it is a legal responsibility that the user of any source water to guarantee that the water used in any process of drug manufacture meet the requirements set by the Drinking Water Inspectorate (DSI) issued by most pharmacopeia bodies (USP, 2021)

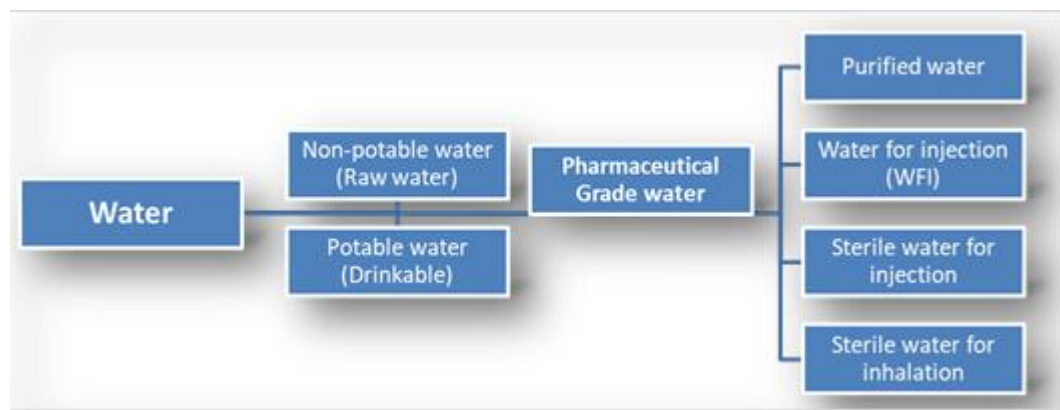


Figure 7 How source water can be used

This section discusses the two primary water sources at BTG.

- Borehole Water System (BWS)
- Potable Water

4.4.1 Borehole water systems

A borehole stream running through BTG has been licensed to be used in emergencies. Most recently over the 2022-2023 Christmas period a hard frost and subsequent thaw ruptured the main water pipe resulting in 4 days without potable water and having to use the BWS. Borehole water, according to the World Wildlife organisation “is water found underground in the cracks and spaces in soil, sand, and rock, often called an aquifer and is the primary source of springs and wells” (Hermann, 2022) .

To retrieve borehole water, it needs to be extracted using a pump allowing withdrawal of water from the aquifer (Teckna, 2023). Borehole water is not free of micro-organisms and its quality varies subject to location. The ground naturally harbours contaminants such as weedicides and pesticides. Furthermore, nitrates in the soil leach out entering the groundwater due to heavy rainfall, which is the primary disadvantage of a borehole water system (Wang et al., 2015). Further filtration, as illustrated by Figure 8, Water Treatment Flow Path, is required before the water is safe for drug manufacturing.

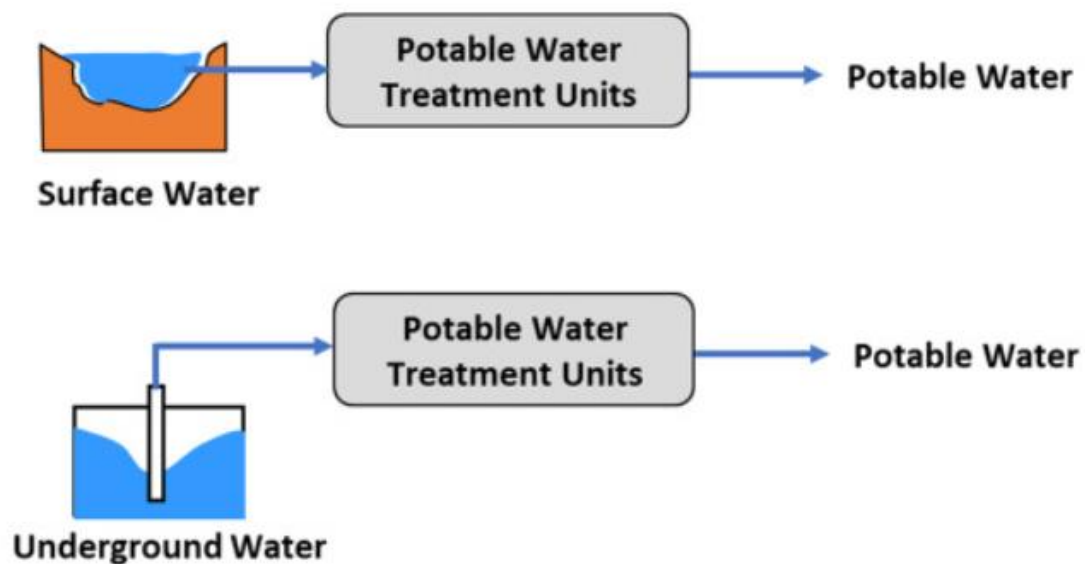


Figure 8 Water treatment flow path

4.4.2 Potable Water

Potable water is water that is safe for human consumption. Potable water must contain low levels of dissolved salt and microbes. The contaminant levels allowed in

potable water are generally considered safe for use in preparation and cleaning of equipment (Welsh Water, 2023).

Although potable water has no direct product contact, it is the starting water for PW and WFI, and the condition of the potable water will dictate the treatment required to render it safe for further processing (Medicines Agency, 2020).

Similarly to borehole water, further filtration is required to use potable water for drug manufacture and due to its conditional restraints pre-treatment is necessary to minimise damage to downstream purification processes.

4.5 Purified water Pre-Treatment

Particulates and by-products of microorganisms will enter an unprotected purification system from the potable water feed. Wetted surfaces such as storage tanks, point of use valves, components, and pipework present opportunities for biofilms to grow.

According to VWT, *“biofilm is a layer composed mostly of glycoproteins and heteropolysaccharides in which bacteria can multiply even when the concentration of nutrients in the water is very low”* (Veolia, 2020). Biofilm is exceptionally difficult to remove and cannot be detached by rinsing. If water is left to stagnate, the cells will grow forming colonies and become embedded in a matrix known as EPS (Extracellular Polymeric Substance) which protects the organism from the external environment (Chai et al., 2018), necessitating a chemical sanitisation which is an environmental health and safety concern. Therefore, to prevent this, it is important to treat the feed water before beginning the purification process.

Pre-treatment is a critical part of producing PW. Research shows that it is standard practice, to feed potable water through the following components prior to purification; sand filter, softeners, carbon, and micron filters before on-going polishing takes place.

4.5.1 Components of Pre-treatment

Figure 9 illustrates a common pre-treatment pathway for potable water. Below is a description of the pre-treatment system used by BTG.

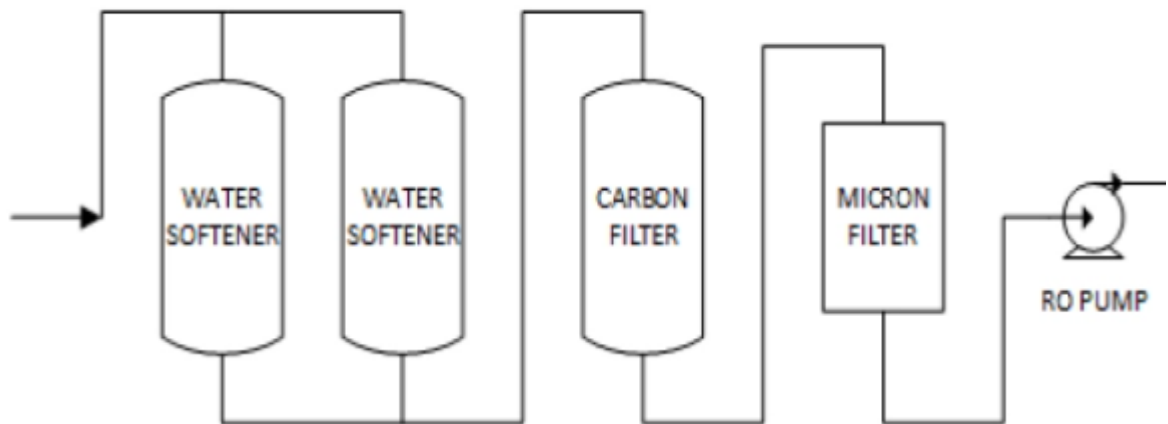


Figure 9 Components of Pre-treatment

4.5.1.1 Sand Filter

According to Emis, a knowledge centre for best techniques, sand filtration is used for the removal of suspended matter, as well as floating and sinkable particles. The wastewater flows vertically through a fine bed of sand or gravel. Particles are removed by way of absorption or physical encapsulation (Gelinkte, 2010).

Research into pre-treatment methods for pharmaceutical grade water show that sand filtration is typically the very first stage of filtration and removes larger microbes from the potable water feed to prevent damage to finer filters and processes down the line (Water Professionals, 2023).

The sand filtration process works by water flowing vertically down the sand bed removing smaller particles by each layer. The larger particles become trapped in the upper layer of sand and overflow when the sand filter goes through a backwash cycle, which decompresses the sand bed and regenerates the system (Reijnen, 2022).

4.5.1.2 Organic Scavenger

Dissolved organic matter can be present in water in the form of humic and fulvic acids which can foul deioniser resins and RO membranes which in time will reduce their performance (Al-Reasi et al., 2013). During organic scavenging the water is passed through a bed of ion-exchange material which is contained in a vertical cylindrical vessel. The ion-exchange resin has the capacity for exchanging chlorides held on the resin, for the organic matter in the supply water (Ameri Water, n.d.). During the service cycle, water is fed under pressure into the vessel containing the ion exchange resin. As water flows down through the resin bed, the organic matter is exchanged for chlorides (Sheha & Refai, 2021). The water is collected through a resin retaining filter located at the bottom of the vessel connected to a riser tube. The water then flows up the riser tube and leaves for the next stage of processing. Periodic regeneration is required since the exchange resin has a finite capacity for organic material (All Water Technologies, 2023). The scavenger is regenerated with a brine solution to remove the organic material contained on the ion exchange resin.

4.5.1.3 Water Softeners

Water softeners remove chlorine to prevent oxidative damage of scaling or fouling to the RO membranes and Continuous Electro De-Ionisation (CEDI).

The softeners remove the total hardness from the feed water by exchanging calcium and magnesium (hardness ions) in the feed water, with sodium ions held on beads of ion exchange resin contained within the softener vessels (Kushal Joshi, 2022).

When all the sodium ions in the resin bed have been exchanged the resin is exhausted and cannot remove any further hardness from the feed water. It then requires regeneration by passing a concentrated common salt (sodium chloride) solution through it to displace the hardness ions with sodium ions before it can remove further hardness from the water (Fliers, 2023).

In general, there are two softeners in parallel to maintain a constant flow of water through both units whilst at the same time allowing continuous service operation when one softener is in its regeneration. This type of operation ensures a flow of water through the softeners (The Water Guy, 2022).

4.5.1.4 Carbon Filtration

Typically, set-up in series sequence, 10µm and 5µm carbon depth-filters are located downstream of the softeners to remove particles from the water to protect the RO system. Activated carbon cartridge filters are used to remove free chlorine and particulate material from the softened feed water (Department of Health, 2022).

4.5.1.5 Micron Filtration

Micro filters remove endotoxins and bacteria from the product water. Micro-filtration at 0.2µm is a finer filter than carbon filtration and will remove further microorganisms (Veolia Water Technologies, 2021).

Once the feed water has completed the pre-treatment cycle, the water is circulated in a storage vessel in readiness for purification.

4.6 How is purified water manufactured?

Three different technologies were researched for this project:

- Ultrafiltration (UF)
- Distillation
- Reverse Osmosis (RO)

4.6.1 Ultrafiltration

Ultrafiltration uses multiple semi-permeable polymeric membranes to filter pre-treated water under high hydrostatic pressure. The membranes are constructed of hollow fibres and mechanically filtered to prevent debris and particulates from flowing into the permeate stream (Christy, 2002). Figure 10 shows a UF set-up in practice. The pre-treated water flows either inside small shells or in the lumen of the fibre as illustrated in Figure 11.

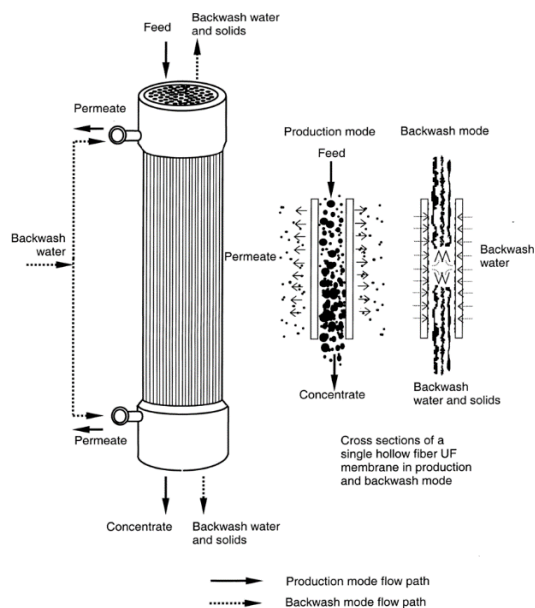


Figure 10 Ultrafiltration filter diagram



Figure 11 Ultrafiltration unit in operation

The pre-treated water flows inside the hollow fibre membrane from one end and water small molecules, and ions form an ultrafiltrate through the membrane wall under pressure from the external membrane. Large particles such as macromolecules, suspended solids and colloids are trapped inside the membrane silk to achieve ultrafiltration (Ferry, 1936).

UF is a process very similar to reverse osmosis or microfiltration, in that it uses a membrane, but the difference is the size of molecules it can retain. Figure 12 is a standard set-up of an UF system (<i>UFLEX™ | Veolia</i>, n.d.).

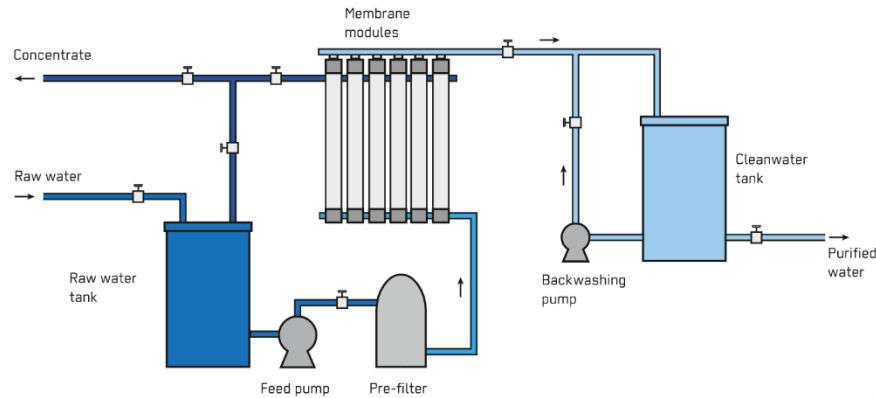


Figure 12 Ultrafiltration piping and instrumentation diagram flow

According to the USP ultrafiltration uses semipermeable membranes. However, unlike reverse osmosis units, ultrafiltration characteristically uses polysulfone with intersegmental “pores” that have been carefully enlarged. Membranes with differing molecular weight known as “cutoffs” can be created to preferentially reject molecules with molecular weights above these ratings (USP, 2021).

All ultrafiltration processes work principally by a molecular sieving. Ultrafilters with molecular weight cutoff ratings in the range of 10,000–20,000 Daltons are typically used in water systems for removing endotoxins. This technology is suitable as an intermediate or final purification step (Yoon et al., 2006). As with reverse osmosis, successful performance is dependent upon pre-treatment of the water by upstream unit operations such as softening, scavenging and filtration.

Areas of concern for ultrafiltration include:

- Compatibility of membrane material with heat and sanitising agents
- Membrane integrity, fouling by particles and microorganisms
- Seal integrity

Control measures involve filter membrane composition, sanitisation, flow design, cartridge replacement, elevated feed water temperature, monitoring total organic carbon (TOC) and differential pressure, all of which come at additional cost and resource (USP, 2021).

Recent advancement in technology has paved the way for a different material to be considered to the standard polymeric filter. Ceramic ultrafilters are exceptionally durable and can be chemically cleaned or steam sterilised, but they do require higher operating pressures resulting in higher operational costs. Ceramic ultrafilters are significantly more expensive than polymeric filters and are more easily damaged (*Ceramic UF - Membracon*, n.d.).

4.6.2 Distillation

Distillation stills can provide chemical and microbial purification through different methods such as thermal vaporisation, mist elimination, and water vapor condensation. Several designs are available, including single effect, multiple effect, and vapor compression.

A single effect uses 1 boiling chamber that requires significant amount of energy to heat the incoming water. Whereas a multiple effect uses more boiling chambers and recycles the energy from one chamber to the next, heated steam preheats the water for more efficient working similarly in vapor compression the hot distilled water preheats the incoming feed water giving up its latent heat for vaporisation (Pharmaguideline, 2022; Puretech, n.d.).

Typically, in large scale operations the latter two configurations are normally used since their generating capacity and efficiency are significantly higher. Similarly, to UF and RO the source water must meet a certain specification for the removal of hardness and silica impurities that could cause fouling or corrode the heat transfer surfaces. According to the USP and Ph EUR the distillation process does not ensure or guarantee absolute removal of contaminating ions, organics, and endotoxins. Most stills are recognized as being able to accomplish at least a 3–4 log reduction in these impurity concentrations (USP, 2021),(Medicines Agency, 2020).

Figure 13 show what a water for injection still used in practice looks like.



Figure 13 Water for injection still

For this project a Multiple-effect Water Still (MWS) was considered as a water purification method. A MWS is designed to produce pyrogen-free distillate from regulated feedwater.

The MWS is constructed of 4 columns mounted in series as shown in Figure 14, increasing the overall efficiency of the system through energy conservation resulting in reduced cooling water and plant steam utility consumptions, and therefore, reducing the operating costs of the equipment (Steris, 2023).

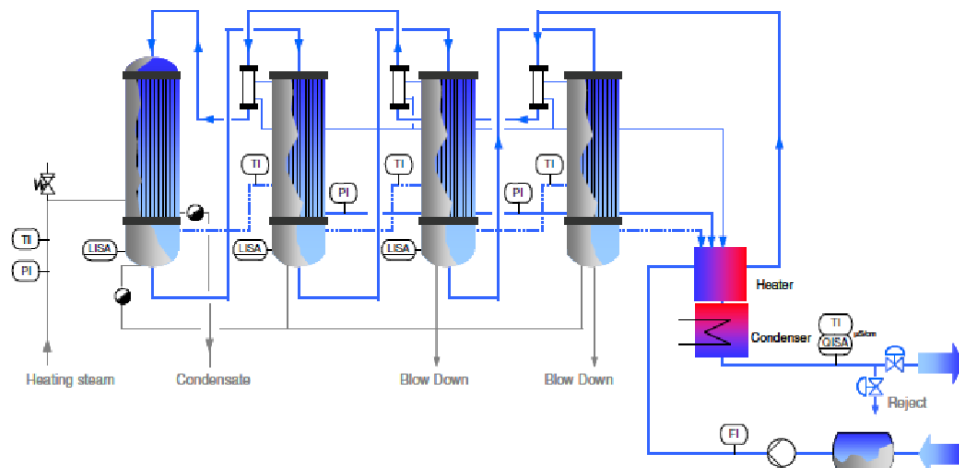


Figure 14 Distillation process flow

The feed water temperature is progressively elevated as it flows through each column. As additional columns are added to the equipment more heat energy is absorbed by the feed water. As the temperature of the feed water is elevated to the boiling point, less plant steam is required for evaporation.

Multi-effect (Figure 13) is the most popular method of generation in Europe. The main advantage of this method is the reliability resulting from the design simplicity in which no moving parts are used in the process of PW generation (Siemens & Allen-Bradley, 2020). Since the process is carried out at high temperature, i.e., $>85^{\circ}\text{C}$, this method gives a higher level of confidence in the microbiological purity of the water obtained (Siemens & Allen-Bradley, 2020).

The process of Distillation is summarised below:

4.6.2.1 Line Filling and Heating Up

The feed water fills the break tank and is pumped at high pressure through pre-heaters. The purpose of the pre-heaters is to heat all the columns and condensers to the minimum distilling temperature.

During this step the pre-heaters, columns and condenser will stabilise to their normal operating temperatures. When the condenser temperature is at the minimum distilling temperature setpoint, typically set to 96°C , then transition from the heating up step to the sanitisation step occurs. During this process any distillate produced is rejected to drain (Parikh, 2022).

4.6.2.2 Sanitisation

The purpose of the sanitisation step is to produce distillate for a specific period to flush and sanitise the internal surfaces to remove contaminants and impurities from the unit.

4.6.2.3 Distillation

This method of producing PW uses a staged evaporation and condensation process. Plant steam is applied only to the first column evaporator with the subsequent columns using the steam produced in the previous column as the source of energy. Similarly, cooling water is applied only at the condenser to condense pure steam into PW. After the first column feed water is used as the cooling source. This is

evaporated as the pure steam from the preceding column is condensed producing distillate (ISPE, 2016). The remaining pure steam is condensed producing PW.

Areas of concern for ultrafiltration include:

- Carryover of organic impurities
- Gas impurities such as ammonia and carbon dioxide
- Conductivity variations during start-up and operation

Similarly, to UF the control measures involve automatic sanitisation on start-up, elevated feed water temperature, and monitoring TOC and conductivity (ISPE, 2016).

4.7 Reverse Osmosis

There are different processes of manufacturing PW. Figure 15 shows a commonly practised method following pre-treatment.

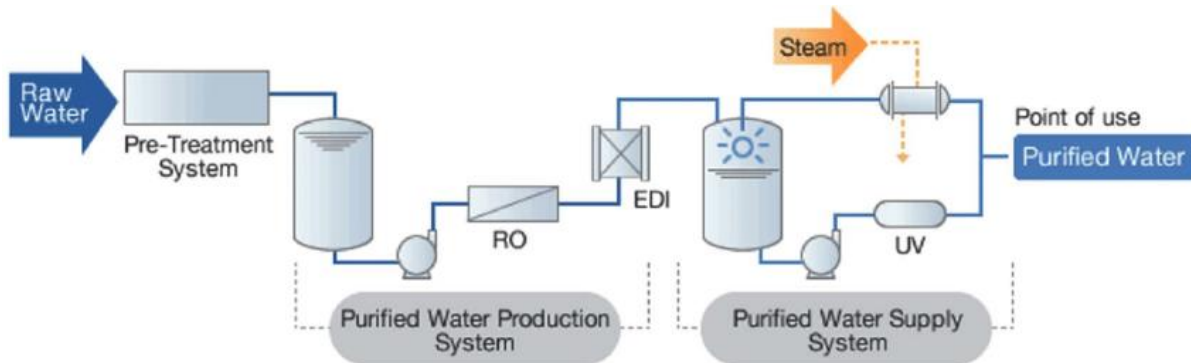


Figure 15 Common purified water filtration process

The current Quattro PW generation plant used for the last 16 years at BTG adopts the same process flow:

- RO Membrane
- CEDI
- UV

4.7.1 Reverse Osmosis Membranes

Osmosis is the process which takes place when water molecules move from high concentration to a low concentration through a semi-permeable membrane. The membrane will allow water molecules to pass through, but not ionised or larger molecules, so that it can act effectively like a molecular filter (Pharmainform, n.d.).

During osmosis the water molecules in the more diluted solution will migrate into the more concentrated solution. This migration can be stopped, and reversed, by the application of a pressure gradient in opposition to the natural direction of flow. Thus, water molecules can be forced to migrate from the more concentrated solution to the less concentrated solution (Puretec, n.d.).

This process is known as reverse osmosis, and it can be used either to concentrate solutions or to purify water. This is achieved by separating the feed stream into a concentrate stream containing most of the dissolved material present in the feed, and

a permeate stream which is purified water as demonstrated by Figure 16 (Puretec, n.d.).

It is necessary that reverse osmosis membranes operate with a concentrate stream otherwise the permeate quality and membrane lifetime will be adversely affected (Choudhary, 2022).

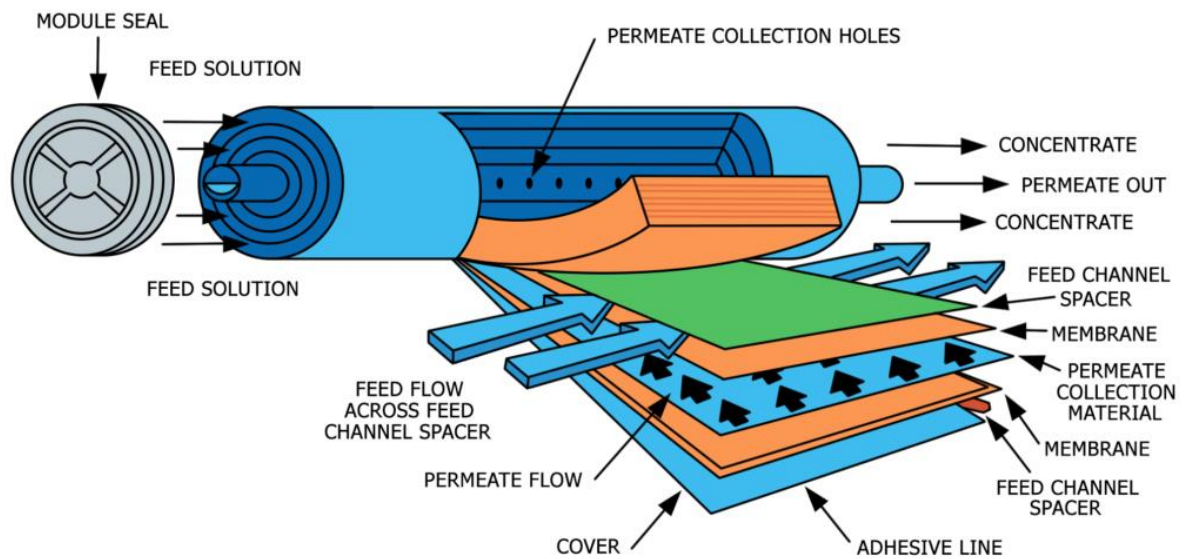


Figure 16 Reverse osmosis membrane

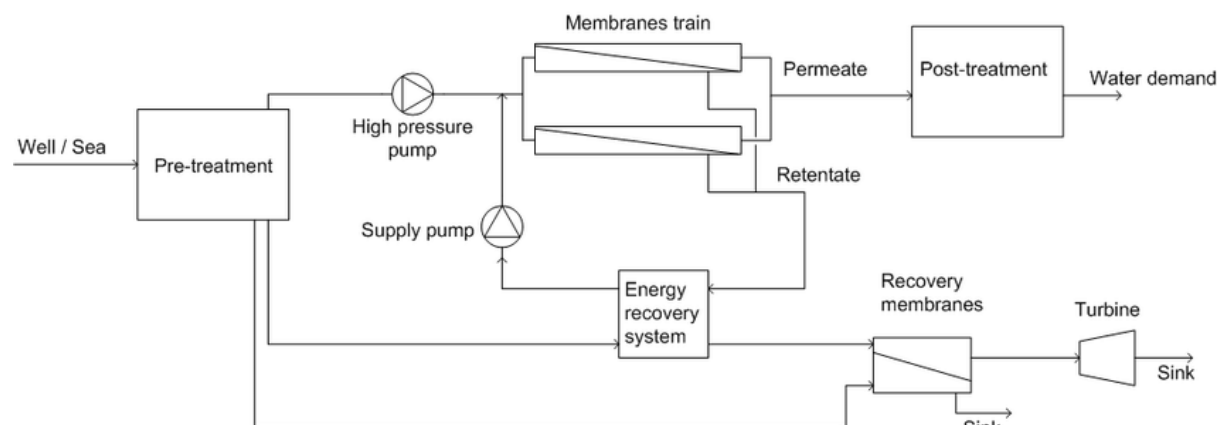


Figure 17 Schematic set-up of flow through reverse osmosis membranes

Figure 17 is a schematic of RO membranes operating in parallel. Most Reverse Osmosis units operating with potable feed water convert approximately 75% of the feed into permeate. Higher and lower conversion may be

achievable or advisable depending on the impurities present in the feed water and the degree of pre-treatment (Puretec, n.d.).

4.7.2 Continuous Electro-Deionisation

The CEDI is designed as a polishing device, to remove the final traces of ionic impurities from the product water. The CEDI is a continuous process for producing high purity water using ion-selective membranes, ion exchange resins, and electricity. Direct current (DC) electric potential is the driving force for removing ions from the feed stream while continuously regenerating the resins.

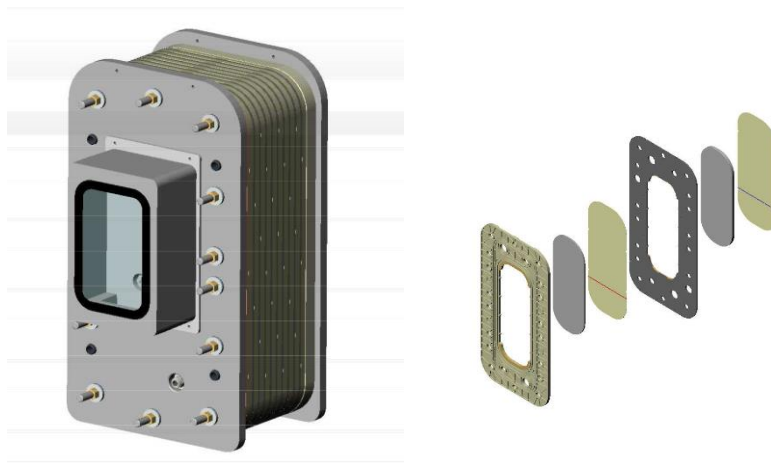


Figure 18 Continuous electrode ionisation stack

4.7.3 How the CEDI system works

Feed water entering the system flows into resin/membrane compartments. The feed stream flows parallel to the membrane surface where resins capture dissolved ions. Electric potential drives captured cations through the cation membranes and captured anions through the anion membranes. Cation permeable membranes transport cations, such as sodium (Na^+) ions, out of the diluting compartment, but prevent anions from leaving concentrating compartment.

Anion permeable membranes transport anions, such as chloride (Cl^-) ions, out of the diluting compartment, but prevent cations from leaving concentrating compartment. The waste stream removes concentrated ions from system as illustrated in Figure 19 (Evoqua, 2019; Lenntech, n.d.).

- (1) Water Inlet
- (2) Product Water Stream
- (3) Charged streams, -ve and +ve
- (4) Anion permeable membrane
- (5) Cation permeable membrane
- (6) Waste Outlet
- (7) Dilute (Product Water) Outlet

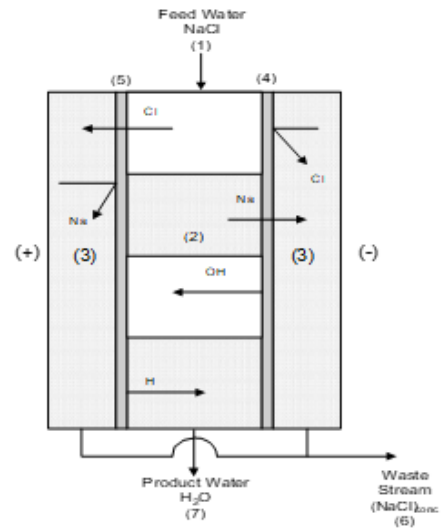


Figure 19 Diagram of how continuous electrode ionisation works.

4.7.4 Ultra-Violet Light

Ultraviolet Irradiation is the final stage of the purification process and UV is used in to limit the number of bacteria and endotoxins in the product water. UV Can only be used in systems operating continuously.

According to Choudhary, 2008, short wavelengths of UV light harm microorganisms (Choudhary, 2008). UV works by penetrating cell walls of bacteria destroying the deoxyribonucleic acid DNA of the microorganism which in turn inactivates and prevents them from reproducing.

Following the UV stage, the water flows into an PW storage tank and circulated at >1m/s around a ring main.

4.8 How is PW monitored?

Regardless of how PW is produced the monitoring cycle remains the same.

Monitoring water quality is a continuous process carried out using online instruments feeding back to a Building Management System (BMS) where the data is stored (Sciotino J A, 1992). These online instruments are calibrated to ensure they are compliant and accurately record the data produced by the PW generation plant.

These includes:

- Flow rates
- Pressures
- Temperatures
- Conductivity
- TOC
- pH

Furthermore, a robust internal sample plan is required to ensure the PW specification outlined in Table 4 is maintained.

The sample plan includes offline sample testing involving in-house testing and external analysis by a laboratory. Continuous monitoring and sampling of the PW gives a high degree of assurance that the designed system will consistently meet purified water specification and will not impair product safety, quality, effectiveness, or efficacy (Sciotino J A, 1992).

4.9 Selection

4.9.1 Introduction

This section seeks to justify why one technology was chosen over the others. It will outline the advantages and disadvantages of the systems and how the final selection was made.

4.9.2 Ultra Filtration

4.9.2.1 Ultra filtration Advantages

- Effectively eliminates particulates
- Low maintenance
- Low energy consumption

(Gelinkte, 2020)

4.9.2.2 UF Disadvantages

- Expensive filters
- Regular changeout
- Sensitive to oxidative chemicals
- Fragile
- Pressure and volume limitations

(Gelinkte, 2020)

Although UF is an effective method for purifying water. BTG requires the PW generation system to continuously produce 4m³/h which would put significant strain on the filters requiring a 6-month replacement frequency at a cost of £4,530.08.

Although BTG was very interested in the UF system, research showed that UF systems would typically be integrated as an intermediate or final purification step and not as the main component of purification on this scale (USP, 2021). The research showed that UF could be integrated as a filtration step on an RO system.

Furthermore, the general conclusion regarding carrying out a regular thermal sanitisation was that the filters degrade the more they are subjected to elevated

water temperatures. Although BTG were initially interested in a UF system due to its low running costs and low maintenance, it did not meet the objective of the project to carry out regular thermal sanitisations.

4.9.3 Distillation

4.9.3.1 Distillation Advantages

- Produces high quality water
- Natural distillation process
- No filters / membranes
- Versatile
- In-built sanitisation process

(Wood, 2021)

4.9.3.2 Distillation Disadvantages

- High operating costs
- Contamination carryover
- Variation in process
- Complex design
- High initial cost

(Deepak, 2015)

The distillation process has a variety of different designs and is considered a robust technique based on the phase change it undergoes. Although distillation is a process that relies on evaporation and is a technology that has been used for millennia it is a relatively new adoption for the manufacture of purified water in the pharmaceutical industry (Deepak, 2015). The distillation process does not use any filters but rather relies on evaporation of steam. It has proved a very successful and versatile process. However, since it relies on condensers and evaporators, both of which are prone to blockages and require a chemical clean it did not fully meet the project objectives. Furthermore, pre-heating the water to approximately 80°C to make the distillation process more efficient requires a significant amount of energy. For example, to manufacture 4m³/h of PW, would require 1,293kg/h of plant steam, which is nearing the maximum capacity of steam on site(1800kg/h). Additionally, the distillation option

was the most expensive at £455,000 compared to the UF at £298,000 and RO at £305,506, because of these shortfalls the distillation process was not selected.

4.9.4 Reverse Osmosis

4.9.4.1 RO Advantages

- Filters most microorganisms
- Environmentally friendly
- Low maintenance
- Thermal sanitisation
- No chemicals
- Known entity

(Crail & Allen, 2020)

4.9.4.2 RO Disadvantages

- Waste water produced
- Filter change required (3 years)
- High initial cost

(Scaveta, n.d.)

Reverse Osmosis is the industry standard for purifying water. Reverse osmosis relies on large filters that can withstand, heat and chemicals and effectively filter away microorganisms in feed water. Recent advancement in technology has discarded the notion that RO discharges large amounts of wastewater (Scaveta, n.d.).

For example, the Quattro system discarded 990l/h (770l/h through RO concentrate, and 220l/h through the CEDI concentrate) to produced 2000l/h of PW. Newer RO units include a recovery RO system, capturing 100% of the RO concentrate leaving only the CEDI waste (VWT, 2023a), which can be re-directed to other utilities like a hotwell feeding a boiler. Furthermore, the RO unit is manufactured completely from stainless steel and can be thermally sanitised, a relatively quick process. Although the RO system relies on filtration, the filters after a thermal sanitisation expand and contract as to regenerate the filters, prolonging their lifespan; according to Veolia, a RO membrane can last up to 5 years in operation, whereas carrying out a chemical sanitisation requires 12-month changeout. Likewise, there is an option to heat the water by using either steam or an emersion heater adding further versatility to the process. The RO unit was not the most expensive option, and it satisfied all the aims and objectives of the initial project scope. This is why this method of PW generation was selected for this project.

4.10 Justification of chosen solution

As previously highlighted, the Quattro served the Wales site for 16 years and had begun to incur considerable cost.

The most recent service by VWT strongly recommended replacing the following:

- Ultraviolet light unit - it was operating with an obsolete control panel
- Critical controller with a flickering liquid crystal display (LCD) which is obsolete.
- Continuous Electro De-Ionisation module highlighting that the module has reached the end of its typical service life
- Replacing the organic scavenger resin media and the sand filter media, emphasising that the media has reached the end of its typical service life whilst being under a relatively heavy load..

Estimated cost of approximately: £30,000.00 See Appendix 7 for report.

Additionally, the most recent repairs in 2022 included the:

- Replacement Ultra-Violent lamp and quartz sleeve: £2,704.00
- Replacing a failed Continuous Electro De-Ionisation module: £16,012.00
- Replacing 2 timer heads on the scavengers: £1,914.00
- Media recharge: £6,113.50 + £5,138.50

Total cost of £31,882.00

Two of these repairs required a 3-day unplanned sanitisation costing BTG £1,200.00 for the chemical sanitisation and £50,000.00 per day downtime.

Total cost of £334,282.00

Considering the money spent on breakdowns and repairs to keep the plant running, it was justifiable to replace the Quattro. A project scope initiated the consideration for BTG to replace the Quattro with a unit that is modern, reliable, and robust. A Wales investment strategy was used in support of the project scope to determine the budget for the project.

Following agreement from the Leadership team, a budget of £430,000 to purchase a new PW generation plant was agreed. Veolia Water Technologies were the choice contractor since they offered a comprehensive package which met the project aims:

The Orion 4000 (Figure 42) unit is a thermally sanitised, integrated packaged system which produces pharmaceutical grade purified water from a potable feed water. It is designed to operate on a continuous basis and can always produce purified water except when performing a thermal sanitisation, or during cleaning or maintenance.



Figure 20 Orion 4000

VWT understood the requirement to replace and upgrade the existing obsolete Quattro 2000 at BTG. A new PW system would double the existing capacity from 4 m³ /hr to feed the 2x existing 10m³ purified water tanks. These current tanks supply an existing ring main distribution system which feed critical utilities as detailed in Figure 4.

The solution proposed by Veolia was based on the brief and water samples provided by BTG and summarised below is the justification for choosing this option.

Orion 4000S, which is designed, manufactured and validated to Good Automated Manufacturing Practice (GAMP). The system is fully compliant with the latest FDA, ISPE, USP, Ph Eur and JP specifications to provide complete confidence in exceeding all pharmaceutical standards.

The Orion unit is a skid mounted unit complete with interconnecting pipe work and cabling. The process components incorporate carbosofts (softening and carbon filtration), cartridge filtration, reverse osmosis (RO), continuous electro deionisation (CEDI), membrane degassing and ultraviolet treatment (UV). The Orion includes the facility for each component to be automatically Hot Water Sanitisation (HWS) at 80-85°C.

The additional features are outlined below to give reduced usage on raw water, salt, electricity, and effluent production.

- **Increased Reverse Osmosis Recovery:** The Orion's reverse osmosis system operates to produce a product flow equivalent to some 75% of the feed flow, with 25% of the feed flow passing to drain. However, the Orion S unit offers an additional reverse osmosis based effluent recovery system which improves efficiency to > 90% water recovery and avoids the need for any separate effluent tank or RO concentrate pumps.
- **Orion recycle:** When the purified water tanks are full, the S series Orion allows for additional sustainability features, which include:-
 - a. Cooling Heat Exchanger reduces water to drain during recycling mode.
 - b. Variable Speed Drive pumps allow the unit to operate at 50% consumption (less flow and pressure), saving both water and electricity.

Based on a recent Orion case study; Andy Moore, a Calibration Team Leader at Pharmaron commented:

"While the new Orion unit had to be built on two skids to facilitate access into the building, a big part of the challenge was getting it to function properly for where it is in the building. The installation and commissioning went to schedule, and although there were some teething problems to deal with, the switch has been a real success."

(O'Berine & Moore, 2020)

In light of the research undertaken it was clear that the Orion 4000 was the best choice for upgrading the PW generation plant at BTG, Wales.

Chapter 5 Work carried out

5.1 Introduction

This section seeks to explain why the project was necessary and uses a risk rank to justify the importance of replacing the obsolete Quattro. It will also outline the investment strategy that was used to set the project budget. Additionally, this section addresses how the duration of the project was set and each stage was implemented.

5.2 Investment strategy

To determine the business risk of the project an investment strategy was developed. This supported the implementation of an ongoing site improvement programme to confirm that facilities, plant, and equipment could support their core function and meet future business needs.

The investment strategy found that the Quattro system at BTG was out of date and could no longer meet the demand required to grow as a business. Bi-annual reports from VWT (Appendix 7) highlighted that spare parts were no longer available; equipment was failing and support for the Quattro would be reduced due to its obsolescence.

The planned improvement programme strengthened the company's reputation as a Biopharmaceutical manufacturer at the highest level and added substantial value to the business.

The investment strategy was developed as part of the Wales site operational risk management plan and was completed using an assessment matrix against the criteria outlined in Appendix 3 Asset Assessment; the results are below.

Location	Engineering Description	Identification	Factor Scores					Additional Factors				Additional Score (ExFx GxH)	Total Score (AxBx CxD Score x ExFx GxH Score)	Investment strategy
			Fact or A	Fact or B	Factor C	Fact or D	Asset Score (AxBx CxD)	Factor E	Fact or F	Factor G	Factor H			
			Operating factors with respect to:					Validation Assessment	Lead to replace	Remaining Useful life	Replacement cost			
			Condition	Criticality	Maintenance History	Usage								
Utilities	Quattro	976	4	5	1	5	100	5	4	3	2	120	12,000	Year 1

Table 7 Assessment risk rank

Factors A to D assess the operating influences whereas factors E to H assess any additional elements associated with the project. A score of 12,000 points is considered high and ensured the project went ahead during the 2022-2023 financial year.

Although the Quattro was very well maintained and serviced bi-annually, ranking 1, spare parts were becoming scarce and workarounds were constantly required to remedy issues, because of this the condition was ranked at 4/5 and deemed poor. Furthermore, the Quattro was the only means of producing PW on site and as such was constantly manufacturing PW again ranking 5/5. Due to the age of the Quattro, there was no validation assessment in place for the system which was heavily criticised by the FDA and MHRA during a recent audit. Given a global pandemic had caused worldwide shortages and increased lead times, the lead time for a replacement unit was 12 months posing additional risk to BTG. In the event of a failed unit a hired temporary unit would have been required which is why it was ranked 4 and not 5. The replacement cost of a new system was reasonable and given the Quattro had in effect paid for itself over 16 years, the cost was ranked relatively low at 2. This risk rank was good evidence to justify a replacement PW plant.

5.3 Setting the budget

A User Requirement Specification (URS) for a PW Generation Plant was sent out to three different suppliers of UF, Distillation and RO for quotations. A URS clearly defines what the user wants the system to do. It specifies the functions required, the data on which the system will operate, and the operating environment as well as defining any non-functional requirements applying to the system. Appendix 4 contains a snapshot the URS for this project.

The URS was based on the following requirements:

- Output of 4m³/h
- HWS capability
- Meets the PW specification in Table 4
- BS ISO 22519:2019 compliant
- Automatic control / monitoring from a Human Machine Interface (HMI)
- Connected to BTG's Building Management System (BMS).

The 3 suppliers quoted based on BTG's URS:

- OPTION 1 UF supplied by Merco: **£298,000**
- OPTION 2 RO supplied by VWT: **£365,506**
- OPTION 3 Distillation supplied by Finn Aqua: **£455,000**

Furthermore, additional work was required to upgrade critical supply utilities:

- Electric supply and control
- Compressed air and process air
- Feedwater and chilled water
- Stainless steel pipework

The cost of this was calculated at: £24,865

The following infrastructure upgrades were also necessary for the project:

- GRP Enclosure
- Fire and security system
- Groundwork preparation and drainage

The cost of these were: £39,629

BTG Leadership Team were presented with a capital investment project scope and decided on Option 2 RO supplied by VWT due to them fully meeting the URS design.

Furthermore VWT, a preferred supplier of BTG, are the industry leaders in pharmaceutical water generations systems and have an exemplary proven record with multiple projects on site.

VWT service department and local engineers are well equipped and experienced with supporting and servicing critical utilities as required by pharmaceutical manufacturers. VWT contractually ensure maximum uptime and optimum system performance for a long-lasting purified water production system (VWT, 2023).

The BTG procurement process was followed during the selection of the principal contractor, however only VWT could meet BTG's expectations on both technical and timeframe requirements.

The budget for the entire project came to **£430,000 ±5%**. This was based on the following quotations:

- Option 2: **£365,506**
- Critical utilities **£24,865**
- Infrastructure **39,629**
- +/- 5% **£21.500**

5.4 Implementation period

A 6-week maintenance window was scheduled to allow for the removal, installation, and commission of the PW generation plant and to carry out all the necessary upgrades. During this period no manufacturing was possible due to removing the existing PW generation plant. The 6-week window was divided into:

- Preparation work
- Removal
- Installation
- Commissioning and Qualification

5.4.1 Preparation Work

The preparation took place outside the maintenance window and did not affect any manufacturing schedule.

This included extension of the existing concrete plinth and repositioning of an emergency exit door to accommodate for a larger GRP enclosure. Figures 20, to 24 illustrate this.



Figure 21 Existing enclosure and Emergency door into plant room



Figure 22 Existing enclosure side view



Figure 23 Reinforced footprint to accommodate larger enclosure (marked in red outline)

Figure 22 shows the existing enclosure with the freshly laid concrete plinth in preparation for the larger enclosure to be housed. The dimensions of the GRP can be found in Appendix 5.

Since the Orion was double the output of the Quattro it was necessary to recharge the sand filter to ensure the correct flow rate was being achieved to meet the new demand. The feed water supply to the Quattro was 3.8 m³/hr at a pressure of 2.25bar whereas the Orion required 6.8m³/hr and 4.5bar, which is why a recharge was necessary. Figure 23 shows the pre-treatment sand filter post recharge which was carried out by VWT using resin, carbon, and salt.



Figure 24 Pre-treatment sand filter unit after re-charge

Overhead fuel lines and pipework as shown in Figure 24 needed to be re-positioned not to impede the larger GMP enclosure.

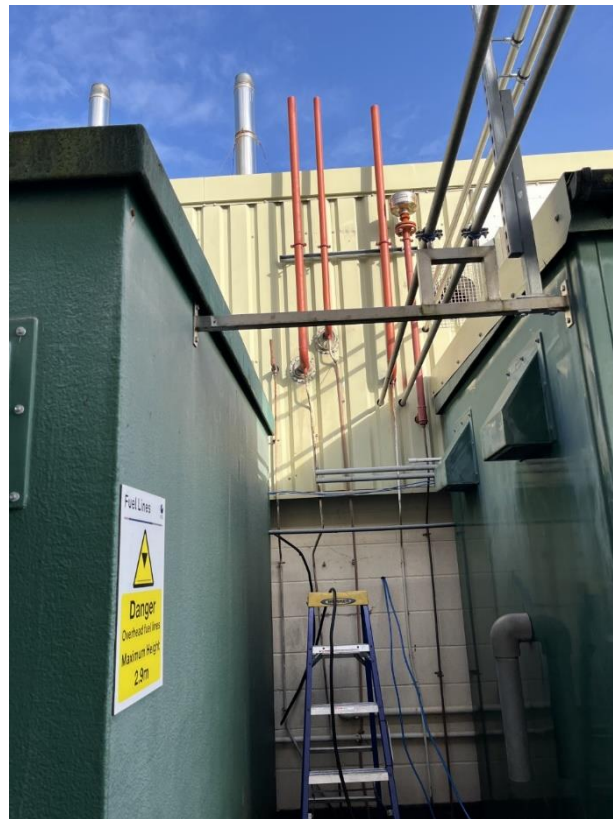


Figure 25 Overhead fuel lines and vent pipework

One of the final pre-requisites was to raise a fire impairment notice for the duration of the project to comply with BTG's insurance policy and all fire and security systems were removed temporarily in preparation to disconnect and remove the GRP.

Prior to removing the Quattro, VWT carried out end of life calibrations on all monitoring equipment including temperature and conductivity meters, flow, and pressure transmitters, which supported internal decommissioning documentation.

The above work all took place before the start of the 07th of February when all utilities were isolated, locked-off and signed over to the project lead.

5.4.2 Removal

The 6-week maintenance window began on the 07th of February 2023. All supply systems were isolated and locked off, these included electrical and mechanical isolations. Figure 25 to Figure 33 capture the removal of the Quattro and GRP from the area.



Figure 26 Quattro in place before removing - angle A

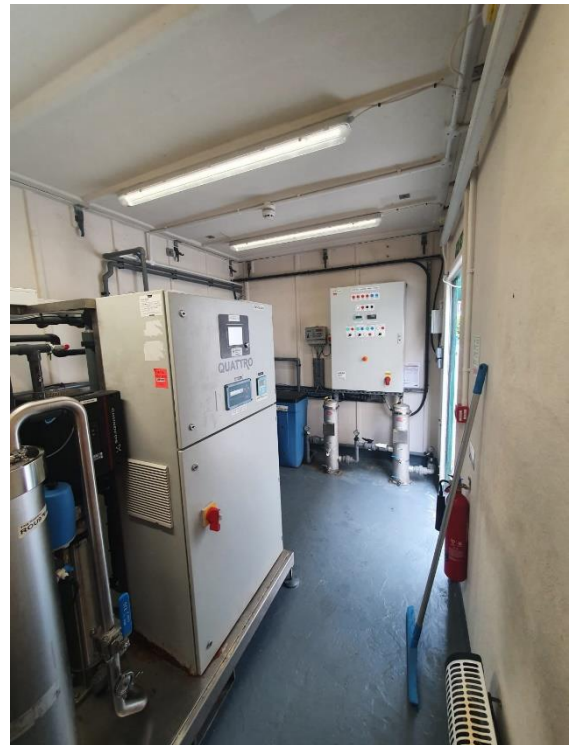


Figure 27 Quattro in place before removing - angle B



Figure 28 The removal of the Quattro from the glass reinforced plastic enclosure.



Figure 29 The glass reinforced plastic enclosure empty, and utilities removed



Figure 31 Jekko SPX532 preparing to lift the enclosure



Figure 30 Jekko SPX532 lifting the enclosure



Figure 32 Jekko SPX532 moving the enclosure



Figure 33 Jekko SPX532 placing the enclosure on a flatbed trailer



Figure 34 All utilities and glass reinforced enclosure removed

Circled in red is the pretreatment enclosure before supplying the PW system.

5.4.3 Installation

Figure 34 to Figure 43 illustrate week two of the installation process which includes a bespoke GRP enclosure, the new Orion 4000 and all associated utilities required for its operation.



Figure 35 The larger glass reinforced plastic enclosure in place to accommodate the Orion

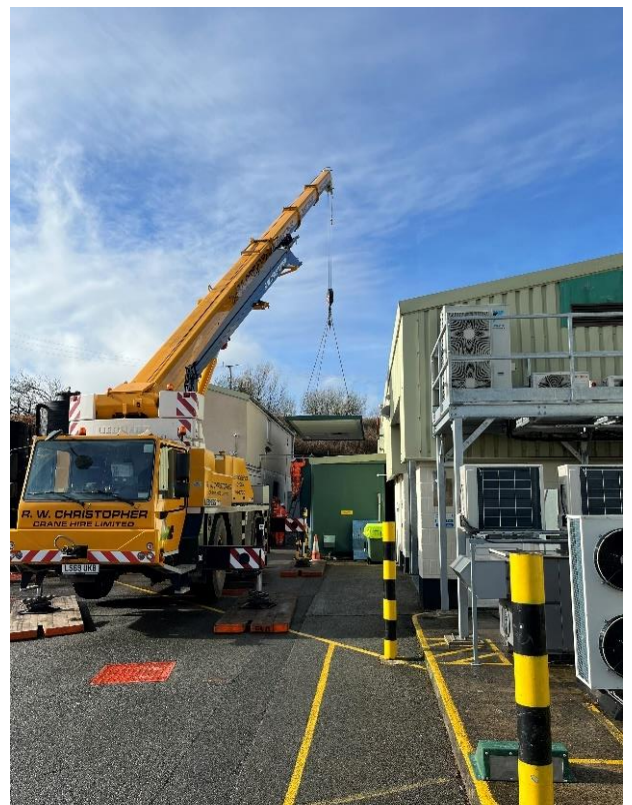


Figure 36 Crane installing the roof of the new glass reinforced plastic enclosure



Figure 37 Delivery of the Orion 4000 plant

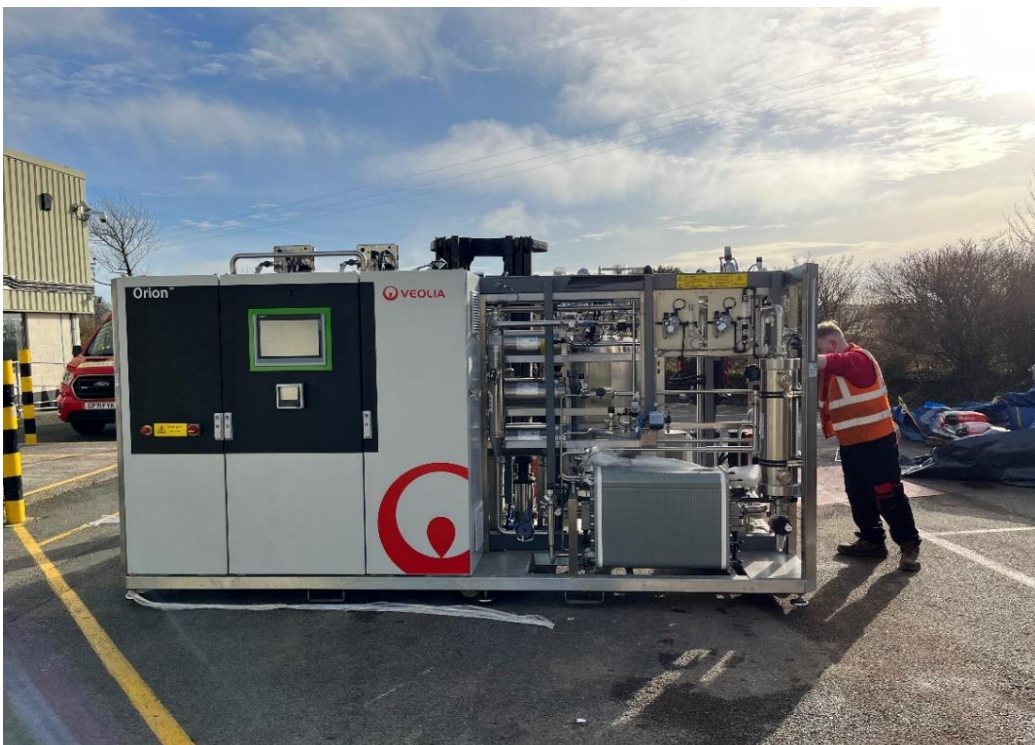


Figure 38 The Veolia Orion 4000 purified water generation system unwrapped



Figure 40 Orion being positioned in the new enclosure

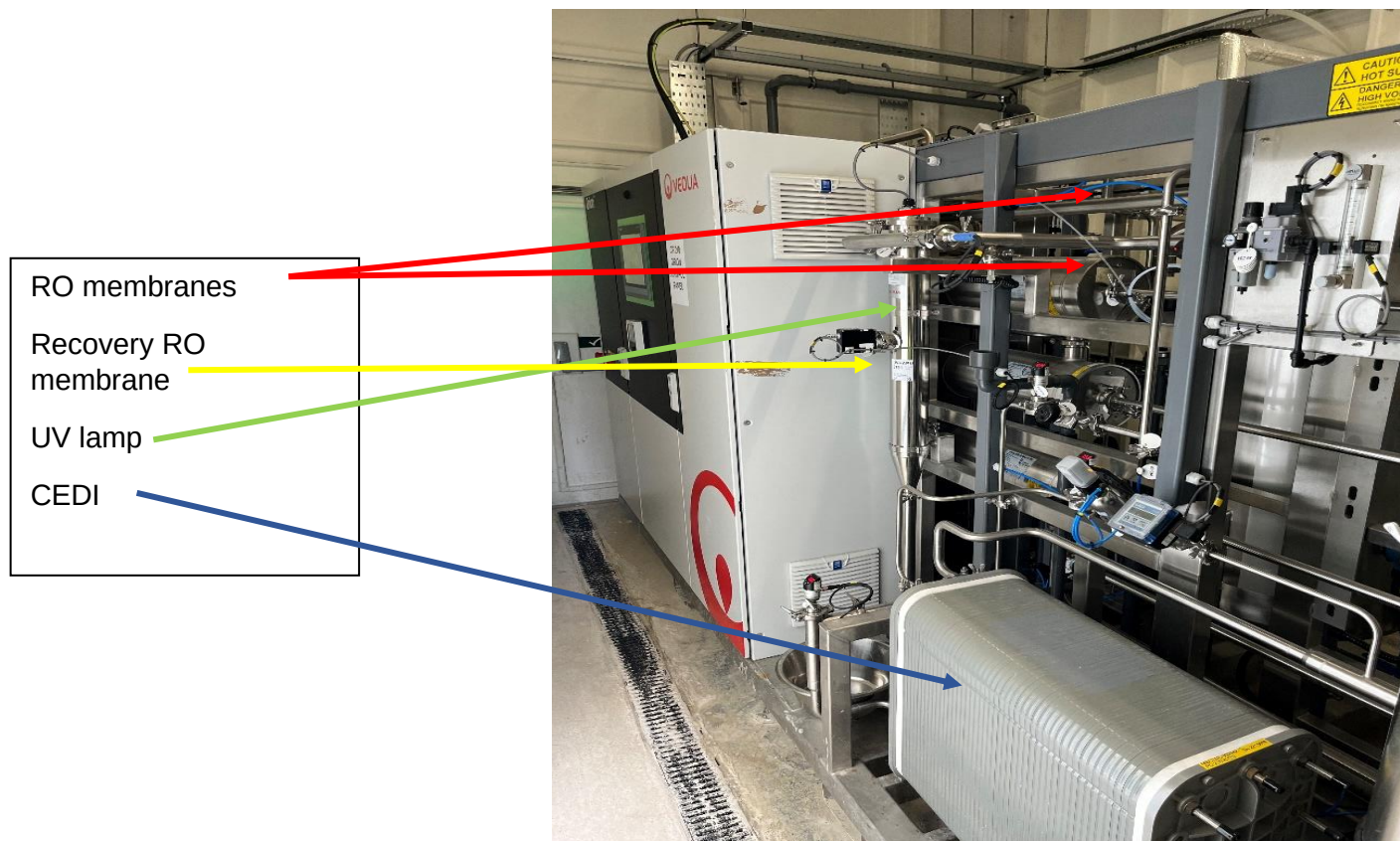


Figure 39 View of continuous electrode-ionisation unit in the enclosure

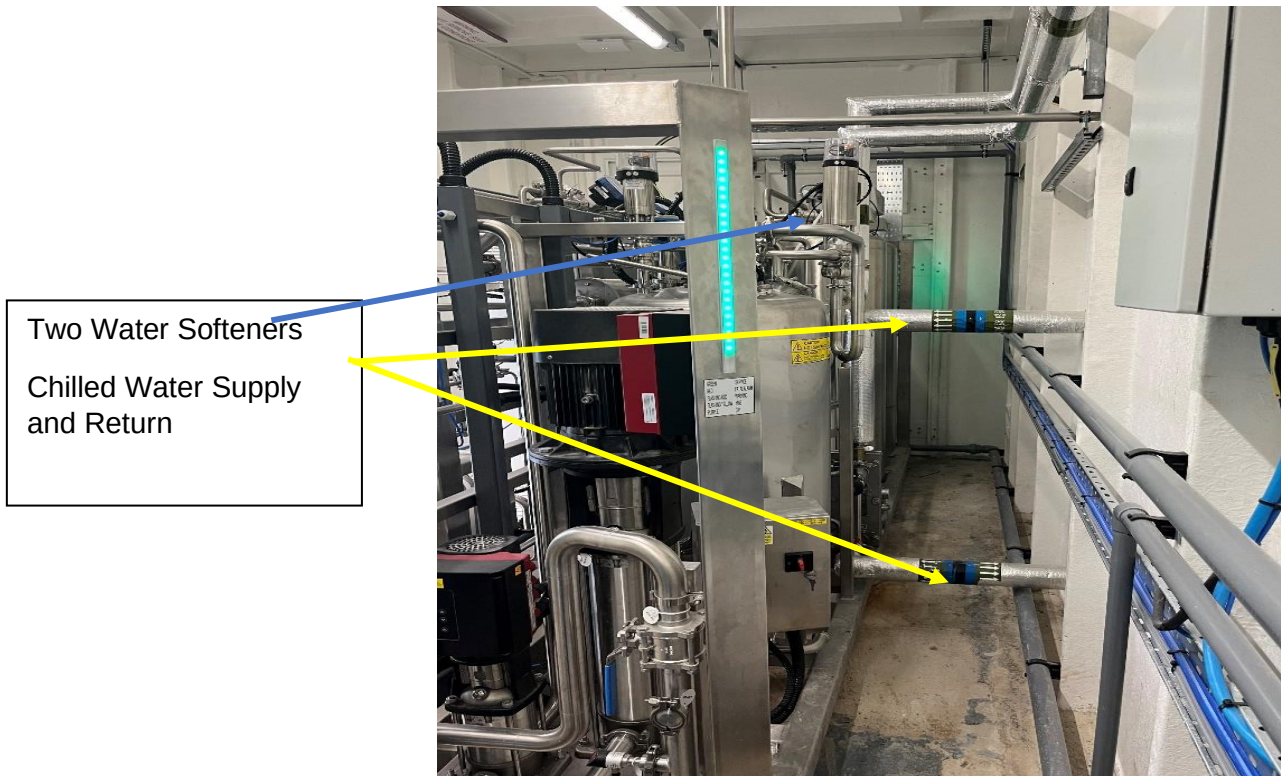


Figure 41 Orion sideview with utilities



Figure 42 Orion sideview

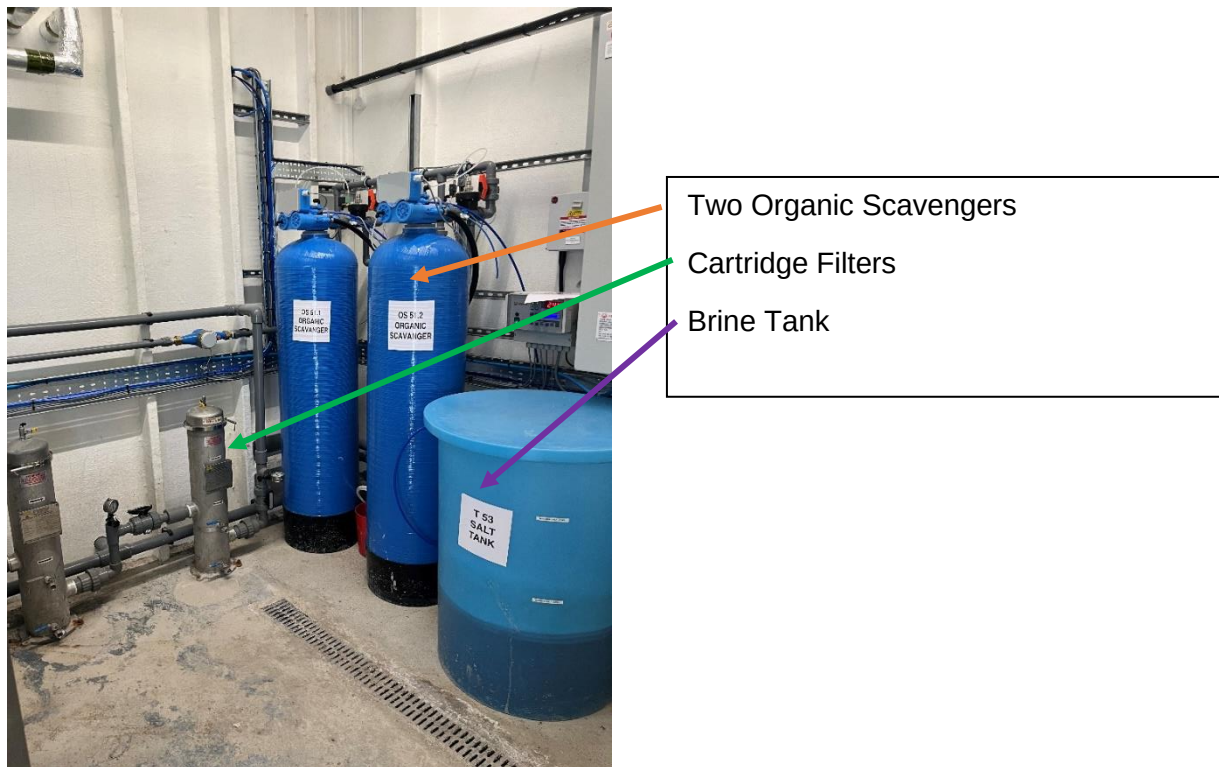


Figure 43 Two Scavengers in Parallel / Cartridge filters and brine tank

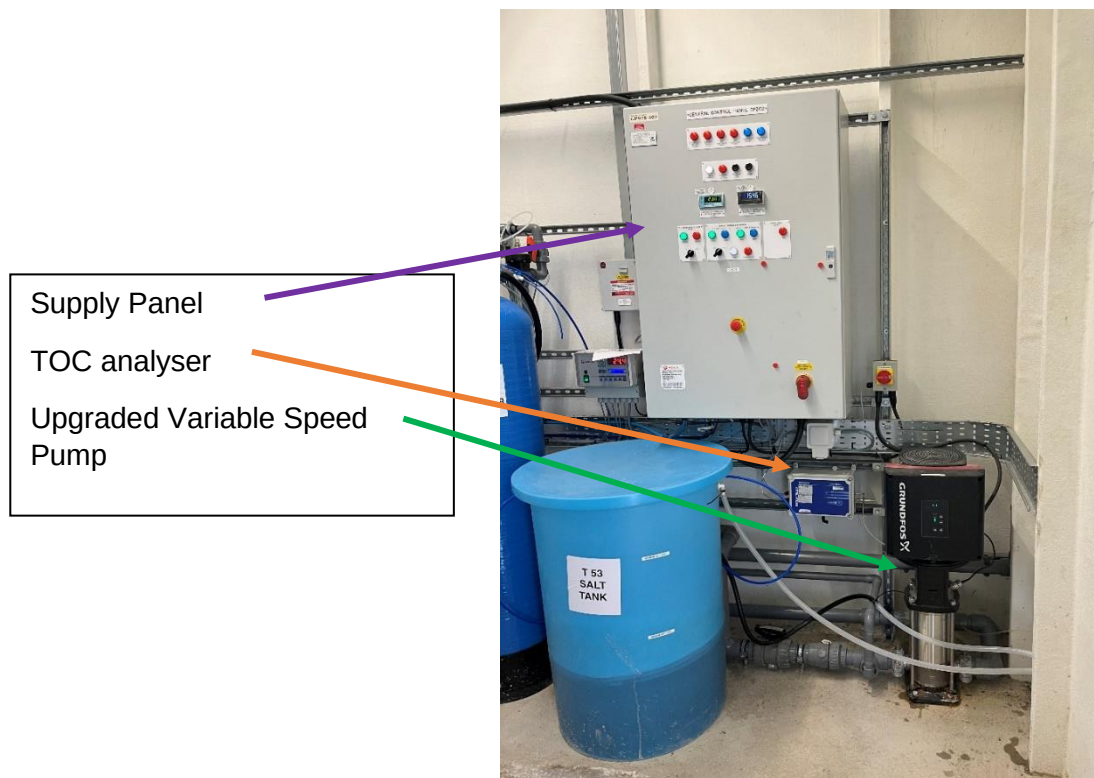


Figure 44 Control panel / Brine tank / Filtered water variable speed driver pump

5.5 Commissioning and Qualification

Commissioning is a critical part of any project and provides documented evidence to demonstrate that all key aspects of the project described in the URS operate in conformity with the client requirements and design intentions (ESC, n.d.).

This means proving that the Orion will provide the specified quality, quantities, and rates of flow at the designated outlet be capable of performing a HWS and to be monitored on the BMS system.

The commissioning of the PW generation project followed the International Society for Pharmaceutical Engineering (ISPE) Good Practice Guide – *Commissioning and Qualification of Pharmaceutical Water and Steam Systems* (ISPE, 2007)

Prior to beginning commissioning an inspection of the system took place which sought to identify:

- General cleanliness
- Visibly sagging or unsecured pipework
- Disconnected pipework
- Damage to equipment
- Leaks
- Identification of components or pipework

Following this, commissioning and qualification activities took place and captured in a comprehensive pack which is summarised in Table 8.

Walk down and check piping and instrumentation diagram ensuring isometric drawings are representative of the installed system
Check that installation records for the system equipment and components have been created. Also check vessel internals for items like spray balls and vortex breakers.
Check that the water system has been installed in accordance with the design, installation drawings, specifications, datasheets where used, and manufacturers' instructions. This includes gaining confirmation that planned backflow prevention (including air breaks for drains) equipment has been adequately installed.
Perform pipe flushing with soft or de-ionized water to remove construction debris. Use mechanical cleaning methods, as necessary.
Perform pipe system pressure (i.e., hydrostatic or pneumatic) tests.
Perform cleaning and passivation of stainless-steel equipment and piping systems.
Check that a documented and approved material joining program (welders' certificates, procedures, ISO drawings, and NDT), including joining of metals used on "product contact surfaces" has been utilised during construction of the system and that appropriate joints have been examined/inspected.
Check that specified piping material was received and installed, as specified. Check heat numbers of materials which would be joined by welding. Check received materials of construction versus materials specifications for components, which will be in direct contact with the pharmaceutical water or steam.
Check that the piping system specified to be sloped and drained was constructed to achieve drainage to low points. Systems should be sloped to aid in drainage of the water.
Check that instrumentation "loop checks" have been performed.
Check that instrument inspection and calibration was performed per GEP and manufacturer's recommendations.
Test "usability" of each sample point – by use of correct sample bottles (size and volume). Confirm that area ergonomic conditions (i.e., acceptable ventilation, sample point access, etc.) are suitable to conduct sampling.
Perform start-up and checks of support utilities, electric, water, air, pump motor run, and pump hot alignment and lubrication checks.
Check for adequate fluid flow per design within the system, including spray balls operation.
Check the purified water generation system feed water flow, quality, pressure, and temperature.
Perform tests to confirm specified operation of the unit operations in pre-treatment and final treatment, including shutdown, start-up and alarming. Included in these tests are specific automation system tests – valve sequencing, interlocks, loop tuning, and connections between water systems and process systems. This data can be compared to the FAT to determine system performance.
Perform tests to confirm the operation of heating and/or cooling exchangers that exist within the steam system (i.e., run hot water sanitisation cycle and cool down for operation after sanitisation).
Perform and certify system safety tests (i.e., relief, emergency shutdown, continuity, etc.).

Table 8 International Standard for Pharmaceutical Engineering Commissioning Checklist

Two issues occurred during commissioning:

- Software glitch
- Low feed water

The root cause of the software glitch was a modification implemented during the FAT in December 2022.

History of the modification

During the FAT an alarm, "PT43-02 Analogue out of range" appeared. This was found to be generated from a modulating valve closing immediately combined with the effect of osmosis from the recovery RO which together created a vacuum on the sealed line. This in turn operated the pressure transducer out of its working analogue range.

Resolution

A modification was introduced to expand the working analogue range which was applied and tested and proved successful. However, during commissioning the same alarm occurred and needed to be investigated. When the software engineer attended site, it came to light that the modifications introduced during FAT were not saved correctly and the software needed to be modified and saved again. Version 9.2 of the modified software was saved and stored on file to prevent any recurrence.

A lack of supply water to the Orion from the pre-treatment caused a low-level alarm preventing commissioning to continue. This was an oversight on VWT's part since the pre-treatment system had been recharged to prevent this issue from occurring however, the recharge was insufficient.

The issue was that the direct online (DOL) pump was incapable of supplying the necessary 6.8m³/h at 4.5bar.

Two resolutions were proposed. Firstly, increasing the diameter of the common piping to match the rest of the piping from 1" to 1 ½" would reduce the line pressure and increase the flow.

The second proposal was to replace the DOL pump with a variable speed drive (VSD) pump (Figure 41) which could be set to maintain the required 6.8m³/h at 4.5bar. This was the easier option since BTG had a spare VSD pump on site which was installed on the same day causing no delay to the commissioning.

Following these resolutions, commissioning and qualification were signed off as complete.

Chapter 6: Results and Discussion

6.1 Introduction

This chapter presents the results of the project and compares them the 'Aims and Objectives' in Section 2.4 to determine whether the brief has been met.

The main objective of the project was:

1. Upgrade critical utilities to support the Orion.
2. Improve the infrastructure.

The following criteria were set for the project aims:

1. Meet current and future water demand.
2. Alternative method of sanitisation.
3. Compliant to regulations.
4. Automatic control and continuous monitoring.

6.2 Measuring the project objectives

6.2.1 Upgrade critical utilities to support the Orion

As Table 9 shows, a significant number of utilities required upgrading to support the installation of the Orion.

Table 9 compares the utilities needed to run the Quattro and Orion.

UTILITY	PLANT	
	Quattro	Orion
Feed Water	2.75m ³ /h @10oC; max flow 3.75m ³ /hr @ 2-6 BarG	4.495 m ³ /hr @10oC; max flow 6.795m ³ /hr @ 2-6 BarG
Drain capacity	max flow. 1.75m ³ /hr Chemical resistant	max flow. 3.995m ³ /hr Chemical & heat resistant
Electrical load	Normal Operation (running) 9.9 kW FLC Normal Operation 29.6 kW 24A	Normal Operation (running) 11.9 kW FLC Normal Operation 34.6 kW FLC Normal Operation with Electrically Heated HWS 56 kW, 100A
Chilled water	Not required	Maximum 4.4m ³ /hr feed at 7°C / return at 11°C
Compressed air	Not required	Instrument Air 20 litres/min intermittent @ 6 to 9 barg, to the Orion Control Panel (8mm push fit) 167 litres/min @ 2 to 9 barg, to the Orion Degasser Module (12mm push fit)

Table 9 Supply utilities comparison.

Two new additional utilities were required for the installation of the Orion; a chilled water feed for cooling down the system after a HWS and compressed air for instrumentation control.

A significant upgrade to the electrical supply was necessary due to the current draw of the HWS. A new MCB and 25mm armoured cable was fitted to meet the 100A demand.

Furthermore, the feedwater and drainage capacity were double that of the Quattro and needed to be improved.

This work was completed during the preparation before the installation phase of the project.

6.2.3 Improvement of infrastructure

As previously mentioned, the infrastructure supporting the project required upgrading and amending. This included the emergency exit door to the plant room being re-positioned, a fire impairment notice to cover the length of the project, a new concrete plinth and drainage system, additional lighting and a bespoke enclosure to accommodate the project.

Table 10 compares the dimensions of the Quattro enclosure with the Orion enclosure. The challenge was that the Orion and its enclosure replaced the Quattro and its enclosure in the same footprint. This was because BTG was once an operational farm, and over the years space has become scarce. Any additional space needs to be created or replaced. This was another benefit of the Orion 4000 - a bigger unit would not have fitted in the location.

DIMENSIONS OF PLANT		
(mm)	Quattro	Orion
Length	2500	4500
Width	1400	1600
Height	2100	2326
DIMENSIONS OF GRP ENCLOSURE		
(mm)	Quattro	Orion
Length	5250	6750
Width	3000	3250
Height	2750	3771

Table 10 Dimensions of plant and enclosure

The infrastructure was all upgraded to accommodate the project and caused no delays or additional cost to the project. It was therefore considered a success.

6.3 Measuring the project aims:

6.3.1 Meet current and future water demand

Since the completion of the project in March 2023, the Orion 4000S has exceeded expectations. The output is augmented by the recovery RO, which captures 90% of the 25% concentrate waste stream - equating to 500l/h when in operation depending on the demand. If the distribution storage tanks are full then the Orion will enter recycle mode and circulate at 50% of the water around the system thus saving energy and water consumption. This contrasts with the Quattro which did not have any recovery or recycle system and was discharging 990l/h constantly to drain.

The maximum output produced by the Orion was found to be $\sim 4\text{m}^3/\text{hr}$, see Figure 52 for validation of the output. The output of the Orion satisfies the current operational demands highlighted in Table 2. It also provides a contingency of an additional $\sim 0.8\text{m}^3/\text{hr}$ for increased load on the system. It therefore meets this project aim.

Furthermore, since the installation of the Orion in February – March 2023, Figure 45-47 show a noticeable step change to incoming water. This is because of the Orion's ability to go into a recycle mode when there is less demand, which was not an option on the Quattro. This has had a significant saving of water and is under review.

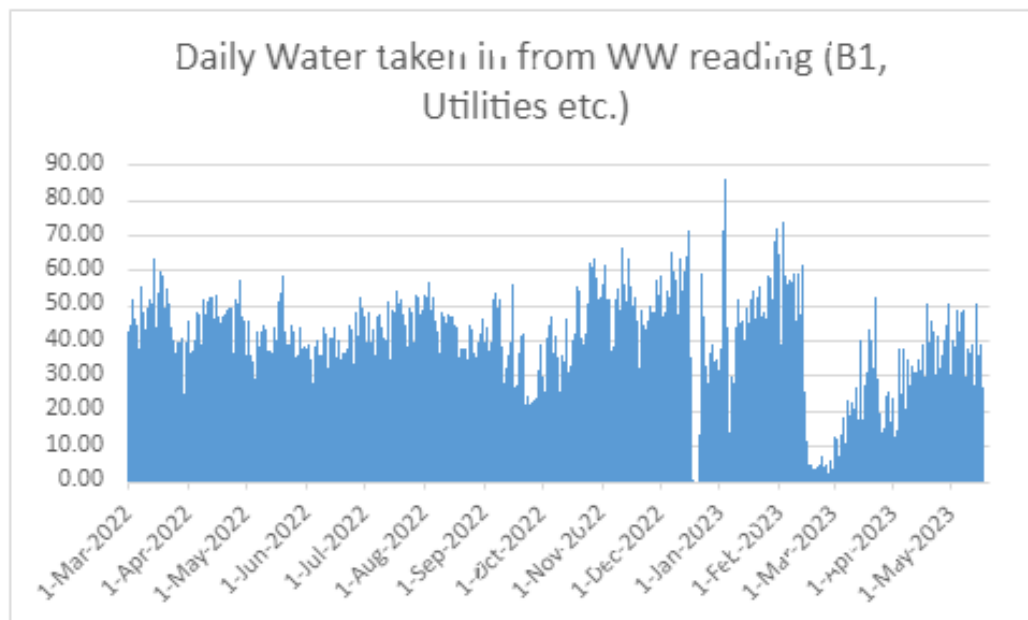


Figure 45 One-year review of water intake from supplier

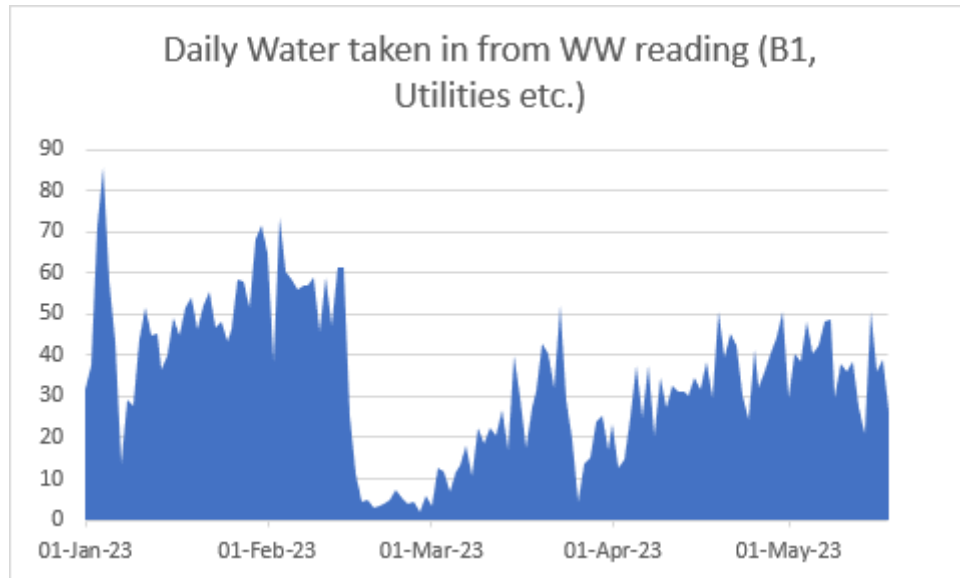


Figure 46 Five-month review of water intake from supplier

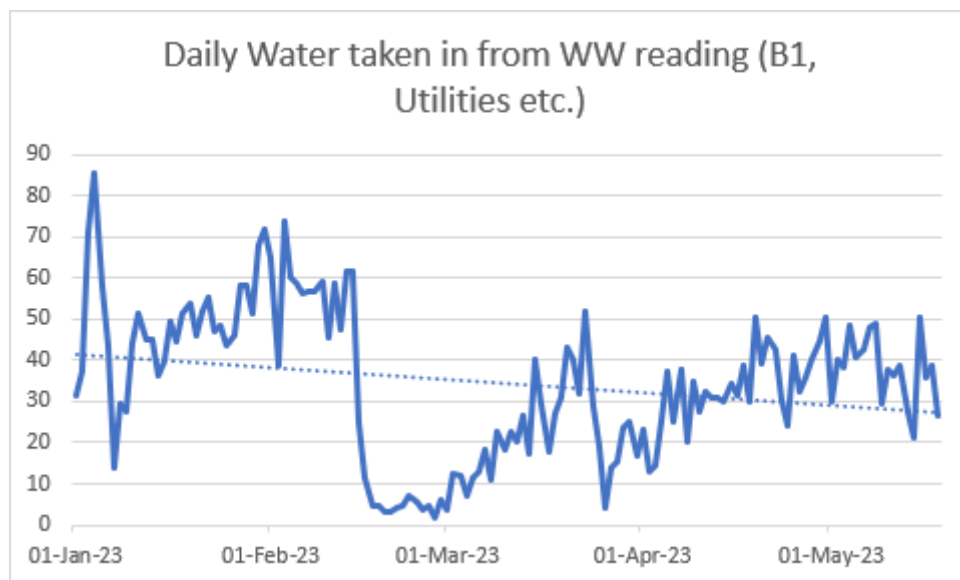


Figure 47 Five-month average review of water intake from supplier 01

6.3.2 Alternative method of sanitisation

The Quattro used a lengthy chemical method of sanitising exposing ABS and uPVC pipework to oxonia, a peroxyacetic acid, antimicrobial agent at high pressure for a lengthy time. As mentioned this is both harmful to the environment, expensive and a potential health risk, riddled with safety procedures. Although the method of chemically sanitising a water system is well documented and authorised by several bodies, BTG, are an environmentally conscious company who were awarded a Green Dragon Environmental Standard in 2014, and therefore wanted to move away from this method of sanitising (Serb Pharmaceuticals, 2014).

The sanitisation method of choice was thermal sanitisation. The USP state that “frequent use of thermal sanitisation at appropriate temperatures should eliminate the need for other sanitisation methods”.

The Orion system can be sanitised using hot water. The heat sanitisation process involves the heating of the water via an electric immersion heater located within the multi-purpose tank to 85°C – highlighted in Figure 48.

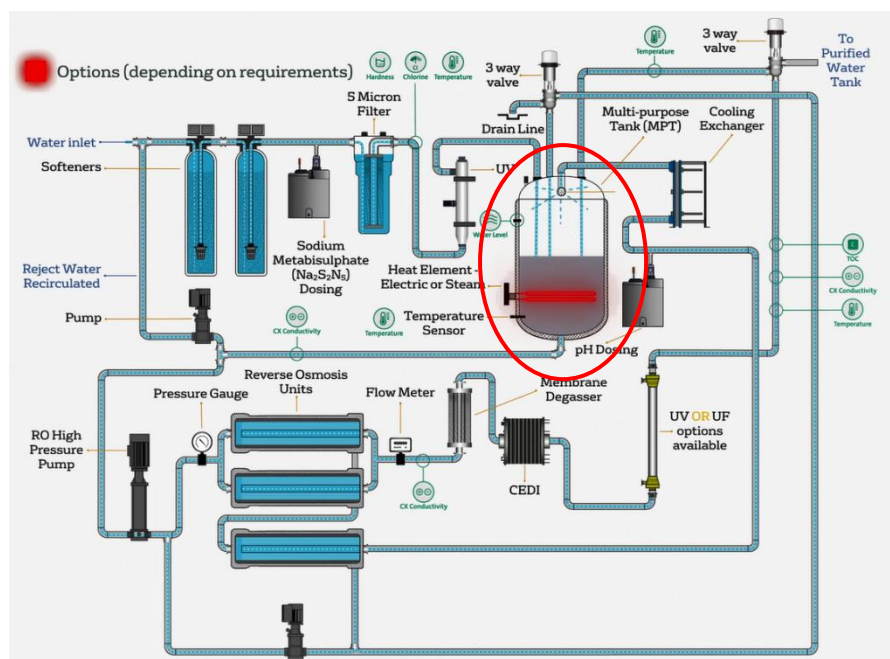


Figure 48 Hot water sanitisation schematic - multipurpose tank heating via emersion heater

The hot water is re-circulated through a loop and passes through the key components including softeners, RO membranes, CEDI stack, Degasser and UV, illustrated by Figure 49. The hot water is fed up to the distribution storage tank make up valve and back through the return line to the multipurpose tank.

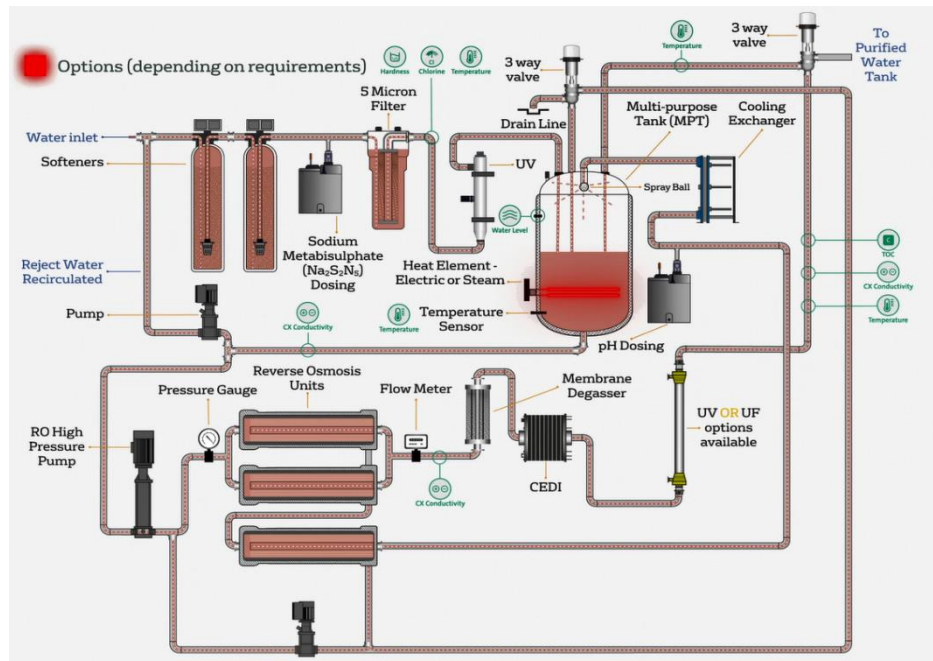


Figure 49 Hot water sanitisation flow path through critical components up to the distribution storage tank

A temperature sensor is located in the return line back to the multi-purpose tank. This monitors the return temperature during the HWS cycle and ensures 85°C is being maintained. When the system temperature, as recorded by all sensors, exceeds 80°C the system enters the sanitisation mode and continues to circulate and maintain 80°C for 1 hour, thus ensuring the sanitisation process is completed.

This improved method of sanitisation has several key benefits as compared to the Quattro in Table 11:

	Sanitisation	
	Quattro	Orion
Duration	3 days	6 hours
Method	Chemical	Hot Water
Downtime Cost	Up to £150,000	Up to £12,500 (6 hours = $\frac{1}{4}$ downtime)
Operational Cost	£1,200	£97.92 @ £0.34kWh
Specialist Operator	2	0
Sequence	Manual	Automatic / Pre-programmed
Testing	Manual checks	In-line monitoring

Table 11 Quattro vs. Orion Sanitisation

The HWS option exceeds the chemical process in every way. The benefits of pre-programmed sanitisation are invaluable to BTG. For example, the system can be pre-programmed to sanitise during the early hours of the morning in-between any critical processing. More frequent sanitisations can now take place, achieving better control of contamination. Furthermore, in the event of a breakdown where the integrity of the system is broken, the downtime post repair is significantly less than it would be with a chemical sanitisation. Figure 50 shows the HWS configuration screen on the HMI, where the sanitisation can be pre-programmed to take place at any given time of day, weekly, fortnightly or according to BTG's needs. Furthermore, the step settings are seen to the right-hand side where different parameters can be inputted if required. Figure 51 displays the HWS trend at the end of the cycle having achieved $>80^{\circ}\text{C}$ for at least 1 hour.



Figure 50 Hot water sanitisation configuration screen



Figure 51 Hot water sanitisation trend

6.3.3 Compliant to regulations

As previously mentioned, there is a requirement that ensure all components are manufactured from SS 316/316L which also includes product contact parts.

The biggest non-compliance of the Quattro was the material which was fabricated using a combination of SS, ABS and uPVC parts. It was incumbent on BTG as a pharmaceutical manufacturer to be engaged in biopharmaceutical manufacture at the highest level and continue to adapt and amend equipment as guidance and legislation are released. Therefore, the Orion is constructed of the 300 series stainless steel, including the frame as illustrated in Figures 52-49.



Figure 52 Orion 4000 skid manufactured from 300 series stainless steel



Figure 54 CEDI manufactured from stainless steel



Figure 53 Reverse osmosis membrane housing manufactured from stainless steel

The polymers used for the Quattro were prone to damage and harboured contamination. Historically, it was difficult due to the age of the equipment to source new parts for the Quattro, such as ABS check valves, ball valves, unions and rotameters. This led to situations where parts were repaired multiple times rather than replaced for new. Furthermore, any gluing being undertaken on pipe would take 1 hour per bar of drying time, adding on to the already prolonged process.

The Quattro material was also restricting any other forms of sanitisation being implemented. However, with the Orion, several sanitisation options are available, including chemical, UV and hot water - which is the preferred choice. The Orion is a modern, state of the art, compliant PW generation plant and is easily maintained with off the shelf spares and stainless-steel pipe work that is more robust and not as easily damaged or broken.

6.3.4 Automatic control and continuous monitoring

The Orion operates automatically and requires very little human interaction apart from when there is an issue that needs resolved. It continuously collects data and adjusts the output accordingly. Including the fully automatic configurable HWS process. The system takes care of itself via a Siemens S7 PLC and HMI control panel that provides a central control for the operation of the unit. The HMI provides status, operational and trending information with remote communication to the Engineering BMS system.

Several monitoring options exist on the Orion, including hardness, chlorine, pH, TOC and conductivity. It controls the flow, temperature and pressures of the system to maximise efficiency and output even having an inbuild recovery and recycle mode when the system demand is low.

Furthermore, the system is connected to BTG's BMS system that is continuously monitored and stores data which is useful for analysis or fault finding. The Orion is compliant to the 21 Code of Federal Regulations (CFR) part 11 that states any electronic records and electronic signatures are treated the same as paper records and handwritten signatures. In other words, all changes to the process not only require a user unique login but any changes are electronically stored and traceable.

Figures 56 - 58 contrast the Quattro and Orion HMI panel demonstrating the technology development difference over 16 years.

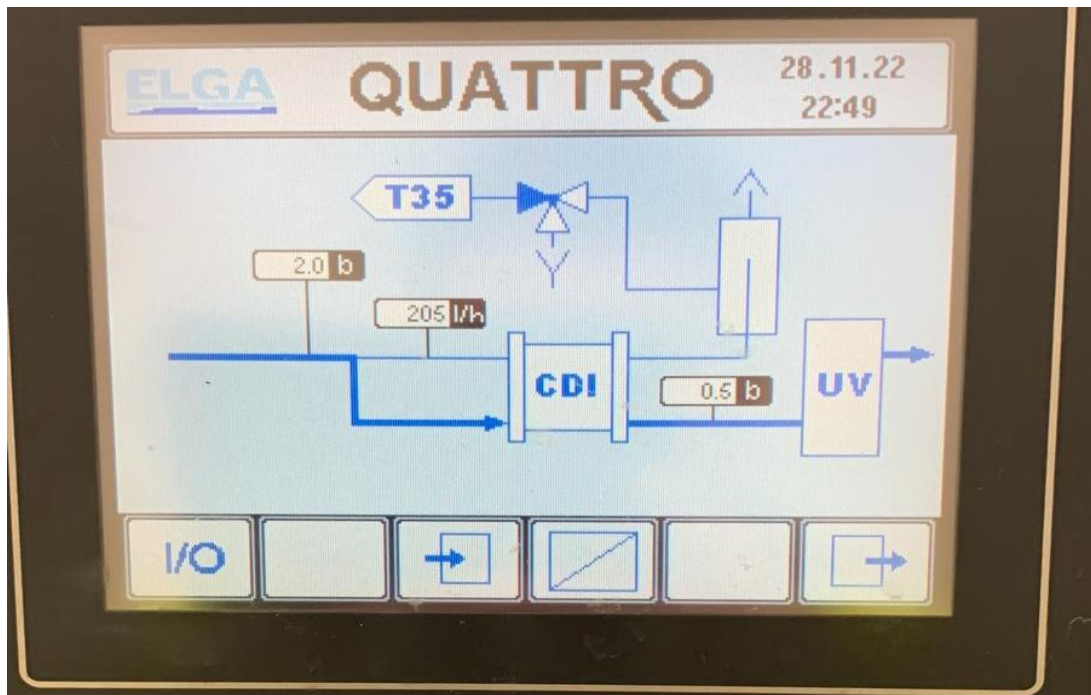


Figure 56 Quattro control panel screen 1 with continuous electrode ionisation and ultraviolet lamp. Measuring flow and pressure

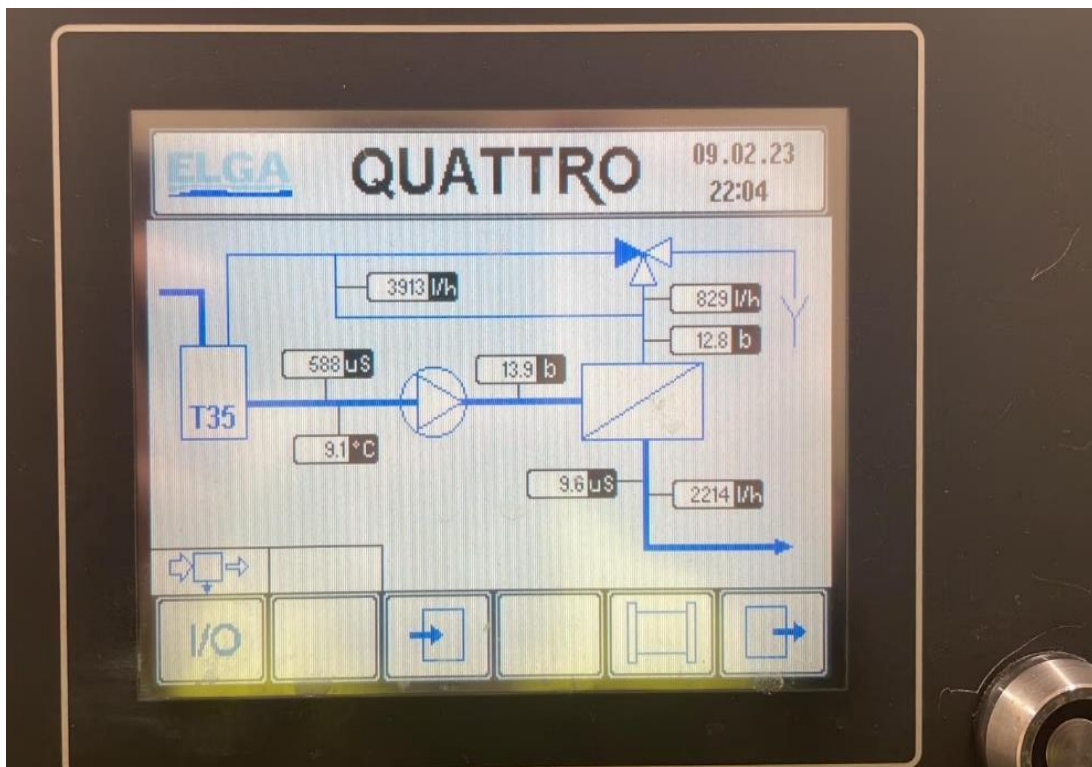


Figure 55 Quattro control panel screen 2 with high pressure pump and reverse osmosis membrane. Measuring flow, temperature, pressure and conductivity



Figure 57 Quattro control panel screen 3 highlighted 2,008l/h output and a recirculation line back to the storage tank. Monitoring temperature and conductivity.

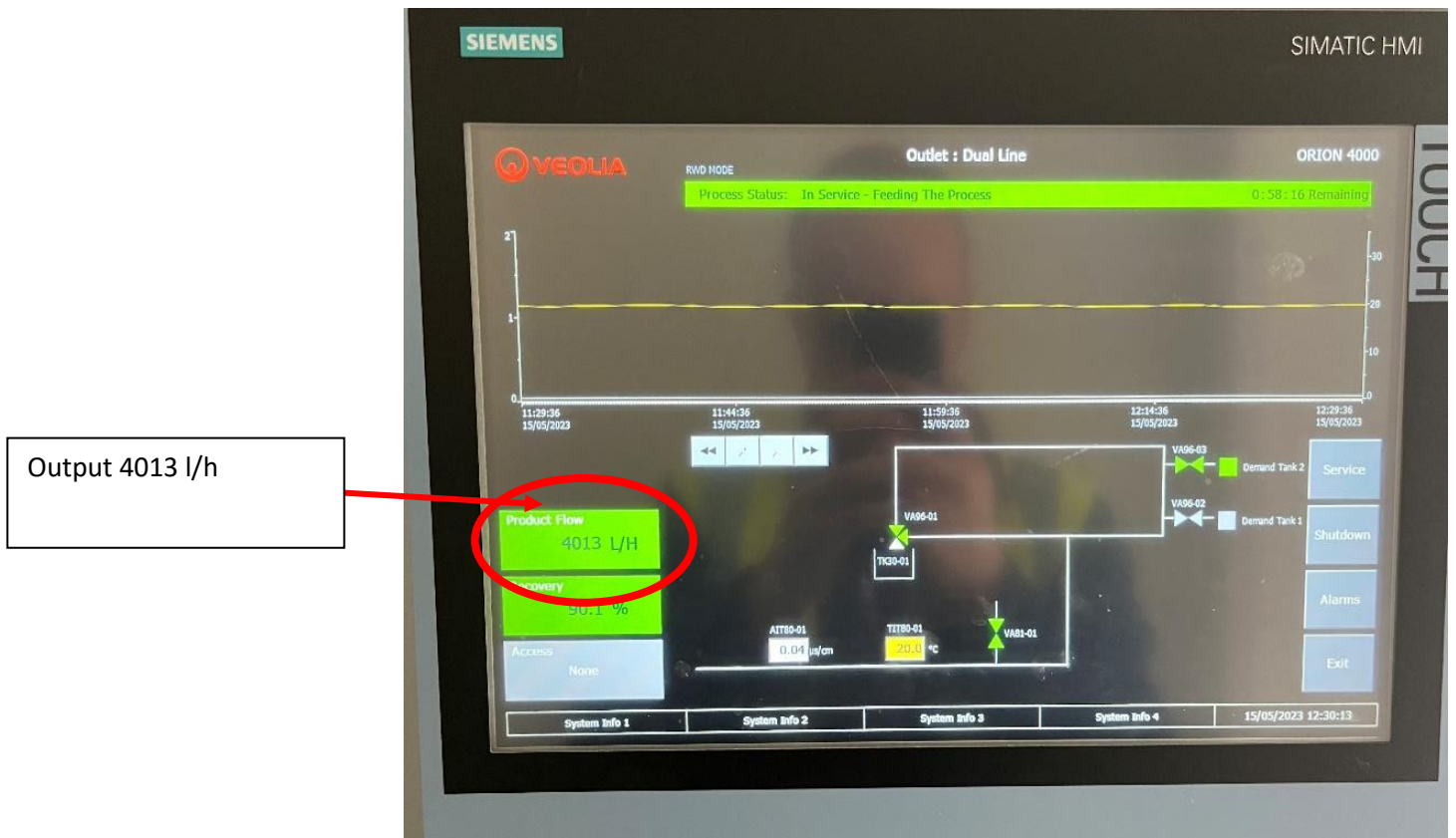


Figure 58 Orion control panel in service with output flow of 4,013 l/h. Measuring temperature and conductivity



Figure 59 Orion control panel trending temperature data



Figure 60 Orion continuous in-line monitoring. Measuring total organic carbon, temperature, conductivity, and parts per million

Chapter 7: Conclusion

This project sought to replace the current PW generation system used in the Wales BTG site. It looked at different technologies that were available and found the best option to be a RO unit supplied by VWT. This was based on thorough research into currently available technologies and a justification of the chosen system.

The early stages of the project were difficult following the impact of a global pandemic. However, with good communication and organisation, a robust timing plan was developed to meet a tight maintenance window whereby the Orion was installed and qualified successfully. This project was qualified using an approved validated strategy and the completion of a VSR (Appendix 8) qualified the Orion for routine, concurrent use of the system. Finally, the success of this project was not only measured by the aims and objectives but also on the budget and timeline, all of which were met.

7.1 Personal Reflection

When carrying out this project I encountered many challenges. PW is a critical component in the manufacture of life saving medications, and it took some time to fully appreciate the gravity of the regulations around PW and how to implement them at BTG. Quickly I learned the need to involve different specialists to assist with the project who advised on certain requirements for the project. Although, it was initially difficult to involve other members of staff, it proved invaluable in the long term to see the project come to fruition. One of the biggest hurdles was the delay one day before the project start date. Everything and everybody were aligned to begin the project but due to processing of a critical batch this was delayed by one week, and although it was initially frustrating it taught me valuable lessons about the importance of being respectful, patient and not presuming to know everything. Although making last minute changes to my project was difficult, guidance from my line manager was important. Going through the experience has improved my understanding of how projects at times can change at the last moment due to unforeseen events.

Chapter 8: Recommended further work

Upgrading the PW generation plant was the first of two phases in upgrading the entire PW system at BTG. Given the first phase was successful, phase 2 will focus on replacing the PW distribution system.

Figure 61 illustrates the completion of phase one, having upgraded the PW generation plant (circled red) from the Quatro 2000 to the Orion 4000. However, an old ABS system further downstream of the Orion needs a significant upgrade to improve the distribution ring main, which is currently manufactured from ABS plastic and a range of obsolete parts.

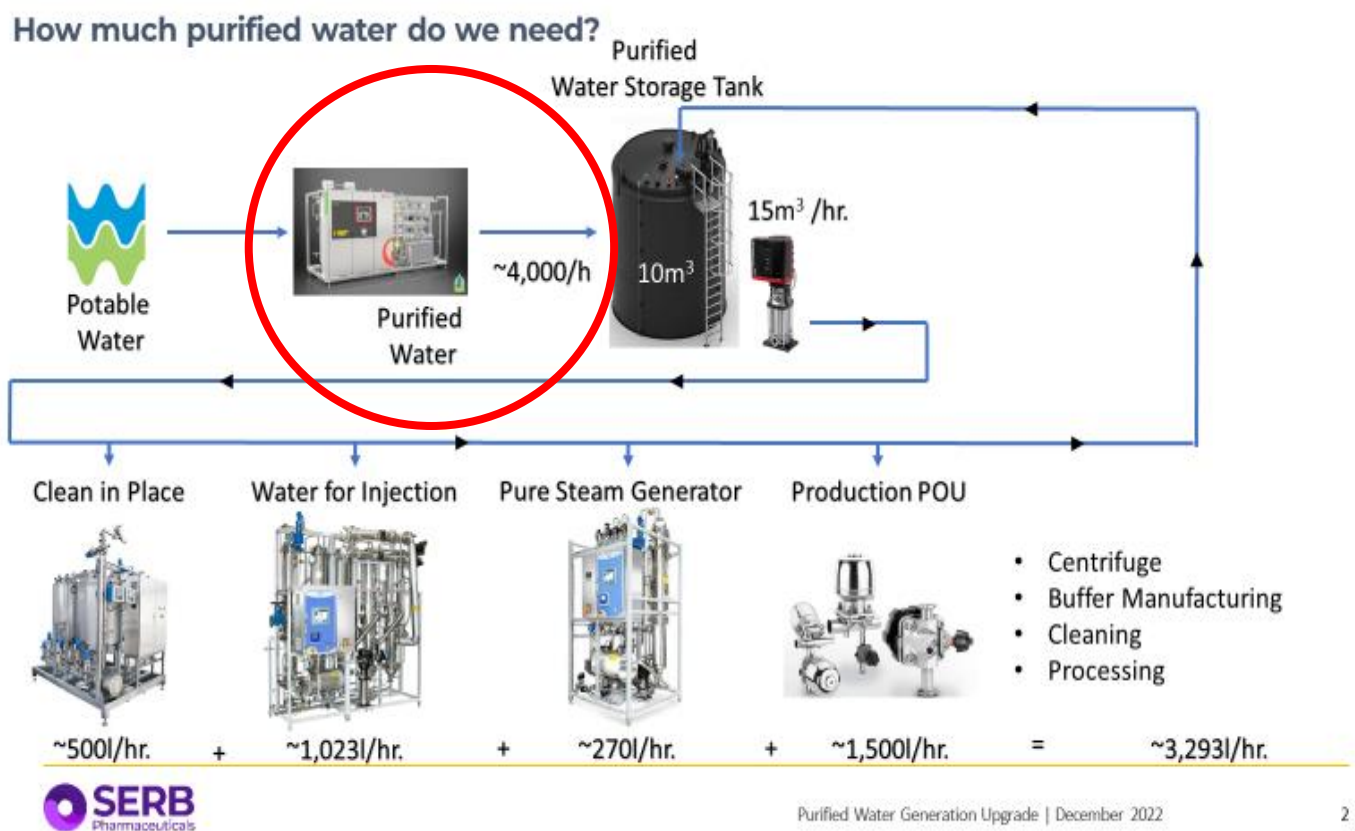


Figure 61 Flow diagram following phase 1 completion.

Phase two of this project is to upgrade the PW distribution system as illustrated in Figure 62.

The replacement and upgrade of the PW distribution system has already been purchased and will be implemented in the November 2023 shutdown.

The additions include:

- 200 meter, 2inch S/S ring main
- 1x 10m³ S/S storage tank
- 1x Hygienic centrifugal pump
- 14x Automatic S/S points-of-use valve with sanitary sample point
- Ozone generator for sanitisation
- Control upgrade

Phase two is a £495,000 investment that will ensure longevity and control the use of the PW at BTG. The project requires a new validated PW storage and distribution system with ozone sanitisation and will continue to meet the standards and quality of water that will be based on the US & Ph EUR, ISPE guidelines and cGMP standards.

Phase 2 – Upgrade PW Distribution

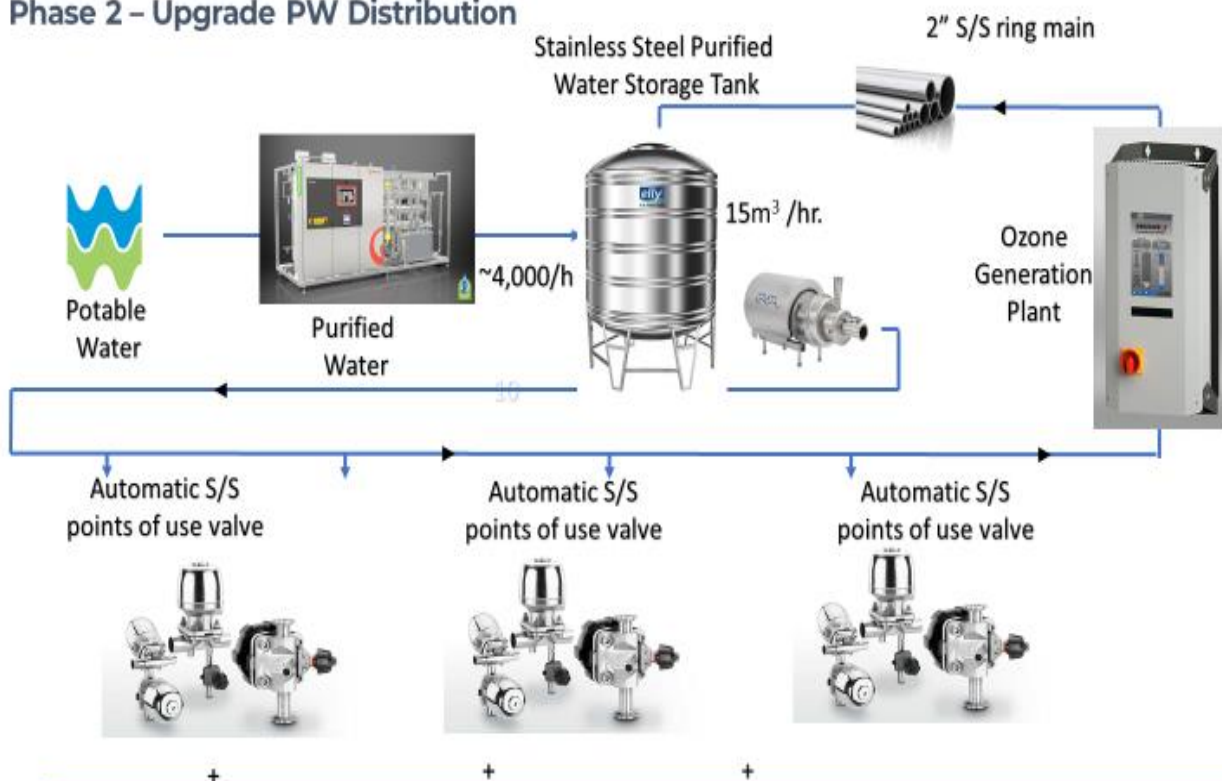


Figure 62 Flow diagram following phase 2 completion

The benefits of phase 2 include:

- Reduced sanitisation downtime on the PW distribution ring main to 2 hours using ozonated water rather than a 4-day oxonia chemical sanitisation.
- Fully automatic stainless-steel points-of-use valves within the facility
- Confidence in a new control system
- Maintain a turbulent flow at 1m/s through the ring main sanitary centrifugal pump at up to 15,000.
- Required flowrate of >1 m/s on loop return is approximately. 6,500 l/hr.

Phase two is due in November 2023 and will be fully implemented via the same method of qualification used in this project.

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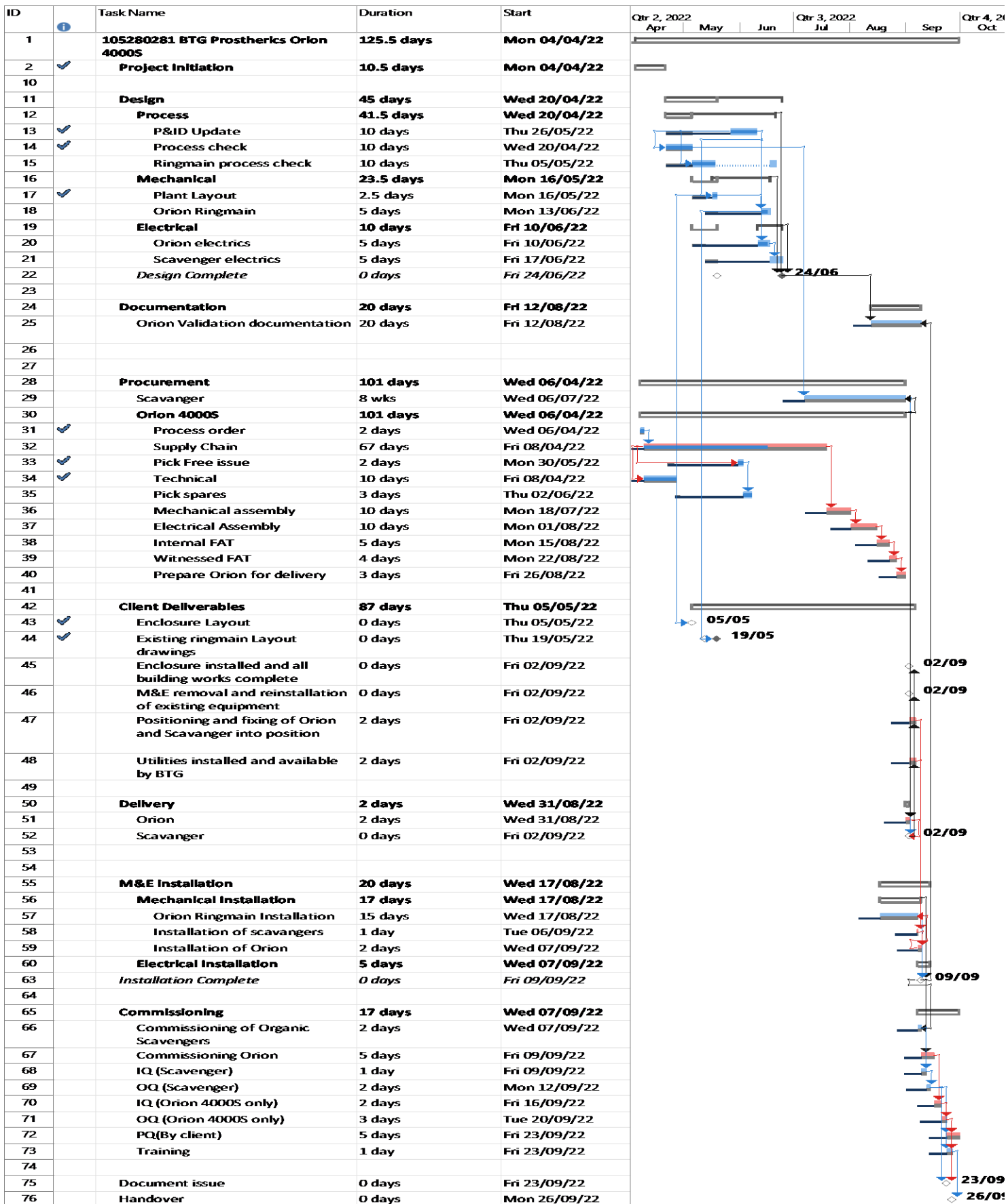
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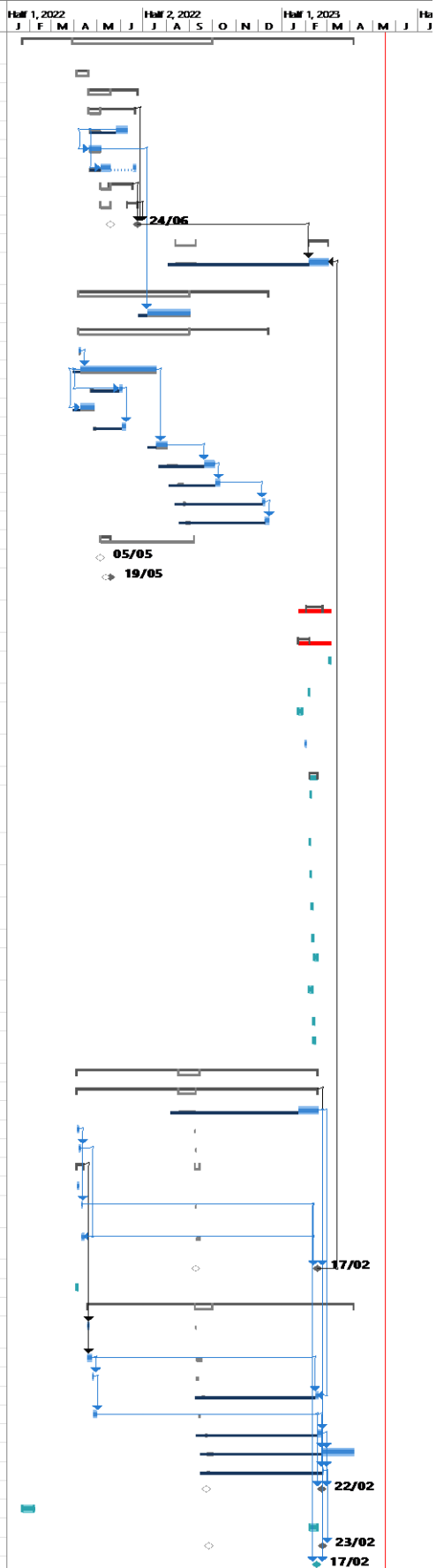
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APPENDIX 1 – Gantt Chart Revision 01 and 02



ID	Task Name	Duration	Start	Finish	Predecessors	% Work Complete	Half 1, 2022 J F M A M J J A S O N D	Half 2, 2022 J F M A M J J A S O N D	Half 1, 2023 J F M A M J J	Half 2, 2023 J F M A M J J
1	105280281 BTG Prosthetics Orion 4000S	297 days	Sun 23/01/22	Wed 05/04/23		100%				
2	Project Initiation	10.5 days	Mon 04/04/22	Wed 20/04/22		100%				
10	Design	45 days	Wed 20/04/22	Fri 24/06/22		100%				
11	Process	41.5 days	Wed 20/04/22	Mon 20/06/22		100%				
12	P&ID Update	10 days	Thu 26/05/22	Fri 10/06/22	8FS+25 days	100%				
13	Process check	10 days	Wed 20/04/22	Thu 05/05/22	12SS	100%				
14	Ringmain process check	10 days	Thu 05/05/22	Mon 20/06/22	12SS+15 days	100%				
15	Mechanical	23.5 days	Mon 16/05/22	Fri 17/06/22		100%				
18	Electrical	10 days	Fri 10/06/22	Fri 24/06/22		100%				
21	Design Complete	0 days	Fri 24/06/22	Fri 24/06/22	11,15,18	100%				
22	Documentation	20 days	Mon 06/02/23	Fri 03/03/23		100%				
23	Orion Validation documentation	20 days	Mon 06/02/23	Fri 03/03/23	21,65FF	100%				
24	Procurement	174 days	Wed 06/04/22	Wed 14/12/22		100%				
25	Scavenger	8 wks	Wed 06/07/22	Wed 31/08/22	13	100%				
26	Orion 4000S	174 days	Wed 06/04/22	Wed 14/12/22		100%				
27	Process order	2 days	Wed 06/04/22	Fri 08/04/22	6FS-3 days	100%				
28	Supply Chain	67 days	Fri 08/04/22	Mon 18/07/22	27	100%				
29	Pick Free issue	2 days	Mon 30/05/22	Thu 02/06/22	28SS+33 days	100%				
30	Technical	10 days	Fri 08/04/22	Tue 26/04/22	28SS	100%				
31	Pick spares	3 days	Thu 02/06/22	Tue 07/06/22	29	100%				
32	Mechanical assembly	10 days	Mon 18/07/22	Mon 01/08/22	28	100%				
33	Electrical Assembly	10 days	Mon 19/09/22	Mon 03/10/22	32FS+7 wks	100%				
34	Internal FAT	5 days	Mon 03/10/22	Mon 10/10/22	33	100%				
35	Witnessed FAT	4 days	Mon 05/12/22	Fri 09/12/22	34FS+38 days	100%				
36	Prepare Orion for delivery	3 days	Fri 09/12/22	Wed 14/12/22	35	100%				
37	Client Deliverables	9.5 days	Thu 05/05/22	Thu 19/05/22		100%				
38	Enclosure Layout	0 days	Thu 05/05/22	Thu 05/05/22	16SS	100%				
39	Existing ringmain Layout drawings	0 days	Thu 19/05/22	Thu 19/05/22	17SS	100%				
40	Utilities installed and available by BTG	16 days	Thu 02/02/23	Thu 23/02/23		100%				
41	Preliminary Work	11 days	Mon 23/01/23	Mon 06/02/23		100%				
42	FAS to remove all call points and supply cabling	2 days	Sun 05/03/23	Mon 06/03/23		100%				
43	End of life calibration Veolia	1 day	Mon 06/02/23	Mon 06/02/23		100%				
44	FP Hurley ground work preparation	5 days	Mon 23/01/23	Fri 27/01/23		100%				
45	Phillips Electrical Services 100A supply cable	2 days	Tue 31/01/23	Wed 01/02/23		100%				
46	Coinciding with M&E installation	9 days	Tue 07/02/23	Fri 17/02/23		100%				
47	Phillips Electrical Services removal/disconnection electrical equipment	1 day	Wed 08/02/23	Wed 08/02/23		100%				
48	FP Hurley remove mechanical equipment and pipework	1 day	Tue 07/02/23	Tue 07/02/23		100%				
49	Portacover to remove GRP enclosure	1 day	Wed 08/02/23	Wed 08/02/23		100%				
50	Morgan Marine to install new GRP enclosure	1 day	Fri 10/02/23	Fri 10/02/23		100%				
51	FP Hurley to screed floor	1 eday	Sat 11/02/23	Sun 12/02/23		100%				
52	Phillips Electrical Services to re-install cabling and	5 days	Mon 13/02/23	Fri 17/02/23		100%				
53	FP Hurley to re-install mechanical equipemnt and	5 days	Mon 06/02/23	Fri 10/02/23		100%				
54	Delievery and Installation Orio	1 day	Sun 12/02/23	Sun 12/02/23		100%				
55	Portacover/Hurley to position Orion & scavenger	2 days	Sun 12/02/23	Mon 13/02/23		100%				
56	M&E installation	214 days	Mon 04/04/22	Fri 17/02/23		100%				
57	Mechanical Installation	214 days	Mon 04/04/22	Fri 17/02/23		100%				
58	Orion Ringmain Installation	20 days	Mon 23/01/23	Fri 17/02/23		100%				
59	Installation of scavengers	2 days	Mon 04/04/22	Tue 05/04/22		100%				
60	Installation of Orion	2 days	Wed 06/04/22	Thu 07/04/22	59	100%				
61	Electrical Installation	8 days	Mon 04/04/22	Wed 13/04/22		100%				
62	Panel Modifications	2 days	Mon 04/04/22	Tue 05/04/22		100%				
63	Installation of scavenger electrical	1 day	Mon 11/04/22	Mon 11/04/22	59FS+3 days	100%				
64	Installation of Orion Electrical	3 days	Mon 11/04/22	Wed 13/04/22	60FF+4 days	100%				
65	Installation Complete	0 days	Fri 17/02/23	Fri 17/02/23	57,58,63,64	100%				
66		1 day	Mon 04/04/22	Mon 04/04/22		100%				
67	Commissioning	239 days	Mon 18/04/22	Wed 05/04/23		100%				
68	Commissioning of Organic Scavengers	2 days	Mon 18/04/22	Tue 19/04/22	61	100%				
69	Commissioning Orion	5 days	Mon 18/04/22	Fri 22/04/22	61	100%				
70	IQ (Scavenger)	1 day	Mon 25/04/22	Mon 25/04/22	69	100%				
71	IQ (Orion 4000S only)	4 days	Tue 14/02/23	Fri 17/02/23	69,58FF	100%				
72	OQ (Scavenger)	4 days	Tue 26/04/22	Fri 29/04/22	70	100%				
73	OQ (Orion 4000S only)	5 days	Thu 16/02/23	Wed 22/02/23	71FS-2 days	100%				
74	PQ(By client)	30 days	Thu 23/02/23	Wed 05/04/23	73,72	100%				
75	Training	1 day	Thu 23/02/23	Thu 23/02/23	73,72	100%				
76	Document issue	0 days	Wed 22/02/23	Wed 22/02/23	73,72	100%				
77	Preliminary Work	12 days	Sun 23/01/22	Sun 06/02/22		100%				
78	Coinciding M&E Work	9 days	Tue 07/02/23	Fri 17/02/23		100%				
79	Handover	0 days	Thu 23/02/23	Thu 23/02/23	75	100%				
80	Installation Complete	0 days	Fri 17/02/23	Fri 17/02/23	57,58,63,64	100%				



APPENDIX 2 – Validation Plan

Validation Strategy

The validation approach will be performed according to the level of validation identified with CC65642 'Purified Water Generation Upgrade', which has been assessed in accordance BTG-GBL-SOP-VL-000007 'Equipment, Plant, Facilities or Utilities Validation Procedure'. The validation strategy is summarised below in table 1:

Table 1 – FAT/SAT/IQ/OQ/PQ Tests Required

Type	Test Title	Acceptance Criteria
FAT	Factory Acceptance Test for PFW Generation System X977 (ORION)	Factory Acceptance Test (FAT) aims to confirm, at the vendors premises, that the construction and operation of the Purified Water Generation System X977 (ORION), conforms to the design intent and that it will comply with Current Good Manufacturing Practice (cGMP). This shall include (as a minimum): • Verification of the Engineering Drawings and P&ID • Verification of System Components • Instrumentation Installation and Calibration Check • System Pipework – documentation / certification • Welding (welders qualification / gas certificates / welds samples verification) • Installation Verification of Control System Components including electrical input / output testing • Recommended Spare Parts List • Functional Testing Alarms • Functional Testing The BTG FAT will act as a 'wrap-around' document in support of the pre-approved test scripts as supplied by the system supplier (Veolia).
SAT	Site Acceptance Test for PFW Generation System X977 (ORION)	SAT will capture acceptance testing following delivery of the system BTG Wales. This shall be performed by the supplier and witnessed by BTG personnel. Test scripts shall aim to verify the condition of the system against the FAT following delivery. Functional tests that have been performed during the FAT should be repeated. A detailed list of all SAT tests to be performed should be approved as part of the SAT. When starting the SAT, all critical instruments must have calibration certificates issued no earlier than 6 months before the start date of the SAT. Testing should include, but is not limited to, the following: • Parts and pipes labelling verification. • Pressure test report. • Cleaning and passivation report. • P&ID diagram verification.

Type	Test Title	Acceptance Criteria
		• Verification of technological components for compliance with specifications. • Verification of critical utilities' pipelines welding documentation. • Verification of dimensions of the layout of the main devices. • Air gaps verification. • Pipeline routes verification. • Dead legs verification. • Verification of sanitization and sterilization of system parts. • Performing system capacity tests. • Verification of electrical and pneumatic components. • Verification of digital & analogue inputs and outputs of the PLC controller. • Verification of 4-20 mA measuring chains. • Verification of software version & HMI interface. • Main switch operation verification. • Alarms verification. • Power failure / system recovery test. Actual required test scrips will be captured and approved within the SAT protocol. The justification for leveraging must be documented in the SAT report. Note: where testing is sufficiently captured (performed according to pre-approved protocols stating acceptance criteria, integrally documented using Good Documentation Practice, tests evidence present and results approved by QA) within FAT and remains unaffected by the transportation and installation, FAT results may be leveraged to SAT.
IOQ	Installation and Operation Qualification for PFW Generation System X977 (ORION)	The scope of IOQ qualifications should include, but not be limited to, the following tests and verifications: • PLC software verification. • Utility connection. • Connection to the BTG PFW sub-loop, the loop valve will remain closed until the 3 days water quality test results demonstrate that the purified water specification is achieved in repetitive manner. • Daily sampling will continue in-between the IOQ phase until PQ. • Critical instrument verification installation & calibration. • Calibration requirements. • System calibration. • SOP/WI identification. • RERS testing. • Alarms. • Power failure and recovery testing. • Verification of installation including adequate lagging.

Type	Test Title	Acceptance Criteria
		• Operation and Maintenance Instructions and Spare Parts List verification. • Electrical diagrams verification. • Installed Hardware / Software verification. • Inputs / outputs verification. • Configuration verification Compliance with CFR 21 Part 11 verification. OQ testing will also include: • Hot water Sanitisation (HWS) verification - This shall verify the HWS of the skid (Orion) and the subloop post installation. This will be done using a thermal imaging camera to determine where the cold spots are on the sub loop, and once this has been determined, a temperature mapping exercise will begin over the period of the HWS period with thermocouples placed on the coldest positions and will be documented within the IOQ. The system controls utilising the 4 calibrated probes on the generation system. If at any time the temperature drops below the desired value, the HWS will not proceed. The HWS process is based on temperature and time. Once the HWS is complete it will continue to recycle (recirculate) until the conductivity is below the desired value. All test results must meet the requirements of the protocol satisfactorily. • The water produced by the Orion will not enter the distribution tank until the 3 consecutive day sampling results have been approved. Assessment of the quality of water produced by the purification plant under conditions of use (i.e., whilst the Orion is producing water, it will continuously run to drain to prevent assessment purely under recirculation. This will be achieved by diverting the return of the sub-loop to drain rather than back to the multipurpose tank). To release for PQ, all of the following specifications will need to be met for the output of the system (post UV): • Specific electrical conductivity ≤ 1.1 $\mu\text{S}/\text{cm}$ • TOC ≤ 500 ppb • Nitrates ≤ 0.2 ppm • Total bacteria count ≤ 350 cfu / 10 ml • Heavy metals $\leq 0.1\text{ppm}$ • Endotoxins ≤ 0.25 EU/ml

Type	Test Title	Acceptance Criteria
		Following the verification of suitable water the water shall be released to the distribution loop to allow for Sanitisation of the PFW ring main B (distribution loop) in preparation for PQ. The system shall be released for phased PQ on successful completion approval of the IOQ protocol. This will be captured as a pre-requisite for PQ. Note: where testing is sufficiently captured within SAT (performed according to pre-approved by QA protocol, documented utilising data integrity principles), the evidence of the test results are present, results are approved by QA and remains unchanged by the transport, installation and start up activities/commissioning the results may be leveraged to IOQ. Actual required test scripts will be captured and approved within the IOQ protocol. The justification for leveraging must be captured in IOQ report.
PQ	Performance Qualification PFW Generation System X977 (ORION)	The Performance qualification will commence once IOQ report is fully approved. Successful completion of the distribution sanitization shall be captured as a prerequisite to PQ testing to ensure the system is in a fit state for testing. The scope of the qualification is to verify the performance of the system while under routine challenge. Performance qualification will be undertaken using a staged approach PQ1 prospectively, with PQ2 and PQ3 concurrently as follows: Note: Approval from System owner, Validation, QC & QA shall be required prior to progression through the defined phases, this shall be built into the test script, with an interim VSR required prior to stage 2 & stage 3 for release in GxP use. Stage 1 – Performed prior to release of water for manufacturing use Intensified monitoring shall be conducted for 2 weeks in accordance with WHO / USP guidance to include: - Sample the incoming feedwater daily to verify its quality - Sample each step in the purification process. - Sample at each point of use & any other defined points When the first 10 sets of data are available, inclusive of bioburden, this stage water will be recirculated around the distribution system but will not be used for GMP purpose. The normal usage of the water from the loop will be simulated by daily draining 60% of the total tank volume. Following which, once all data is confirmed to be within specification, the system may be used for equipment cleaning, however none of the systems will be released for GxP use until all results are available, evaluated and approved by the quality department confirming all specifications have been met.

Type	Test Title	Acceptance Criteria
		A Risk assessment will be documented as a pre-requisite to allow for this. Stage 2 – Performed following to release of water for manufacturing use AT RISK 2 weeks duration required by WHO / USP guidance Should include testing from output of purification system as well as from distribution system. Water can be used for GMP processes as defined in the risk assessment Stage 3 – PQ Stage 3 Routine monitoring for an extended duration of 12 months to allow for observation of any sessional variance. Water may be used for GMP manufacturing processes, this is captured as routine practice, any adverse trends will be reported within a quality event at the time of discovery and a review of the full 12 months data will be captured within the PQ & summarised within the final VSR. All test results must meet requirements of the protocol satisfactorily.
VSR	Validation Summary Report	Interim - This will be generated upon completion of PQ stage 1 & PQ stage 2 activities to allow for progression to concurrent PQ. Final – This will be completed upon completion of all PQ activities. All test results must meet the requirements of the protocols satisfactorily.

Validation Rationale

The test schedules shall be written to demonstrate compliance with GMP and predetermined BTG specifications detailed within the scope of works and supplier proposal package.

IOQ testing will verify and document that the system is installed in accordance with approved design drawings, user and functional specifications. Testing shall also ensure that the necessary documentation is in place to demonstrate suitability of installed components, devices, and instrumentation with regard to cGMP criticality. BTG asset management systems are updated with suitable planned maintenance/calibration schedules are in place. The IOQ will also aim to verify the operation and efficiency for the hot water sanitisation process to allow following approval of IOQ report for progression to the PQ.

IOQ testing will also verify and document that the system operates in accordance with approved functional requirements and that required BTG standard operating procedures (SOPs) and/or work instructions (WI) are in place prior to PQ testing.

The PQ will confirm that the unit is capable of consistently meeting the pre-defined in BTG specification water quality during a period of 'in use'. This will further confirm the system operates at the required rates of manufacture detailed in the scope of works and supplier proposal package.

The system/process will be fully validated and fit for purpose upon approval of the final Validation Summary Report (VSR).

Validation Deliverables

The following details the deliverables for the validation of the PFW Water Generation System X977 (ORION) at BTG, Wales.

Table 2 – Document Approvers Responsibility

Document / Deliverable	System Owner (Engineering)	Validation	QA	IT	QC	Supplier (VEOLIA)
Design Qualification	A	A	A	NA	NA	O
Factory Acceptance Test – Wrap	O	A	A	NA	NA	O
Factory Acceptance Test – Supplier	A	A	A	NA	NA	O
Supplier Site Acceptance Test	A	A	A	NA	NA	O
Site Acceptance Test	O	A	A	NA	NA	NA
Supplier IOQ	A	A	A	A	A	O
BTG Combined IOQ	O	A	A	A	A	NA
Performance Qualification	O	A	A	A	A	NA
Interim Validation Summary Report – release for Concurrent PQ	O	A	A	A	A	NA
Validation Summary Report	O	A	A	A	A	NA
Vendor deviations	A	A	A	IR	IR	O
BTG/ internal Deviations	O	A	A	IR	IR	NA

APPENDIX 3 – Asset Assessment Risk Rank

Appendix I

Procedure for applying an Asset assessment to equipment and infrastructure.

Using the assessment matrix below enter the following details and carry out the assessment against the criteria contained in Tables A, B, & C of this procedure. It is recommended to use a spreadsheet for this process.

Step 1. Field 1. Enter location number of asset as identified in Computerised Maintenance Management System (Q4) or asset list.

Step 2. Field 2. Enter equipment description as identified in site Computerised Maintenance Management System (Q4) or asset list.

Step 3. Field 3. Enter Asset PUK number as referenced in the site fixed assets list available from Finance.

Step 4. Field 4. Enter asset identification. Equipment / Building number

Step 4. Fields 5 to 8 (Factors A to D). Assess the operating factors including asset condition, Engineering criticality, evidence of maintenance history and usage requirements. Refer to Table A of this procedure for the assessment criteria for each factor.

Step 5. Field 9 - Multiply resulting values to get a total for the Asset score.

Step 6. Fields 10 to 13 (Factors E to H). Assess the additional factors associated with Asset management life cycles. Validation Assessment, Lead time to replace, remaining life cycle and cost for replacement. Refer to table B of this procedure for the assessment criteria for each of the factors.

Step 7. Field 14 - Multiply resulting values to get a total for additional factors that affect the asset.

Step 8. Field 15. Multiply operating and additional factors together to get a total asset score.

Step 9. When all equipment has been assessed the results can be compared and segregated into categories as shown in Table C. Assets that yield the highest values (81 to 100%) should receive the highest level of investment focus

Equipment Criticality Analysis Matrix |

1. Location Number	2. Engineering description	3. PUK	4. Equipment ID	Criticality Scores					Failure Modes and Effects Scores					15. Total Score (ABCD Score x EFGH score)
				5. Factor A	6. Factor B	7. Factor C	8. Factor D	9. Equipment Score (AxBxCxD)	10. Factor E	11. Factor F	12. Factor G	13. Factor H	14. Additional Score (ExFxGxH)	

Equipment FMECA Factors		Scoring				
Factor	Description	Good 1	2	3	4	Poor 5
Factor A	General condition of asset	1	2	3	4	5
Factor B	Engineering Criticality	1	2	3	4	5
Factor C	Maintenance history of asset	1	2	3	4	5
Factor D	Asset usage requirements	1	2	3	4	5
Factor E	Validation Assessment	1	2	3	4	5
Factor F	Lead time to replace	1	2	3	4	5
Factor G	Remaining useful life	1		2		3
Factor H	Cost of replacement	1		2		3

Table A – Asset Operating Criticality Assessment.

Factor A - Condition criticality assessment		Factor B – Engineering criticality assessment		Factor C – Maintenance History criticality assessment		Factor D - Usage criticality assessment	
Poor Condition	5	>120	5	No service history	5	Daily usage	5
Below Average condition	4	91 - 120	4	<2 years	4	Weekly usage	4
Average Condition	3	61 - 90	3	<4 years	3	Monthly usage	3
Good Condition	2	30 - 60	2	<6 years	2	Quarterly usage	2
As new condition	1	<30	1	Full service history	1	Annual usage	1

Table B – Asset Additional Factors Assessment.

Factor E – Validation assessment		Factor F – Lead time to replace		Factor G – Remaining useful Life assessment.		Factor H - Replacement costs assessment	
Critical	5	>9 months	5	<2 years	3	>50	3
		6 – 9 months	4				
Non-Critical	3	3 – 6 months	3	2 - 4 years	2	20 – 50K	2
		1 – 3 months	2				
Indirect	1	<1 month	1	4 years or more	1	<20K	1

Table C - Asset Results Categorisation.

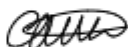
Plant criticality	Asset category (assessment comparative score)	Operating criteria	Investment tactics
Year 1	A (Between 81 - 100%)	High risk of impact to business	High investment priority
Year 2	B (Between 61 - 80%)	Medium risk of impact to business	Medium investment priority
Year 3	C (Between 31 - 60%)	Low risk of impact to business	Low investment priority
Non-Critical	D (Between 1 - 30%)	No immediate risk to business	No investment plans.

APPENDIX 4 – User Requirement Specification

Document ID:	WAL-FUV-URS0007-001
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USER REQUIREMENTS SPECIFICATIONS PFW GENERATION SYSTEM (ORION) TAG NUMBER X977

Completion of the following signature section signifies the approver(s) has read, understands, and authorises the use of this User Requirement Specification (URS) for the above-mentioned System.

Responsibility	Position	Name	Signature
Author / System Owner	Senior Engineer	Iwan Rees	 Electronically signed by: Iwan Rees Reason: I Approve this document Date: Dec 5, 2022 19:42 GMT
IT Group	IT Service Delivery Lead	Robert Clarke	 Electronically signed by: Robert Clarke Reason: I Approve this document Date: Dec 5, 2022 12:35 GMT
Validation compliance	Validation Lead	Charis Elliott	 Electronically signed by: Charis Elliott Reason: I Approve this document Date: Dec 5, 2022 11:17 GMT
Engineering	Senior Engineering and Infrastructure Manager	Jason Mainwaring	 Electronically signed by: Jason Mainwaring Reason: I Approve this document Date: Dec 5, 2022 11:36 GMT
EHS and Risk Management	EHS and Site Services Lead	Robert Evans	 Electronically signed by: Robert Evans Reason: I Approve this document Date: Dec 6, 2022 11:51 GMT
Quality Control	Quality Control Specialist (Sterility Assurance)	Chris Pulham	 Electronically signed by: Chris Pulham Reason: I Approve this document Date: Dec 5, 2022 12:51 GMT
Quality Assurance	QA Officer	Iestyn Gordon	 Electronically signed by: Iestyn Gordon Reason: I Approve this document Date: Dec 5, 2022 11:26 GMT

7.1.3. **Critical Points of Failure Analysis**

Item	Requirements / Specifications
7.1.3.1	Conductivity < 0.2 µS/cm
7.1.3.2	TOC < 100 ppb as C
7.1.3.3	Bacteria < 10 cfu/ml
7.1.3.4	Endotoxin < 0.125 Eu/ml
7.1.3.5	Pressure < 2.0barg
7.1.3.6	See attachment 1 Functional Design Specification section 6.5 Alarm list for failure analysis.(DOVLON3025)

7.1.4. **Modes of Operation**

Item	Requirements / Specifications
7.1.4.1	Shutdown
7.1.4.2	Service
7.1.4.3	Hot Water Sanitisation - HWS
7.1.4.4	Clean in Place - CIP

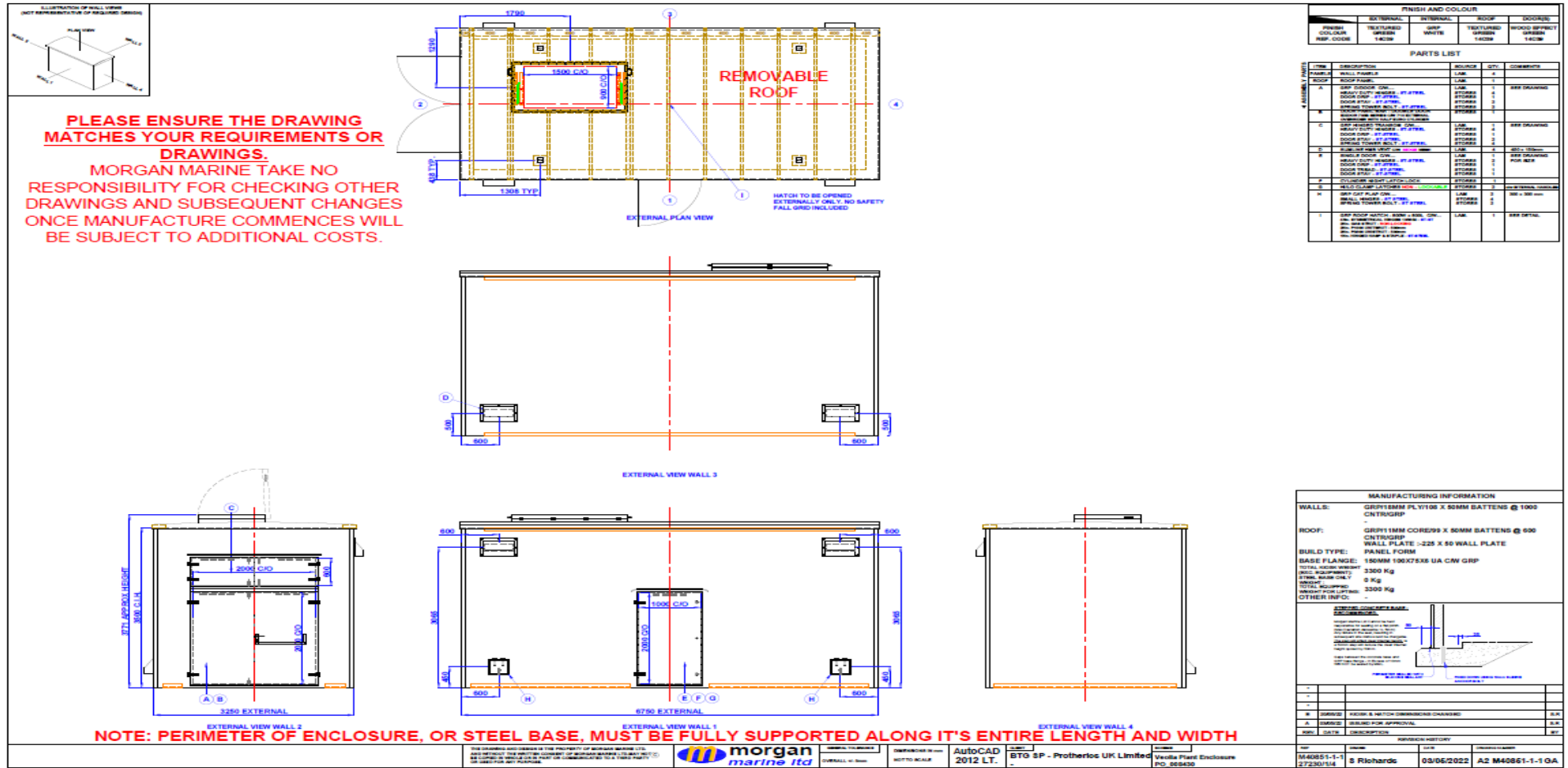
7.1.5. **Capacity, Performance and Timing Requirements**

Item	Requirements / Specifications
7.1.5.1	4000 litres/ hour of purified water supplying the B1 manufacturing facility.

7.2. **Required Action on Failure**

Item	Requirements / Specifications
7.1.6.1	Fatal alarm - Alarms that stops the unit according to the alarm shutdown sequence. The alarm will remain active until the user resets the alarm from the HMI terminal. Once the alarm is reset, then the system can be restarted
7.1.6.2	Warning alarm - Alarms that don't stop the unit. The warning will only be cleared once the measured value falls below the AH (alarm high) threshold or rises above the AL (alarm low) threshold. Some warning alarms will turn into fatal alarms as an additional adjustable delay expired: Hardness AH, chlorine AH, pH AH, pH AL.
7.1.6.3	Fatal and Warning alarms ought to be audible alarm
7.1.6.4	Visual alarm on HMI
5	Capable of sync with SCADA to create alarm alert
7.1.6.6	Fatal alarm - Alarms that stops the unit according to the alarm shutdown sequence. The alarm will remain active until the user resets the alarm from the HMI terminal. Once the alarm is reset, then the system can be restarted

APPENDIX 5 - Morgan Marine Design of Enclosure



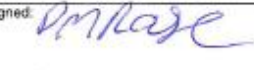
APPENDIX 6 – Installation and Commissioning Pack

	ORION III Installation & Commissioning Instructions	DOWION3007
		Issue 5
		17 May 2018

DOWION3007

**INSTALLATION AND COMMISSIONING PROCEDURE
FOR
ORION III RANGE OF PRODUCTS**

Client: PROTUMICS	Address: SA445JT
Unit Size: ORION 4000	
Reference: 368108	
	Serial Number: U22 ORIO 453 105280281

Commissioning Procedure Completed		
Tested by: JEFF FORKER	Signed: 	Date: 03 MAR 2023
Position: SERVICE ENGINEER		
Reviewed by: DAMIAN ROUSE	Signed: 	Date: 03 MAR 2023
Position: Service Engineer		

5	17 May 2018	Section 8.5 references corrected and re-paginated.	MG	NRM	RP
4	06 Dec 2017	Section 6 DOVLON3005 split into A, B & C. Sections 7.2.4 TP106 & 8.6.4 Orion 8000 & 1000 changed to 9000 & 12000. Section 7.3 brine measurement tank description added. New sections 8.1.2 & 8.1.3 power cable security checks added. Section 8.1.10 changed to add purge option. Section 8.6.4 valve number now VA11-09.	MG	NRM	RP
3	19 Jul 2017	General errors corrected. Section 7 revised to add checks, TP106 & 128 detail revised. Section 8 all tables revised, procedures re-ordered and sub sections added.	MG	NRM	RP
2	16 Jun 2016	Removal of requirement for instrument configuration documents, configured during FAT or using manufacturers operating instructions.	MG	NRM	RP
1	20 Nov 2015	First Issue	PJD	NRM	MG
REV	DATE	REVISION DESCRIPTION	BY	CHK	APP

	ORION III Installation & Commissioning Instructions	DOWION3007
		Issue 5
		17 May 2018

8.7 Commissioning Complete

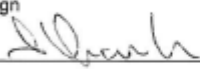
When satisfied with the operation of the unit switch off and divert the return line from the outlet valve(s) to TK30-01.

Restart the unit in auto and check that the product water tank(s) fill following the initial start up procedure.

Switch off.

The Orion is now ready for full testing by the Operation Qualification Procedure.

Checked by

Sign 	Date 20 MAR 2018
--	---------------------

APPENDIX 7 – Veolia Service Report and Quotes

1.	Ultraviolet light unit 'UV70' operating with obsolete control panel, recommend panel is upgraded – 21-Apr-2018 statement still applies, 04-Aug-2016 client aware statement still applies – 12-Sep-2017 – lamp only replaced – Aug-2018 – Quotation updated. Aug-19; Client aware of component obsolescence and continues to monitor. Apr-20; Client is continuing to monitor and is aware the controller has been made obsolete with no spares available. Mar-21; Statement still applies. Client to request upgrade quotation if required. Aug-21; with the client expecting to replace/upgrade the system in 2022, the UV panel etc is to remain and the client will monitor until replaced. Mar-22; action remains ongoing. Sep-22; system being replaced in Feb-2023 with new Orion system Action opened – 20th December 2013 Ongoing Brought Forward; 31-March-2022 Closed Out; 29-September-2022	Protherics / VEOLIA Water Technologies
2.	The MS2050 controller is operating with a flickering LCD display which also observed the displayed data changing whilst flickering. It is recommended to replace the controller to maintain optimum performance and control – 12-Sep-2017 – statement still applies. – 13-Apr-2018; MS2050 is corrupted and could fail at anytime – Aug-2018 – Quotation updated – Aug-19; Client aware of display issue, but reports no problems with controller operation at present. Apr-20; Although the controller is retaining its program at present. The amount of display errors with the text is increasing and becoming unreadable. Should any changes be needed to the settings it may not be possible to load. Recommend replacement. Mar-21; Statement still applies, flicker of display continues. Aug-21; The fault continues. It is recommended to replace this unit during the 2022 upgrades. Mar-22; Action remains ongoing. Sep-22; system being replaced in Feb-2023 with new Orion system Action Opened – 04-August-2016 Ongoing Brought Forward; 31-March-2022 Closed Out; 29-September-2022	Protherics / VEOLIA Water Technologies
3.	Ringmain 'B' - The UV intensity display reported operating erratically. This is identified as possibly due to either the quartz sleeve being in need of cleaning or replacing and/or the UV intensity camera/monitor requiring attention. Further investigation will be required as the ringmain could not be shutdown due to being in demand. Aug-2018 – System off line, further investigation required, suggest next scheduled service visit. Aug-19; Ringmain 'B' UV intensity meter to be evaluated upcoming sanitisations. Apr-20; Display still erratic (27% - 100%) recommend action during the August-2020 shutdown. Options; Upgrade controller to current Veolia type. Replace controller with like-for-like components plus change lamps & quartz sleeves and calibrate. Aug-20; waiting PO. Mar-21; A quotation has been issued to the client for recommended works. No action required from client at present. Aug-21; The condition of this unit continues, (client aware) as before. The unit is in the clients future plans for refurb. Mar-22; action remains ongoing. Sep-22; system being replaced in Feb-2023 with new Orion system Action Opened – 13-April-2018 Ongoing Brought Forward; 31-March-2022 Closed Out; 29-September-2022	Protherics / VEOLIA Water Technologies
4.	CEDI module resistance has increased since last visit, module has reached the end of its typical service life, therefore to ensure continued quality water generated, recommend the module be replaced next scheduled visit, quotation to follow. Apr-20; Quotation issued. Aug-20; Quattro continues with existing CEDI module resistance approximately 200Ω. Mar-21; Module resistance continues at 170-210Ω. Aug-21; Client aware & will continue to monitor until refurb. Mar-22; Action remains ongoing, with the resistance continuing to rise. Sep-22; system being replaced in Feb-2023 with new Orion system Action Opened; 02-August-2019 Ongoing Brought Forward; 31-March-2022 Closed Out; 29-September-2022	Protherics / VEOLIA Water Technologies
5.	The sand filter is failing to fluidise the sand media correctly during the backwash cycle, showing the sand media has become fouled and in turn affecting the service flow rate and the fast rinse flow rate. It is recommended to replace the sand media to improve the flow rates. A quotation is being assembled by the visiting engineer for this. Aug-21; Quotation for recharge re-issued this visit. Additionally a bypass requires to be fabricated by the site maintenance for fitting between the inlet & outlet socket unions, ahead of the sand media being replaced. Mar-22; action remains ongoing. Sep-22; by-pass valve installed 29-Sep-2022, media change being scheduled Action opened; 12-March-2021 Ongoing Brought Forward; 31-March-2022 Closed Out; 29-September-2022	Protherics / VEOLIA Water Technologies
6.	Organic scavengers; As an operational reminder; the resin media in unit has now achieved its typical service life of 3-years since being installed in November-2019. The visiting engineer has recommended the resin media in unit is now replaced, particularly as these units are operating with a heavy load. Mar-22; action remains ongoing, noting the pressure drop has increased to a high 1.6bar. Sep-22; system being replaced in Feb-2023 with new Orion system Action Added; 24-September-2021 Ongoing Brought Forward; 31-March-2022 Closed Out; 29-September-2022	Protherics / VEOLIA Water Technologies

Post Code	SA44 5JT	
Contact - Name	Iwan Rees	
Tel	01239 851122	
Email	iwan.rees@btgsp.com	
Description of work requested	To carry out a media recharge of the PSF240 sand filter, as recommended during the recent PQMC visit. This is due to the service and backwash flow rates having reduced over time. In order to minimise downtime and for ease because of lack of headroom, this quotation includes a replacement vessel which can be loaded prior to removing existing vessel nearer the doorway for emptying. This vessel can then be cleaned and stored, and reused next recharge. Alternatively, two other options for media removal, BTG to employ a local contractor to mechanically remove media (via suction), or BTG cut access hole in top of plant room roof for media extraction pipework to be lowered in. (BTG to make good the access hole afterwards). Labour charge listed is for Veolia to remove media. Exhausted media will be left in 200lt sealable drums for clients disposal.	
Equipment needed to complete work (pumps/hoses etc)	Media extraction tools and equipment.	
Serial No/Location:	PSF240 simplex sand filter, in Building 28	

Parts / Products

LATIS - Part Number	Part Description	UoM	Quantity	Unit Price	TOTAL Price
MEFIF0040	MEDIA SAND FILTERING 0.5-1.0MM 25KG BAG	KG	315.00	£0.70	£220.50
MEFIF0045	MEDIA SAND FILTERING 1.25-2MM 25KG BAG	KG	90.00	£0.80	£72.00
VMFLSP1005	CAM MODIFIED 2510,2750,2850,2900,2910 VALVE	EA	1.00	POA	£0.00
VIC0AB0010	COLLECTING SYSTEM 11/2" ABS	EA	1.00	£91.00	£91.00
T0C0GU0010	200 LT DRUM BLUE POLYPROP RECONDITIONED	EA	4.00	£69.00	£276.00
VITUPV0202	TUBE RISER AND BOTTOM STRAINER 1.52M 50MM 2850/2900	EA	1.00	£89.00	£89.00
VISTAB1015	STRAINER TOP 50MM O/D TUBE C/W PINS 2850/2900/2910 V	EA	1.00	£40.00	£40.00
SEORFL0110	O-RING FL RISER TUBE 11/2" 2850 AND 2900	EA	1.00	£7.20	£7.20
FPSOPV1260	SOCKET G INCH/METRIC PL PVC 11/2" X 50MM	EA	2.00	£5.90	£11.80
TOAVGU0235	CEMENT WET-N-DRY ABS/PVC 500 ML	EA	1.00	£33.00	£33.00
SEORFL0105	O-RING FL TANK 2850	EA	1.00	£22.00	£22.00
VECSZD1005	VESSEL COMP C-2469-A3PWG BLUE 4 INCH TOP HOLE	EA	1.00	£866.00	£866.00
VMFLSP200498	Drive cam assembly	EA	1.00	£10.00	£10.00
Parts / Products Total					£1,738.50

Non Stocked Parts

Part Number	Description 1	Description 2	Quantity	Unit Price	TOTAL Price
R100SV0108	Labour Day Rate	Weekday, 2 men, 2 days	4	£825.00	£3,300.00
-	-		0	£0.00	£0.00
-	-		0	£0.00	£0.00
Non Stocked Parts					£3,300.00
Installation					£0.00
Commissioning					£0.00
Packing & Delivery					£100.00
Other					£0.00
TOTAL					£5,138.50

Alternatively via post to the High Wycombe address below.

VEOLIA Signature	Jeff Porter	Client Signature	
Print Name	Jeff PORTER	Print Name	
Date	21 Apr 2021	Date	
		Order Number*	

Description of work requested	To supply and install a replacement UV lamp and quartz sleeve c/w new seals for the Quattro system in B27, followed by a Quattro and generation loop sanitisation. Chemicals and final H2O2 test strips for the sanitisation are to be supplied by Protherics.
Equipment needed to complete work (pumps/hoses etc)	PPE.
Serial No/Location:	QUAT2000 016 in B27

Parts / Products

LATIS - Part Number	Part Description	UoM	Quantity	Unit Price	TOTAL Price
UVHABU0017	UV LAMP H SIZE H17 MODELS 204, 204S AND 202S	EA	1.00	£232.00	£232.00
UVHATU0010	UV QUARTZ INC SEALS	EA	1.00	£405.00	£405.00
SEKIUV0015	SEAL KIT H UV 200 SERIES FOR 202, 204, 206, 214 & 216	EA	1.00	£69.00	£69.00
	-	-	0.00	£0.00	£0.00
	-	-	0.00	£0.00	£0.00
	-	-	0.00	£0.00	£0.00
	-	-	0.00	£0.00	£0.00
	-	-	0.00	£0.00	£0.00
	-	-	0.00	£0.00	£0.00
	-	-	0.00	£0.00	£0.00
	-	-	0.00	£0.00	£0.00
	-	-	0.00	£0.00	£0.00
	-	-	0.00	£0.00	£0.00
	-	-	0.00	£0.00	£0.00
	-	-	0.00	£0.00	£0.00

Parts / Products Total **£706.00**

Non Stocked Parts

Part Number	Description 1	Description 2	Quantity	Unit Price	TOTAL Price
R100SV0108	Labour Day Rate	Weekday	2	£930.00	£1,860.00
R100SV0121	Expensed Items (bought in)	Hotel	1	£100.00	£100.00
-	-	-	0	£0.00	£0.00

- The price quoted is exclusive of VAT

- Quotation is valid for 30 days from the date of issue

- Quotation is subject to VWS standard published T&C's (copy available on request)

- To accept this quotation please forward a copy of your purchase order via Email to

orders.watertech@veolia.com or via Fax to **+44 (0) 1628 897001**

Alternatively via post to the High Wycombe address below.

Non Stocked Parts	£1,960.00
Installation	£0.00
Commissioning	£0.00
Packing & Delivery	£38.00
Other	£0.00
TOTAL	£2,704.00

Address - Line 2	Ffostrosal,	
Address - Line 3	Llandysul , Ceredigion	
Post Code	SA44 5JT	
Contact - Name	Iwan Rees	
Tel	01239 851122	
Email	iwan.rees@btgsp.com	
Description of work requested	To carry out a media recharge of the PSF240 sand filter, as recommended during the recent PQMC visit. This is due to reduced service and backwash flow rates. In order to minimise downtime and for ease, because of lack of headroom, this quotation includes a replacement vessel which can be loaded prior to moving existing vessel nearer the doorway for emptying. This vessel can then be cleaned and stored, and reused next recharge. Alternatively, two other options for media removal: BTG to employ a local contractor to mechanically remove media (via suction), or BTG cut access hole in top of plant room roof for media extraction pipework to be lowered in. (BTG to make good the access hole afterwards). Labour charge listed is for Veolia to load new media and internals into new vessel & with mechanical assistance, move existing vessel prior to media removal. Exhausted media if possible will be left in 200lt sealable drums for clients disposal.	
Equipment needed to complete work (pumps/hoses etc)	Media extraction tools and equipment. Step ladder.	
Serial No/Location:	PSF240 Simplex Sand Filter, in Building 22	

Parts / Products

LATIS - Part Number	Part Description	UoM	Quantity	Unit Price	TOTAL Price
MEFIFI0040	MEDIA SAND FILTERING 0.5-1.0MM 25KG BAG	KG	315.00	£0.70	£220.50
MEFIFI0045	MEDIA SAND FILTERING 1.25-2MM 25KG BAG	KG	90.00	£0.80	£72.00
VMFLSP1005	CAM MODIFIED 2510,2750,2850,2900,2910 VALVE	EA	1.00	£55.00	£55.00
VICOAB0010	COLLECTING SYSTEM 11/2" ABS	EA	1.00	£91.00	£91.00
SPMETA324047	SPILL FREE MEDIA REMOVAL KIT	EA	3.00	£175.00	£525.00
VITUPV0202	TUBE RISER AND BOTTOM STRAINER 1,82M 50MM 2850/2900	EA	1.00	£89.00	£89.00
VISTAB1015	STRAINER TOP 50MM O/D TUBE C/W PINS 2850/2900/2910 V	EA	1.00	£40.00	£40.00
SEORFL0110	O-RING FL RISER TUBE 11/2" 2850 AND 2900	EA	1.00	£7.20	£7.20
FPSOPV1260	SOCKET G INCH/METRIC PL PVC 11/2" X 50MM	EA	2.00	£5.90	£11.80
TOAVGU0235	CEMENT WET-N-DRY ABS/PVC 500 ML	EA	1.00	£33.00	£33.00
SEORFL0105	O-RING FL TANK 2850	EA	1.00	£22.00	£22.00
VECSZD1005	VESSEL COMP C-2469-A3PWG BLUE 4 INCH TOP HOLE	EA	1.00	£866.00	£866.00
VMFLSP200498	Drive cam assembly	EA	1.00	£11.00	£11.00

Parts / Products Total **£2,043.50**

Non Stocked Parts

Part Number	Description 1	Description 2	Quantity	Unit Price	TOTAL Price
R100SV0108	Labour Day Rate	Weekday, 2 men, 2 days	4	£930.00	£3,720.00
R100SV0121	Expensed Items (bought in)	Hotel etc	2	£100.00	£200.00
-	-	-	0	£0.00	£0.00

- The price quoted is exclusive of VAT

- Quotation is valid for 30 days from the date of issue

- Quotation is subject to VWS standard published T&C's (copy available on request)

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Alternatively via post to the High Wycombe address below.

Non Stocked Parts

Installation	£0.00
Commissioning	£0.00
Packing & Delivery	£150.00
Other	£0.00
TOTAL	£6,113.50

Company Name	PROTHERICS UK LTD	
Address - Line 1	BLAENWAUN	
Address - Line 2	FFOSTRASOL	
Address - Line 3	LLANDYSUL	
Post Code	SA44 5JT	
Contact - Name	IWAN REES	
Tel	01239 858 721	
Email	IWAN.REES@BTGSP.COM	

Description of work requested	X2 TIMER HEAD ASSEMBLIES & LABOUR CHARGE FOR REPLACEMENT OF COMPONENTS AND RE PROGRAMMING OF SELECTRON SCAVENGER VALVE CONTROL UNIT
Equipment needed to complete work (pumps/hoses etc)	
Serial No/Location:	

Parts / Products

LATIS - Part Number	Part Description	UoM	Quantity	Unit Price	TOTAL Price
VMFLIE0020	TIMER HEAD ASSY SELECTRON BLACK	EA	2.00	£484.00	£968.00
-	-	-	0.00	£0.00	£0.00
-	-	-	0.00	£0.00	£0.00
-	-	-	0.00	£0.00	£0.00
-	-	-	0.00	£0.00	£0.00
-	-	-	0.00	£0.00	£0.00
-	-	-	0.00	£0.00	£0.00
-	-	-	0.00	£0.00	£0.00
-	-	-	0.00	£0.00	£0.00
-	-	-	0.00	£0.00	£0.00
-	-	-	0.00	£0.00	£0.00
-	-	-	0.00	£0.00	£0.00
-	-	-	0.00	£0.00	£0.00
-	-	-	0.00	£0.00	£0.00
-	-	-	0.00	£0.00	£0.00
-	-	-	0.00	£0.00	£0.00

Parts / Products Total **£968.00**

Non Stocked Parts

Part Number	Description 1	Description 2	Quantity	Unit Price	TOTAL Price
R100SV0108	Labour Day Rate	Pharma Rate	1	£930.00	£930.00
-	-	-	0	£0.00	£0.00
-	-	-	0	£0.00	£0.00

Non Stocked Parts **£930.00**

- The price quoted is exclusive of VAT

- Quotation is valid for 30 days from the date of issue

- Quotation is subject to VW5 standard published T&C's (copy available on request)

- To accept this quotation please forward a copy of your purchase order via Email to

orders.watertech@veolia.com or via Fax to +44 (0) 1628 897001

Alternatively via post to the High Wycombe address below.

Installation	£0.00
Commissioning	£0.00
Packing & Delivery	£16.00
Other	£0.00
TOTAL	£1,914.00

QUOTATION DESCRIPTION	
Description	Replacement of CDI module due to failure and replacement of CDI power board. Due to obsolescence of the current power board this will be upgraded to the DCR version.

QUOTATION DETAILS								
Line #	Part Number	Part Description	Installed Product Serial Number	Line Description	UOM	Qty	Unit Price (GBP)	Total Price (GBP)
1	MBCDMD0030	MODULE CDI LX-X30 CELL PAIR NON HWS / VU-LXM30X			EA	1	10,195	10,195
2	CEPBCD0012	DISPLAY BOARD FOR 1-16 CHANNEL FOR G2- POWER CONTROLLER			EA	1	1,505	1,505
		CABLE ETHERNET						

1

3	CECADT0001	RJ45, 2MT IP-CABLE2M-G2			EA	1	84	84
4	CEMDCD204378	RECTIFIER 600 VDC 15A MAX O/P 0-5 VDC IP-DCR600V15A-R2			EA	1	1,842	1,842
5	IEPARE0001	REPEATER 4-20MA PSU 1.3 AMP ORION II			EA	1	200	200
6	R120SERLABOR	LABOR		LABOR	EA	2	1,093	2,186
TOTAL(EXCLUSIVE OF VAT) GBP								16,012

*This quotation is valid from 01/05/2023 9:28 AM until 04/05/2023.

* Pricing in GBP currency.

* For inquiries or to accept this quotation please contact or forward a copy of your purchase order via email to quotes.watertech@veolia.com.

* Quotation is exclusive of VAT.

* Commercial Terms Conditions can be found below.

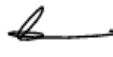
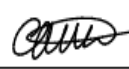
Signature

APPENDIX 8 – Validation Summary Report

Document ID:	WAL-FUV-VSR0044-001
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INTERIM VALIDATION SUMMARY REPORT FOR THE X977 ORION PFW GENERATION SYSTEM

Completion of the following signature section signifies the approver(s) has read, understands, and authorises the use of this Interim Validation Summary Report (VSR) for the above-mentioned System.

Responsibility	Position	Name	Signature & date
Author	Validation specialist	Erica Davies	 Electronically signed by: Erica Davies Reason: Approve Date: Mar 21, 2023 16:08 GMT
System Owner/SME	Senior Engineer	Iwan Rees	 Electronically signed by: Iwan Rees Reason: Approve Date: Mar 21, 2023 15:57 GMT
Production	Director of Manufacturing	Almero Barnard	 Electronically signed by: Almero Barnard Reason: Approved Date: Mar 21, 2023 15:51 GMT
Quality control	Quality Control Specialist	Chris Pulham	 Electronically signed by: Chris Pulham Reason: Approve Date: Mar 21, 2023 16:00 GMT
Quality	QA Lead	Kay Morris	 Electronically signed by: Kay Morris Reason: Approved Date: Mar 21, 2023 16:02 GMT
Validation	Validation Lead	Charis Elliott	 Electronically signed by: Charis Elliott Reason: Approve Date: Mar 21, 2023 15:43 GMT

1 Introduction/System Description

The purpose of this exercise was to define a documented validation programme which provided a high degree of assurance that the designated system/process consistently met predetermined process or product specifications, and which did not impair product safety, quality or efficacy.

This Interim Validation Summary Report (VSR) details the outcome of the validation activities detailed in the Validation Plan WAL-FUV-VP0009-002 'Validation Plan for the PFW Generation System (ORION) Tag Number X977' and associated change control (CC) 65642 'Purified Water Generation Upgrade' for the PFW Generation System (Orion) X977 used at BTG, Wales up to and including PQ phase 1 in accordance with WAL-EPV-PQ0033-001.

This interim VSR provides an executive summary of all the validation activities completed to date for the ORION PFW system, undertaken in accordance with CC 65642 & WAL-FUV-VP0009-002.

Interim approval of WAL-FUV-PQ0033-001 and this interim VSR is required to progress to the next phase of the qualification as per WAL-EPV-PQ0033-001 'Performance Qualification for the X977 Orion PFW generation system'. The remaining actions within the PQ do not impact the progression of these protocol exercises as have been pre-defined within the PQ protocol in accordance with the Validation Plan WAL-FUV-VP0009-002 'Validation Plan for the PFW Generation System (ORION) Tag Number X977'. All exercises that remain open will be completed prior to progression to PQ phase 3, and further concurrent use of the system.

2 Summary

The PQ Phase 1a was successfully approved on 31 Mar 2023 and phase 1b successfully completed on the 7th April 2023. The PQ phase 2 was successfully completed and approved on the 27th April 2023. The PFW Generation System (Orion) X977 and its components are installed and operate as specified according to the requirements detailed in the validation plan which have been adequately documented and controlled according to GxP requirements.

A summary of the predetermined acceptance criteria outlined in the IOQ and PQ are detailed in the relevant sections below.

Completion and approval of this Interim Validation Summary Report allows for progression to the next phase of the qualification (Phase 3) as per WAL-EPV-PQ0033-001 'Performance Qualification for the X977 Orion PFW generation system' and concurrent release of the system in accordance with the scope defined in the approved FEMA (reference WAL-EPV-PQ0033-001, attachment 5). The remaining actions within the PQ do not impact the progression of these protocol exercises. All exercises that remain open will be completed prior to progression to PQ final approval at the end of Phase 3 (12 month review) and continued concurrent use of the system.