

AstraZeneca and Air Products

Our work together

"Operating in a competitive environment means we at AstraZeneca are continually looking at ways to reducing costs without compromising product quality. By better understanding these needs, Air Products have worked with us and have provided flexible customised solutions that will ultimately make AstraZeneca more competitive."

Martin Webster, Utilities and Energy Manager, AstraZeneca's Avlon Works



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Pharmaceutical manufacturer AstraZeneca has significantly reduced the cost of high-purity nitrogen at its Avlon site by installing an Air Products PRISM® High Purity Nitrogen (HPN) on-site nitrogen generation system. The new plant satisfies important standards for reliability and qualification

“The option of Generating our own nitrogen was a concept we could no longer afford to ignore,” explains Martin Webster, utilities and energy manager at AstraZeneca’s Avlon Works on the outskirts of Bristol.

“Our Long term contract with Air Products for on-site nitrogen generation will provide us with nitrogen at just over half the cost of buying liquid nitrogen in bulk.”



As well as the economic benefits of generating nitrogen gases onsite, there are inherent environmental benefits from which AstraZeneca will benefit, including reduced tanker deliveries and other energy consumption reduction benefits.

Importantly for AstraZeneca, the deal brings no penalties in the form of maintenance costs or reliability issues. Air Products takes full responsibility for the capital and maintenance costs for the 1200 Nm³/h PRISM[®] HPN generator, which uses the latest cryogenic distillation technology to supply nitrogen at guaranteed high purity. AstraZeneca pays only a monthly rental charge, for the electricity to run the generator, plus an agreed price for any additional liquid nitrogen consumed above the plant capacity.

Though Air Products is fully responsible for running the nitrogen generator, there are no permanent Air Products staff on the Avlon site. Instead, the generator is monitored continuously from the Air Products bulk gas facility at Llanwern, just across the Severn Bridge in south Wales. Llanwern supplies maintenance personnel whenever necessary, and guarantees supplies of liquid nitrogen – at the same cost as the generated gas – to cover planned maintenance and outages.

The need for validation to strict pharmaceutical standards has not been an obstacle. Although the project has required some new thinking on both sides, the plant



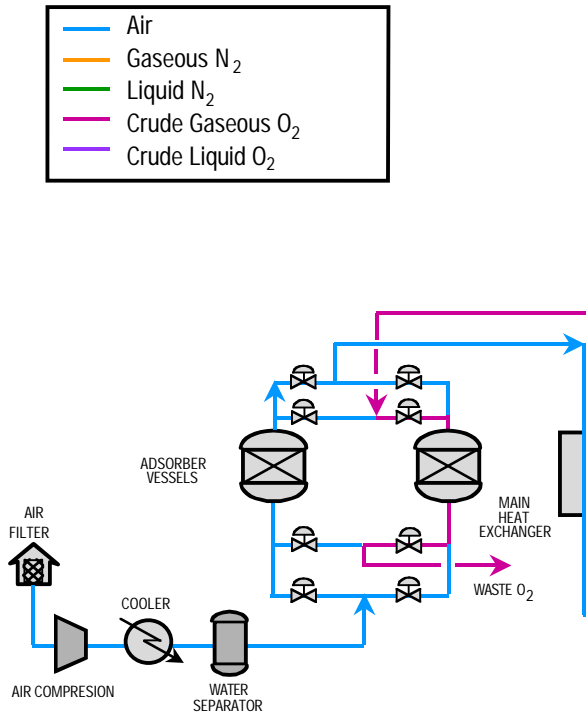
meets AstraZeneca's strict qualification requirements, which include the requirement to adhere to FDA, CGMP or the MCA guidance. As a result, there is the potential to pioneer the use of Air Products on-site nitrogen generation systems at other AstraZeneca sites.

Rapid growth at Avlon

Avlon Works is one of AstraZeneca's key manufacturing locations for bulk pharmaceuticals. Recently the site has been expanding rapidly to meet the growing demand for product introduction.

The site uses nitrogen for inerting process vessels containing flammable vapours and to dry product in filter presses and centrifuges. A smaller amount of liquid nitrogen is also used for cryogenic condensation of organic vapours the resulting nitrogen product is then re-used as nitrogen gas. Members of Air Products' Cryogenic's group have worked closely with AstraZeneca personnel to optimise their cryogenic processes. Until recently all the nitrogen was supplied by liquid nitrogen road tanker and stored in Cryogenic vessels.

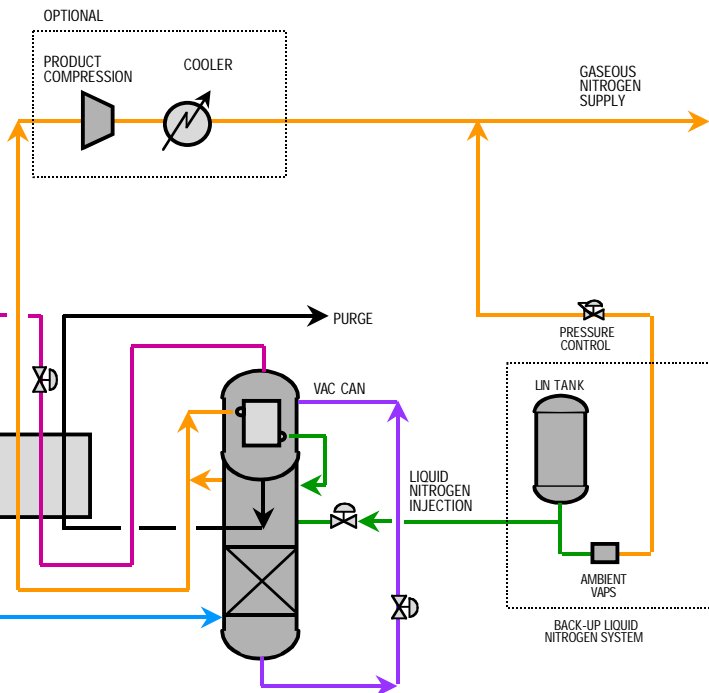
*Air Products PRISM®
HPN system Process
Flow diagram*



But the site's rapid growth has brought change. "Nitrogen consumption on the site has increased fivefold in the last five years, so it was logical to consider a nitrogen generator," says Martin Webster. AstraZeneca had considered on-site generation in the past, but found it inappropriate at the time. Due to the changes in the site's nitrogen requirements the on-site nitrogen generator has proved to be the best technical and most cost effective option. These modular generators use tried-and-tested technology much like the air separation plants that provide liquid nitrogen, though they have a production capacity which is many times smaller and are more compact.

In 1999 AstraZeneca carried out a BETA (Business Engineering Technical Assessment) study to explore the technical, commercial and validation issues surrounding nitrogen use. "This showed us that on-site nitrogen generation was definitely the way forward," says project manager Les Flynn. Towards the end of the year, already convinced of the benefits of on-site nitrogen generation, AstraZeneca began discussions with three gas companies:

Air Products offered the favoured technical and commercial proposal.





Finding the right supplier



An important question was how big the plant should be. AstraZeneca wanted the new generator to supply all the site's requirement for gaseous nitrogen, but apart from the total liquid nitrogen consumption the company had little information about where and when nitrogen was being used. After a programme of measurements and modelling, AstraZeneca agreed on a generator capacity of around 1200 Nm³/h. Any short-term peaks in demand, and ultimate security of supply, would be met using liquid nitrogen. The continued growth of the site, however, made it hard to predict future nitrogen demand. In particular, explains Les Flynn, the engineers who designed the new processes had problems calculating how much nitrogen they would need for drying.

"Correct plant selection was a tricky decision for AstraZeneca, and I think they appreciated the extent of the supply options proposed, and the effort we put into openly explaining them, which helped them to make their decision", says Air Products project manager Nigel Lucas.

"Air Products offered the best technical solutions, combined with the best commercial package", says Les Flynn.

As a result, the two companies signed a contract in January 2000.

Engineering issues

For historical reasons, individual electricity supplies on the Avlon site are limited to a capacity of 400 A, which is not enough to supply the single 500 kW compressor that an PRISM[®] HPN nitrogen generator of this size would normally use. However, this did not prove to be a problem to Air Products. They designed the nitrogen generator around two 250-kW compressors running in parallel, each with its own supply. "The Air Products engineers were very flexible about this design modification, and the dual-compressor arrangement is a successful design" says Les Flynn.



*Air Products' tailored
compressor supply
solution for
AstraZeneca*



To limit the nitrogen generators reliance on other services on-site, including cooling water for the main air compressor, AstraZeneca selected an air cooled rather than water cooled compressor, so the only services required were electricity, and drainage for the pre-treatment section of the plant. While Air Products was designing and building the new PRISM® HPN nitrogen generator, AstraZeneca had time to prepare a foundation for the system, which measures only 14 m x 10 m.

The nitrogen generator, consisting of just four main equipment items, arrived on site just before Christmas 2000, and was commissioned to provide nitrogen to the AstraZeneca very early in 2001. Smooth handover between the previous supply infrastructure and the new Air Products PRISM® HPN nitrogen generation system required careful scheduling, and standby supplies of liquid nitrogen at the local Air Products facility, but was accomplished without incident, says Les Flynn. The nitrogen generator now supplies 1200 m³/h of nitrogen, or just over half the site's current gaseous nitrogen requirement, at a pressure of 6 bar.

Following this commissioning work Air Products continued to work with AstraZeneca to fulfil their stringent qualification requirements, this work included the installation of additional quality monitoring instrumentation and on-going reporting of the plant key performance characteristics.

Nitrogen purity and qualification

Because the nitrogen comes into contact with pharmaceutical ingredients, it is subject to strict controls on contamination. All the nitrogen on the site, apart from that used in the laboratories, has to meet defined quality standards. Key concerns for AstraZeneca were not only the purity of the nitrogen from the generator in normal operation, but what performance Air Products could guarantee under all operating conditions.

AstraZeneca originally specified nitrogen at 99.999% purity, with tight limits on individual gases such as oxygen, water, carbon dioxide and argon. The Analysis conducted by Air Products Tracelab Services showed that nitrogen from the PRISM® HPN nitrogen generator meets this specification comfortably with the exception of Argon. Typical levels of oxygen and water in HPN nitrogen, for example, are less than 0.7 parts per million (ppm) and 0.05 ppm respectively. Gas produced from the nitrogen generator can contain up to 300 ppm of argon, which was too high to meet the original AstraZeneca specification. Martin Webster explains that this specification derived largely from the composition of bulk liquid nitrogen made in large air separation plants. In such plants, argon – a natural component of air – is normally removed and sold separately. For small nitrogen generators, argon removal is impractical, so argon levels are higher.



Although increased Argon content in the product nitrogen, up to 300 ppm, may have stood in the way AstraZeneca and Air Products staff reasoned that since argon is less reactive than nitrogen, it should be acceptable for product contact. After thorough checking by AstraZeneca Quality and Research departments, they were able to revise the minimum nitrogen specification to incorporate this quantity of argon in the nitrogen product gas.

The main contamination concerns for AstraZeneca were carbon dioxide and water. Both of these are removed in majority by the pre-treatment system, upstream of the cryogenic column. The anticipated levels of these contaminants fall well below those stipulated by AstraZeneca's strict quality requirements. However as they are only present in ppm quantities it is difficult to guarantee their absence without the aid of specific monitoring equipment.

Air Products cost effect solution was simply to add a moisture meter in to the process line, which by inference also keeps a check on carbon dioxide levels.

Through the implementation of these solutions, Air Products are now able to guarantee that AstraZeneca Nitrogen specification will be met at all times, thus satisfying their requirements.

A partnership for the future

Based on the success of this project, Air Products and AstraZeneca are looking forward to a long and fruitful partnership in on-site nitrogen generation. The low cost of on-site nitrogen is inspiring AstraZeneca to look at similar projects at other manufacturing sites, the understanding of the validation issues is a key differentiator for Air Products.

Validation has always been important to pharmaceutical manufacturers, and where nitrogen is concerned this importance can only increase. "Most manufacturers have now got to grips with validation of water systems," says Martin Webster, "and I believe the regulators are turning their attention towards nitrogen. We have taken our lead from them. We are the first AstraZeneca site to have what we call 'cGMP-critical utilities'," Webster continues. "We have now qualified all our nitrogen sources, with the help of Air Products, down to the level of individual site users."

For Air Products this meant an audit of its Llanwern site, a source of the liquid nitrogen for the Avlon Works, as well as rigorous checking of the PRISM® HPN nitrogen generator design by AstraZeneca staff. "We qualified the nitrogen generator when it was installed," says Webster, "and we are backing this up with a continuing programme of measurements and reporting."



Experience gained here will stand Air Products in good stead as a supplier for future nitrogen generator requirements, at Avlon and on other AstraZeneca sites. "On this project we found the Air Products people knowledgeable and enthusiastic," says Les Flynn. "Within a couple of years, it is likely that we will need another nitrogen generator on the site. When that happens, as long as our relationship with Air Products has continued to work as well as it does now, Air Products will be our preferred supplier."

*Air Products PRISM®
High Purity Nitrogen
(HPN) on-site nitrogen
generation system
at AstraZeneca's
Avalon Works.*



tell me more

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