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TECHNICAL INFORMATION SHEET 39 - 2016

MEDICAL GASES. QUALITY CONTROL AND QP BATCH CERTIFICATION OF BULK MEDICAL LIQUID OXYGEN

POSITION

The medical regulatory authorities have for many years given a concession to allow the retrospective release by a Qualified Person (QP) of bulk medical liquid oxygen.

The concession allows a batch of medical liquid oxygen to be certified by the nominated Quality Controller (QC) before leaving the filling site but allows the QP to retrospectively certify the batch within a defined timeframe.

This has been standard practice within the medical gases industry for more than forty years with no adverse consequences. This document details the both the practical and the scientific justification for the concession.

This concession has been formally endorsed by the medical regulatory authority, the Medicines & Healthcare products Regulatory Agency (MHRA) in the UK, on the provision that the medical gas supplier can demonstrate that the product being supplied for patient use is of a suitable quality.

HISTORICAL BACKGROUND

Medical liquid oxygen has been manufactured by cryogenic distillation of ambient air using Air Separation Units (ASU) for over a century and supplied to hospitals as a medicinal product for more than sixty years. The operation of ASU's is safe and efficient and has been developed through careful design to ensure that the products produced meet the specified requirements. The ASU plants utilise a high level of monitoring and control to ensure that the process is capable of consistently producing liquid oxygen to a very high level of product purity with limited operator intervention. All product is released for distribution to healthcare facilities by designated quality control personnel.

Traditionally the regulatory authorities in the UK have allowed medical liquid oxygen to be supplied to healthcare facilities prior to batch certification by the QP. This concession was granted based on the robustness of the process and the consistent levels of product purity and quality.

Originally this retrospective release process was achieved by the distribution sites providing the QP with a weekly log of all tanker filling batches which were approved formally by the QP.

With the development of automated tanker loading and analysis processes and the ability for this batch management data to be accessed by secure on-line systems, the QPs are now able to review and certify batches on a more frequent basis.

PROCESS CONTROLS

The manufacturing process for medical liquid oxygen is controlled using various sensors and analysers. The sensor and analyser outputs are monitored in real-time and any adverse trends or excursion outside the specified parameters result in remedial adjustments in accordance with process control principles.

BCGA TIS 39 Published: 01/12/2016 Produced by: BCGA TSC7 ISSN 2398-9386

The total purity of the liquid oxygen being manufactured by the ASU and going into bulk storage vessels is monitored continuously and any product found to be outside the prescribed limit activates the liquid oxygen dump valve which diverts any off-specification product to atmosphere, via a vent valve, in order to prevent it being introduced to the bulk storage vessel(s).

Impurities, such as carbon monoxide (CO), carbon dioxide (CO_2), water (H_2O) and hydrocarbons are removed at the air purification stages prior to the purified air entering the distillation column. This process is monitored by measuring the CO_2 content prior to the ambient air entering the ASU in order to prevent blockage due to icing of internal pipework.

All road tankers are individually analysed prior to filling and after loading to ensure that the product meets the medical liquid oxygen specifications for total purity. Any product batch found to be below the specification limit is rejected by the QC and is not allowed to be supplied to medical customers.

Medical liquid oxygen certification systems have been established that verify that the product specification requirements have been met and this is also verified and signed off by authorised quality control personnel.

The QPs are notified of the batch management results and have access to all required information to be able to assess whether the batch is acceptable to be certified for release to customers and that the manufacturing and filling processes remain under control.

QUALITY MANAGEMENT SYSTEMS

The QPs are actively involved in all aspects of the Quality Management System (QMS) which has an impact on the medical product. As well as the review and certification of batches of bulk medical oxygen release to market, these activities include:

- approval of changes that could have an impact of medical gases;
- performance of QP inspections of medical gas sites;
- participation in inspections by the MHRA and any other regulatory authorities;
- participation in audits of relevant service providers;
- participation in medical product quality reviews;
- participation in validation activities;
- participation in product recall and simulations;
- participation in investigation of quality defects and customer complaints; and
- assistance in the development / improvement of the QMS.

With information provided in the batch record, information systems and knowledge of the manufacturing / QMS processes, the QP is able to satisfy their responsibilities for the certification and release of batches of medicinal product to the market.

RISK ASSESSMENT - MEDICAL LIQUID OXYGEN

Risk assessments for the manufacture and supply of medical liquid oxygen have been developed using accepted industry standard techniques, for example, Failure Mode and Effects Analysis (FMEA) and Hazard Analysis and Critical Control Points (HACCP).

The main potential failures modes are:

(i) Failure of the ‘liquid oxygen to storage dump valve’ to operate;

(ii) Failure of total purity analysers;

(iii) Tanker changing product service or returning from maintenance.

(i) Failure of the 'liquid oxygen to storage dump valve' to operate

The manufactured purity level is continuously monitored using actual values and trending visual indicators, with alarms to notify if the product is below specification.

The 'liquid oxygen to storage dump valve' is tested, as a minimum, on an annual basis to verify that it is operating correctly. Failure of the valve to activate would result in a non-conformance being raised with appropriate corrective actions to prevent reoccurrence.

Post-fill tanker analysis would detect any low purity of product loaded from the storage.

Potential risk: Low (frequency of occurrence low, detectability high).

(ii) Failure of total purity analysers

The total oxygen analysers follow the principle of Paramagnetic Susceptibility to determine the purity of the product (refer to the European Pharmacopoeia monograph). This is an industry standard technique that has proved to be very reliable in an operational environment.

The analysers are calibrated on a defined frequency (usually monthly). Deviation of calibration results are monitored with warning deviations limits identified to ensure that the performance of the analysers is maintained. The non-conformance system is used to investigate and correct any potential quality defects.

The manufactured purity level is continuously monitored with actual values and trending visual indicators. Step changes in performance would be readily observed by the personnel monitoring plant performance.

There are normally different analysers for measuring the 'liquid oxygen to storage' and 'prefill / postfill' at the ASU sites. Any discrepancy between the two analysers would be addressed using the non-conformance system.

Potential risk: Low (frequency of occurrence low, detectability high).

(iii) Tanker changing product service or returning from maintenance

Procedures have been developed and implemented to ensure that all tankers that are either converted from another product or are returning from maintenance are appropriately purged. The procedure requires the tankers to be prefill analysed to ensure that they meet a minimum specification of 99.5 % oxygen.

Potential risk: Low (frequency of occurrence low, detectability high).

POTENTIAL BUSINESS IMPACT OF IMPLEMENTING PROSPECTIVE RELEASE OF MEDICAL LIQUID OXYGEN

The EU Guide to Good Manufacturing Practice, Annex 16, (Certification by Qualified Person and Batch Release), for which the latest revision came into operation from 15th April 2016, states:

Clause 4.1 "Batches of medicinal products should only be released for sale or supply to the market after certification by a QP as described above. Until a batch is certified, it should remain at the site of manufacture or be shipped under quarantine to another site which has been approved for that purpose by the relevant Competent Authority."

The accepted industry practice in the UK for the QP review of the batch records and subsequent batch certification allows this process to be performed retrospectively with the QP certification being performed within a defined timeframe after the filling of the road tankers. This allows for supply chain flexibility to meet UK specific customer requirements in-line with the principles of Annex 16. Should the manufacturers of bulk medical liquid oxygen need to strictly comply with the requirements stated in the revised Annex 16, whereby product must remain on the manufacturing site until QP batch certification is

performed, this would impose serious restrictions on the supply chain. This could result in negative impacts to product availability and introduce additional risk to patient heath.

The manufacture of liquid oxygen by an ASU is a continuous process which produces the oxygen at a quality which meets the specification of the European Pharmacopeia. The product can be used for various customer segments (such as healthcare, pharmaceutical, food and beverage, welding, steel manufacture) and is stored in common large insulated storage vessels.

Medical liquid oxygen is taken from the common storage and transferred to liquid oxygen road tankers to create a batch of medicinal product. This batch is analysed and certified by the authorised personnel based on the process defined within the Site Master File (SMF).

The loading of liquid oxygen road tankers is planned throughout the day to ensure efficient use of fill points and road tankers. Some of this filling is performed 'out of hours' where there are limited personnel available on site, with the quality control review performed by the gas manufacturers' central operating centre (Air Products' OSC, BOC's ROC etc.).

There are various ways in which the manufacturers of medical liquid oxygen could comply with the revised requirements of Annex 16 for performing QP batch certification prior to each tanker leaving the manufacturing site, however each model has significant potential impact to the business and increase risk to customers and patients.

The options include:

(i) Restrict when customers can have tankers delivered to their site to meet QP availability

Potential impact: This would decrease customer satisfaction causing disruption at the customer sites or potentially increase risk of customer run outs, thereby severely increasing the risk to patient safety.

(ii) Continue the same supply chain model (maximum supply chain flexibility)

Potential impact: This would require obtaining additional QP's that would be prepared to work on shift system to cover 'out of hours' filling. Currently there is a shortage of QP's in the UK and it is unlikely that we would be able to attract the correct calibre of personnel to make this model work. It should also be noted that the actual time taken to review and certificate batches of medical liquid oxygen for release is relatively short and would not cover the available hours of these additional QP's.

(iii) Existing fleet of road tankers wait at the manufacturing site until QP is available

Potential impact: This would make the scheduling of trips very challenging, with drivers not able to fill and deliver product to customers due to hours spent waiting at the manufacture site for QP certification. There are both EU and domestic rules that limit the number of hours that drivers are able to drive in a day.

This would also impact on the supply of bulk medical liquid oxygen to customer sites as the customers who are supplied with this product (typically hospital sites) require a regular supply of product throughout the day, and more often than not during the night time hours, due to the hospital sites being more readily accessible for road tankers during 'out of hours' periods.

(iv) Add additional road tankers to the fleet and preload dedicated medical oxygen road tankers

Potential impact: This would increase the number of assets in the supply chain significantly and would increase the risk of incorrect tankers being delivered to customers since there would need to be an additional tanker selection step.

(v) Batch release medical liquid oxygen from separate storage tanks

Potential impact: This would require a major investment in new storage tanks and potentially would require additional tankers if the release needed to be performed into tankers dedicated to medical service (similar to the approach taken in France).

This would have no positive impact on the safety and efficacy of the product.

RISKS WITH NEW MODELS

(i) Increased risk of customers running out of bulk medical liquid oxygen due to inflexibility of supply chain.

(ii) Increased risk of supply chain pressures on QP's to release batches to meet supply chain and customer demands.

(iii) Increased risk of incorrect batches being delivered - some tankers would be able to ship directly and others awaiting release with increased risk of incorrect batch of product being delivered.

(iv) Increased risk of supply chain pressure for drivers to exceed their strictly controlled hours due to waiting at site, driving times and / or tankers being delayed on route.

CUSTOMER AND PATIENT PERSPECTIVE

Hospitals and other healthcare establishments, large and small, are users of bulk medical liquid oxygen and the medical gas industry has developed to meet their requirements. These customers need to be able to request deliveries when their stock begins to run low. Any undue delay in delivery could be critical and risk the hospital running out of medical oxygen. Usage of oxygen at the customer site is dependent on patient need and therefore often requires the delivery schedule be flexible to ensure consistent supply.

Delivery is often required overnight or at weekends. Large liquid oxygen road tankers often have difficulty accessing hospital roads and sites at other times, their presence would also present access problems for other users of the sites as well as increasing congestion on already busy roads.

Scheduling of deliveries to the sites can be quite challenging, typically hospital administration staff work traditional hours (9 to 5 weekdays and not weekends). Additional constraints on the ability to supply would undoubtedly lead to a reduction in customer satisfaction and potentially increase risks to patient safety.

ADDITIONAL TECHNICAL CONSIDERATIONS

Given the sheer volume of product in the storage tank, even if out-of-specification product was transferred to the storage tank, it would take a number of days to create an out-of-specification supply source.

When loading liquid oxygen into a road tanker that has been in service, the temperature of the liquid in the storage tank is always lower that the temperature of the liquid remaining in the road tanker. Hence when the liquid is transferred, the heat content of the tanker and its load would be sufficient to cause the liquid to begin to boil. As the boiling point of argon and nitrogen (the most likely sources of contamination in the liquid oxygen) is lower than that of oxygen, any boiling of the liquid would result in any argon or nitrogen being preferentially vented. Hence, even if the liquid was outside the specification range any transfer processes would automatically improve its quality.

In order to further reduce the potential of manufacturing low purity liquid oxygen, the internal specification limits for bulk medical liquid oxygen are often set at 99.6 %. This is higher than the

minimum specification limit of 99.5 % stated in the Marketing Authorisations granted for bulk medical liquid oxygen.

Every road tanker containing liquid oxygen for medical delivery is reviewed by the manufacturers operating centre(s) to ensure that the pre and post fill results are within specification and not significantly different from the purity readings of the storage tank. The teams located at the operating centres are responsible for the day to day management of the ASUs being used to source the product and they are also aware of any issues that may be experienced with the liquid oxygen being used to fill the site storage tanks.

CONCLUSIONS

Bulk medical liquid oxygen is manufactured and certified using processes that provide a high level of control and quality assurance. Over recent years it has been recognised by the regulatory authorities that there is a low risk associated with the manufacture and supply of this product.

Further, it has been shown that requiring the UK manufacturers to implement the revised EU Guide to Good Manufacturing Practice, Annex 16 requirements for QP's to certify and release bulk medical liquid oxygen product prior to it leaving the manufacturing site would increase the risk of supply failures and potentially impact patient safety.

Therefore it is industry policy that the current *status quo* of allowing the retrospective QP certification and release of batches of bulk medical liquid oxygen within a defined timeframe will be maintained and that the efforts of the industry will continue to be focused on maintaining and further improving compliance with GMP and quality standards.

REFERENCES

1) EudraLex. Volume 4. EU Guidelines for Good Manufacturing Practice for medicinal products for human and veterinary use.

For more information:

British Compressed Gases Association (BCGA) www.bcga.co.uk
Medicines & Healthcare products Regulatory Agency (MHRA)
www.gov.uk/government/organisations/medicines-and-healthcare-products-regulatory-agency

BCGA TIS 39 Published: 01/12/2016 Produced by: BCGA TSC7 ISSN 2398-9386