WFI Generation at Alnylam's Norton Facility

Present and Future States

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Overview of the Norton Manufacturing Facility

- Norton manufactures small interfering RNA (siRNA) Bulk Drug Substance (BDS) for Alnylam's early stage clinical pipeline.
- The molecules are made via solid-phase phosphoramidite synthesis, then modified and purified using unit operations common to the biologics industry (chromatography and ultrafiltration).
  - Upstream is an organic solvent based, anhydrous process
  - Downstream is primarily aqueous with some organic solvents
  - No bioreactors or media vessels, and chromatography only uses two buffers (plus cleaning)
- The facility was constructed as a greenfield with ground breaking in 2016, occupancy in 2019, and initial engineering batches in 2020.

Compendial Waters in Norton

Due to relatively low water demand, Norton's compendial water infrastructure is smaller than most biologics sites.

- USP-Purified Water
  - Small system used for the Quality Control labs
  - Simple system consisting of single pass RO for generation and continuous loop polishing via UV and mixed-bed DI.
  - 2 GPM of Ambient PW (APW) generation capacity
  - 300 gallon ambient storage
  - 1" APW Distribution System (sprayball return to storage tank)
- USP-WFI
  - Larger system used for all manufacturing activities
  - 25 GPM of Hot WFI (HWFI) generation capacity
  - 10,000L Hot WFI Storage Vessel
  - 3" Hot WFI Distribution System (sprayball return to storage tank)
  - 2" Ambient WFI (AWFI) Distribution System (chase-the-tail design)

Why no USP Purified Water system for Manufacturing?

Few uses for USP-PW

- Primary use would be for CIP rinses and washes
  - For those, an alternative water grade would be softened water (non-compendial)
- Only 2 CIPs could use PW for final rinse (no traditional upstream to consumer water)
  - Minimal volume compared to overall compendial water demand
- There is no clean steam at Norton facility, so there is no need for PW as feedwater

Many uses of USP-WFI

- Required for final rinse for majority of CIPs
  - Need relatively high capacity or a large final rinse tank
- Required for vast majority of process users
  - Most process users are in purification and require highest grade of compendial water.
  - Intrathecal molecules have strict microbial requirements, so could not take advantage of more lenient PW limits.

WFI is required for most of the process, and the process uses less overall water than traditional mammalian cell culture processes. For this facility, it is not worth the additional capital and operational costs to have two compendial grades of water production on site.

New WFI Generation Selection

Norton had an established distillation technology and hot WFI storage, why use ambient membrane generation?

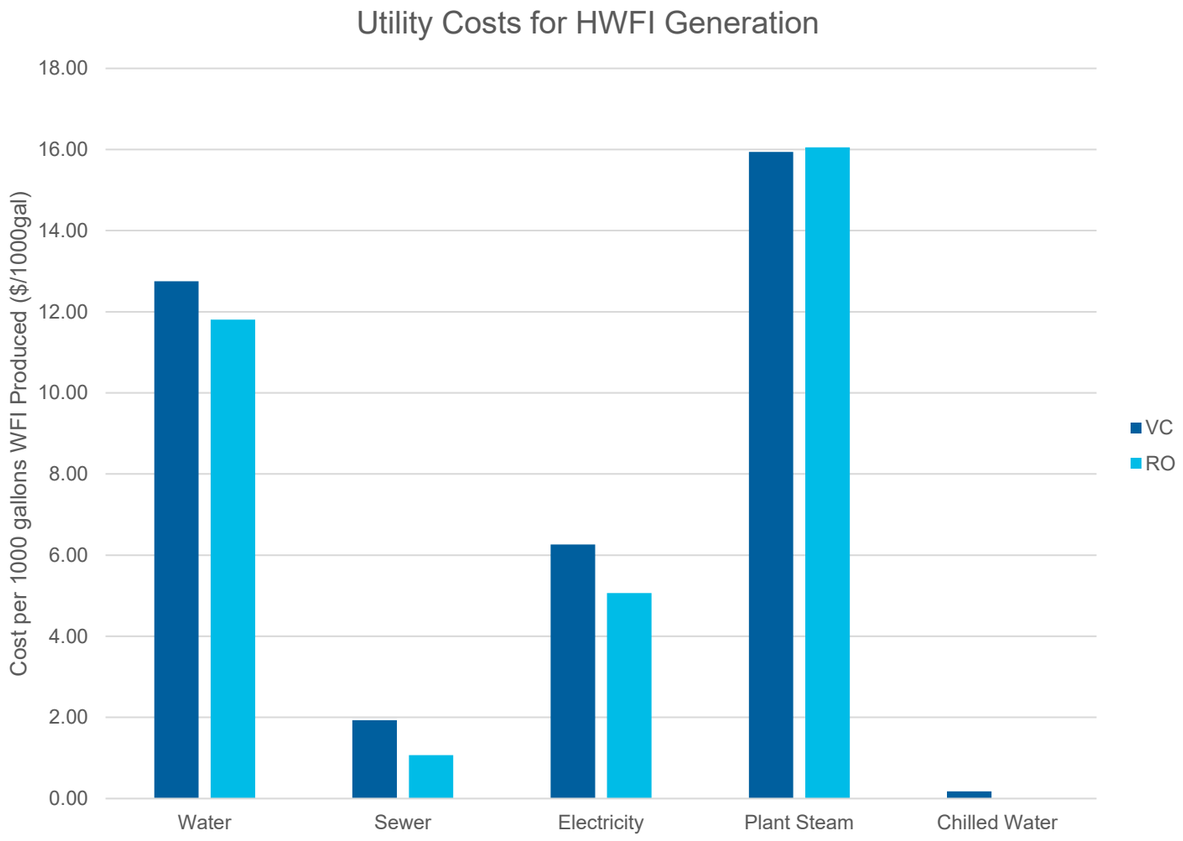
There were several factors that expanded the technologies that were assessed:

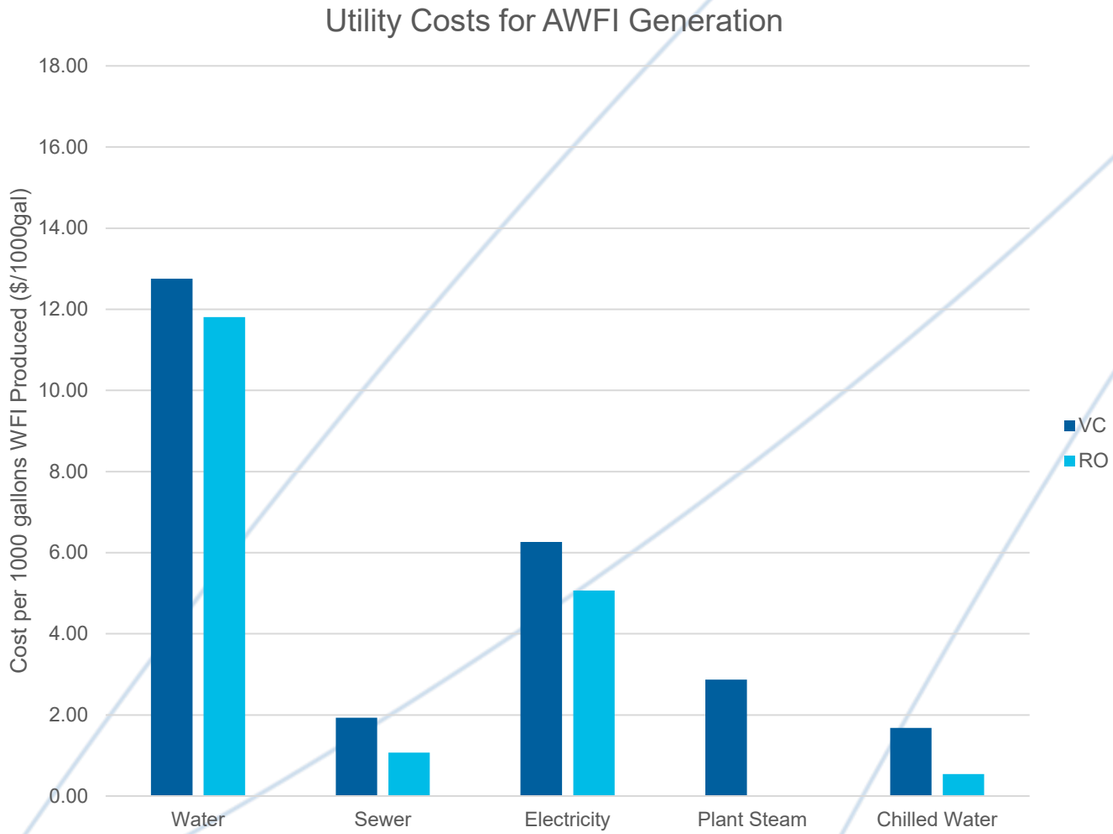
- Updated regulations
  - PhEur began allowing WFI to be made by RO (or equivalent) in 2017
  - Increased adoption of membrane based WFI in the industry
- Space limitations
  - Floor space for a duplicate Vapor Compression and pretreatment skid was challenging in the area
- Future Ambient WFI (AWFI) Storage and Distribution Ambitions
  - Current Hot WFI usage is negligible, AWFI storage and all AWFI distribution will be more efficient
  - VC can produce AWFI, but distillate temperature will be 10 to 15 °C higher than feed water with hygienic HX

WFI Generation Technologies Assessed

- Multi Effect (ME) Distillation ruled out:
  - no high pressure steam on site
  - no PW system for feed water (would need RO pretreatment for silica)
  - no clean steam system for the ME to be a redundant generator
- Vapor Compression (VC) distillation ruled in:
  - established and effective on site since 2021
  - ambient outlet options available
- Membrane based RO ruled in:
  - increasing adoption in industry
  - lower capital cost
  - most efficient ambient generation option
  - ambient waste discharge allows water reclamation (future)

Vapor Compression vs Membrane Based WFI Utility Costs*



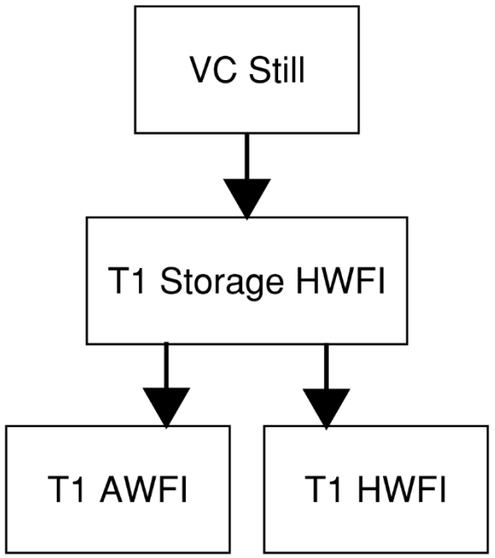


*Note that utility rates have not been updated for 2024. Used for qualitative comparison when systems are producing water at steady state. Does not account for softener regeneration, sanitization, etc. Utility draws based on operational values from both units at Norton.

Norton WFI Plan

The site added another WFI Generation system in 2024 to increase redundancy. The system chosen will also enable future capacity and storage at ambient temperature

Original



Purified Water (PW) System

Package system for generation, storage, and distribution of USP PW

- Softens, dechlorinates, and purifies using single-pass RO
- Distribution loop continuously polishes with 185nm UV, mixed bed deionization, 254nm UV, 0.1µm + 0.05µm filtration.

Pretreatment for Vapor Compression Still

Designed for ~20 GPM pretreatment to feed Vapor Compression Still

- Softens and dechlorinates water
- Polishing softener installed for ammonia removal if municipality starts using chloramines for disinfection
- No particle filters or pH adjustment
- Softeners operate in parallel

MECO PES750MSSH Vapor Compression Still

Peak Output of 12.5 GPM of Hot WFI Output

- Degasses feedwater via steam stripper
- Boils and condenses water to create WFI
- 4 discrete output speeds, minimum 7.5 GPM
- Ability to retrofit for ambient WFI generation
  - Requires additional heat exchangers to approach 25°F of feedwater, and/or a chilled water trim heat exchanger
- Recovers ~85% of feedwater

Membrane based WFI system

12.5 GPM of Ambient or Hot WFI Output

- Softens, dechlorinates, (optionally) adjusts feedwater pH, and filters feedwater
- Purifies water using two pass product staged RO, a degassing membrane, an EDI, and Ultrafiltration
- Continuous output capacity variable from 8.6 GPM to 12.5 GPM.
- Uses a steam heat exchanger on the outlet to produce Hot WFI when required.
- Recovers ~90% of feedwater

Performance Comparison

Both technologies produce essentially identical water.

- No microbial issues since startup
- Conductivity is equivalent
- TOC is equivalent
- Electrical demand of RO is lower during production

Operational Experience

Vapor Compression Still

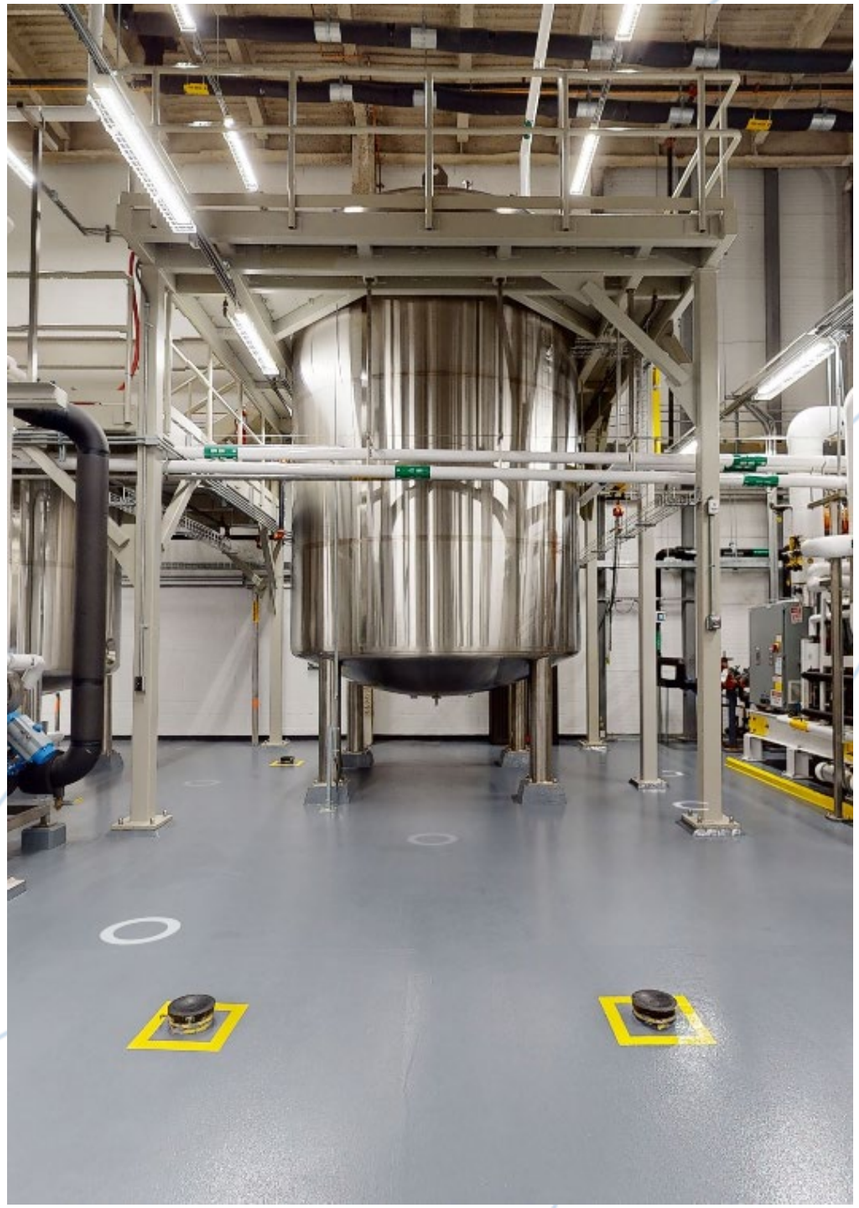
- Needed compressor replacement after ~14 months
  - Early detection via onboard instrumentation (vibration)
  - Corrective actions put in place (by OEM and Alnylam), successfully running for 3+ years
- Less instrumentation can make diagnosis difficult.
  - Minimal troubleshooting required due to distillation being a robust purification method
- Pretreatment requires weekly sanitization

Membrane Based System

- Needed EDI and UF replacement after ~10 months
  - Early detection via onboard instrumentation (DP)
  - Corrective actions put in place since replacement. Need more time to confirm efficacy
- More extensive instrumentation helps with diagnosis, though increases complexity
- Additional instrumentation takes more time to calibrate.
- More spare parts and consumables
- Operators require more in depth training to operate, maintain, and troubleshoot additional components
- Requires a weekly (pretreatment), monthly (RO), and quarterly sanitization (RO+EDI)

Future Outlook

- Future WFI storage tank has been installed (part of greenfield project) and has nozzles for two distribution systems.
- Ambient storage and distribution with ozone is planned due to no Hot WFI users.
- Vapor Compression Still would need to be retrofitted for ambient production



Thank you !

Questions?