SCIENTIFIC DISCUSSION

QUALITY ASSESSMENT

The finished product, Medicinal Oxygen, is an inhalation gas, containing oxygen as the active substance and sole ingredient, contained within a pressurised cylinder. The oxygen, intended for use by veterinarians, is released on demand through the pressure release valve. Oxygen is a natural substance, described in the European Pharmacopoeia and belonging to the group of medical gases.

Oxygen, the most abundant element on earth, is normally only found as a free gas in the atmosphere (approximately 21% v/v) and hence in the air we breathe. It is fundamental to sustaining mammalian life and without it terrestrial mammals would die within minutes. This vital physiological property of oxygen forms the basis for its use in veterinary medicine as an aid in animal life support.

Composition of the Veterinary Medicinal Product

Qualitative Composition	Quantitative composition	Reference to analytical quality
<u>Active Substance(s)</u> Oxygen <u>Other ingredients</u> None	100% v/v	Ph. Eur.

The gas is packaged in compressed form at a pressure of 200 bar (20Mpa) at 15˚C in metal cylinders. The compressed inhalation gas is made available in two different unit volume sizes of white coloured steel alloy cylinders (of nominal water capacities of 15L and 50L). The cylinders are sealed with a pressure release valve and a white cap. This form of packaging is designed to be easy and convenient to use by veterinary professionals. The valve, called Smartop, used with these cylinders has been specifically designed by Air Liquide although the neck fittings are standard and universal. The cylinders and valves meet internationally accepted and published quality standards of the compressed gas industry. The white colouring is used by convention to denote Medicinal Oxygen.

The product is supplied as a non-sterile dosage form. Although no microbiological specification test or limits are applied to the finished product it is clear that pure oxygen in liquid form during manufacture and in compressed form during filling will not support microbial growth. Pressurised cylinders will not permit the ingress of microbes into the primary container during its storage and use.

The containers are made of steel and are produced routinely as weld-free cylinders. Strength has been optimised by addition of other metals such as manganese, chromium, molybdenum and combination alloys. The requirements for cylinders are that they have the ability to withstand & maintain high pressure, that they must be physically durable to withstand transit, handling, storage and also natural radiation and that they are easy to handle (i.e. size, shape and weight are important).

In the presence of moisture, steel can oxidise; rust or traces of corrosion can appear. The presence of a Smartop valve (with residual pressure and non-return valve – "RPV-NRV") guarantees the absence of entry of moisture into the cylinder. Therefore, no chemical reaction at ambient temperature can occur. The product will only be used by veterinarians and will not be used by owners of the target animal/patient. The product, like all cylinders, is expected to remain in one place during and between uses e.g. secured to a veterinary practice wall or other such solid support using suitable strapping or, more commonly, chains. The cylinder is expected to be changed infrequently.

The applicant company has had many years experience of filling medicinal oxygen cylinders for their human product but have nevertheless validated the automatic part of the filling operation. The filling station has been validated according to recognised protocols for validating computer controlled manufacturing steps and a report of the work prepared. A copy of the validation plan for the Monoxal system was included in the dossier. The validation conducted on the human equivalent product was been carried out between November 2003 and July 2005. The validation report for the veterinary medicinal gas was also presented.

Oxygen
O = O
Molecular formula: O_2
Molecular weight : 32

Physiochemical properties:

Appearance	A colourless, odourless and tasteless gas at normal temperature and pressure or a blue liquid below its boiling point
Melting point	-218.4˚C
Boiling point	-183.2˚C at 760 mmHg
Solubility at normal temperature and pressure in: Water –	One volume of oxygen is soluble in 32 volumes of water @ 20˚C and 101 kPa pressure.
Ethanol -	One volume of oxygen is soluble in 7 volumes of ethanol.
Density	0.105 relative to air

The dedicated liquid oxygen storage tank areas at are subject to pharmaceutical GMP quality standards. A suppliers agreement is in place between the ASUs and the medicinal gas packaging units, not to make any changes to the manufacturing process of the active substance, without informing the customers.

The starting material for the active substance is naturally occurring atmospheric air. The purification of the oxygen from this natural gaseous mixture is a purely physical process based on fractional distillation of liquid air. The process, after removal of unwanted particulates, involves the compression and cooling of the air initially at room temperature and then at lower temperatures to produce liquefied air from which oxygen is then obtained by fractional distillation. A flow diagram was included in the dossier.

As the fractional distillation is not absolute this inevitably means that small quantities of impurities (H_2O, CO, CO_2, hydrocarbons, N_2O, Ar, N_2 and O_3), present in atmospheric air, remain in the final product. The bulk of the water and carbon dioxide is removed, during the process, as it would otherwise interfere with the cylinder filling process.

To liquefy air it is necessary to cool it to a temperature well below the critical temperature of its constituents (-122˚C for argon, -147˚C for nitrogen and -119˚C for oxygen), which requires a refrigeration source capable of achieving very low temperatures.

Gas separation by distillation is carried out in double rectification plate columns after the air has been purified and cooled. The principal stages of the cycle are:

- purification of the air,
- cooling
- refrigeration
- gas distillation,
- separation of liquid nitrogen, liquid oxygen and argon
- storage of the finished product.

Separation is totally dependent on the functional capacity of the column stacks. No in-process controls are described.

The purified bulk liquid oxygen, held in a storage tank at the production site, is tested for the following components:

O_2	$\geq$ 99.5 % v/v
CO_2	$\leq$ 300 ppm v/v
CO	$\leq$ 5 ppm v/v
H_2O	$\leq$ 67 ppm v/v

This forms the basis of the Ph Eur. testing requirements for the active oxygen. Upon the release of the liquid oxygen bulk it is transported by road tankers to the filling site. Dedicated tankers are used and an appropriate agreement with the transport company in place to maintain the quality of the product during the transfer process. At the filling site the connections between the tanker and the storage tank are coded in a manner such that cross-contamination cannot occur.

Certificates of Analysis (CoAs) for batches of the active substance manufactured in each of the named production sites were presented. These CoAs correspond to the batches that have been produced without the identity test being recorded. However, since the identity test is the compliance of the limits of the assay, all of the batches meet the specification for the identity test. CoAs for each production site that include the identity test were also presented.

The certificates of analysis demonstrated the compliance of one batch for each of the seven nominated sites.

The primary packaging components are made of steel alloy with suitable valves and tested to the published EN and ISO standards of the compressed gas industry. The Smartop valves utilised are specifically designed for the intended purpose, and the codes for the valves were provided together with a specification and a drawing.

Satisfactory information on the construction and operation of the valves and outlets was presented. Operating instructions were presented together with the specification sheet for the high-pressure valve and diagrams, which give the tolerances applicable.

A lubricant grease is used in or on the Smartop valve connections. This would normally be in contradiction to the statement in the European Pharmacopoeia monograph that greases and oils should not be used in oxygen valve and cylinder fittings presumably because of flammability risk. The grease in question was a perfluorinated material, which is non-flammable and oxygen resistant. It is used only in the manufacture of the Smartop valve to aid in the seating of a gasket and not for routine use in valve connections.

The product information leaflet of this lubricant grease states that it has been specifically developed for "First lubrication and maintenance of valves for oxygen bottles and of equipment for the oxygen producing and oxygen processing industries". Flammability testing has been carried out on the valve and the report was presented. Certificates of Analysis for the cylinders and Certificates of Compliance for the valves were presented.

Although the Smartop valve is a newly developed valve, the materials of construction are the same as the older type of valves widely utilised in the medicinal gas industry, however the operation of the valve is what is innovative rather than the materials of construction.

The materials of primary contact of containers used to store and transport the bulk gas are stainless steel. The types of stainless steel of the internal walls of the fixed cryogenic tanks and vehicles semi-trailers used for storage and transport of liquid medicinal Oxygen are:

Fixed Tanks: 304N X2CrNiN 18-10 or X5CrNiN19-9 according to 10028-7;
Vehicles: 304 X5CrNiN18-10 according to 10028-7

Austenitic steel 304 is perfectly inert with respect to liquid or gaseous oxygen and the quality of the product will not deteriorate. This type of metal is widely used in both pharmaceutical and food industries where it is necessary to guarantee the integrity and protect the products to be stored. Stainless steel is by nature in a "passive" state; there is a film of passivity on the surface, which is chromium oxide, which protects the steel from its environment. As long as this film is not broken, no metallurgical transformation can occur.

There is no problem in terms of corrosion for liquid Oxygen. The surface of the steel being inaffected, there are no particles present which would interact with the liquid oxygen. Stainless steel of type 304 which is used in the construction of cryogenic tanks and vehicle semi trailers are preferred to carbon steels which involve the risk of oxidation in the presence of moisture or air, and have undesirable properties in cold impact strength, which is not the case with the 304 steel.

The 304 stainless steel also has favourable properties with regard to weight in transport and better pressure resistance with lower thickness than with carbon steels. The 304 stainless steel also has the advantage of having a good mechanical resistance at very low temperature (-183°C for liquid oxygen); it is therefore a good material for the storage and /or transport of cryogenic products.

This product presents no TSE risk to the animal being treated or to the professional user of the product. The product contains no other ingredients except for the oxygen purified from atmospheric air. Secondly, assurances have also been provided that any materials likely to be in contact with the oxygen during the manufacturing process, such as lubricants, have also been assessed as posing no risk.

As the product contains only pure oxygen (100% v/v) the Finished Product Release Specification tests for identification and release, are those of the Ph. Eur monograph for Oxygen. The same specification applies throughout shelf life.

Release and Shelf life Specification

Determination	Reference	Specification
Identity	Ph.Eur. ID test C	Complies with the limits of the assay test.
Assay of Oxygen	Ph.Eur.2.5.27	≥ 99.50 % v/v
CO_2 content	Ph.Eur.2.5.24	≤ 300 ppm v/v
CO content	Ph.Eur.2.5.25 Method II	≤ 5 ppm v/v
H_2O content	Ph.Eur.2.5.28	≤ 67 ppm v/v
Fill Weight*	By weight	B15: 4.11 – 4.51 Kg
		B50: 13.75 – 15.00 Kg

*The fill weight is determined during in-process testing.

Declaration of compliance with freedom from residual solvents has also been provided.

No stability data have been presented by the applicant for the active substance nor for the product. The applicant has made a similar product, the human medicinal oxygen product, for many years that is packaged in exactly the same manner as the product that is the subject of this application dossier. From this experience and from the literature it is clear that the active substance is stable and there is no reason to suspect a difference in the case of the finished product.

While this is acceptable from the standpoint of the active substance, nevertheless stability studies on the finished product in the market pack are to be provided. Results of a 5 year stability study conducted on the equivalent human medicinal oxygen product were presented. Although the valve is different in design the materials of construction are the same as those of the new Smartop valve and as such will exhibit the same interaction characteristics with the product.

SAFETY ASSESSMENT (PHARMACO-TOXICOLOGICAL)

Medicinal Oxygen is a gas for inhalation in compressed form. Oxygen is a physiological substance, essential for the maintenance of mammalian life, and this property forms the basis of its use in veterinary medicine. The proposed indication is for respiration during anaesthesia and recovery of dogs, cats and horses.

The Committee for Medicinal Products for Veterinary Use has recommended that oxygen is to be considered as falling out of scope of Council Regulation (EEC) 2377/90.

The most sensitive mammalian systems that elicit adverse effects following excessive exposure to 100 % oxygen under normobaric conditions are the lungs, the central nervous system and the eyes. A lowest toxic concentration of inhalation of 100 % oxygen for 14 hours has been reported for humans. In humans exposed to 100 % oxygen under normobaric conditions, pulmonary irritation and oedema can occur after 24 hours, though symptoms may appear after 10 hours.

Oxygen toxicity is related in part to the production of reactive agents and induced membrane damage. So called oxidative stress is a natural phenomenon omnipresent to mammalian cells. As such, a variety of mechanisms have evolved to defend against such oxidative damage.

Adverse effects can occur if mammals are exposed to excessive levels of oxygen for long periods of time or if high levels of oxygen are administered under hyperbaric conditions. However, oxygen exposures potentially encountered by the user of Medicinal Oxygen would be no different to inhaling natural air. Therefore, repeated exposure to Medicinal Oxygen at atmospheric pressure should be considered no more hazardous to the user than inhaling natural air.

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Mammalian cells and cellular components of all mammalian species are continually being attacked and damaged by free radicals and reactive oxygen species (ROS) that are produced during normal cellular function and metabolism. ROS are able to react with and thereby damage DNA. A variety of mechanisms have evolved to defend against such oxidative damage.

The *in vitro* and *in vivo* data in the published literature demonstrate induction of oxidative DNA damage in blood cells of healthy human subjects after hyperbaric oxygen (HBO) under therapeutic conditions. Also, *in vitro* studies with mammalian cells suggest that such HBO-induced oxidative DNA damage can lead to gross genetic alterations and chromosome aberrations. However, this has not been found *in vivo*.

It is noted that oxygen has mutagenic potential, in particular, when administered under hyperbaric conditions However, given that oxygen exposures potentially encountered by the user of Medicinal Oxygen would be no different to inhaling natural air, inadvertent exposure to Medicinal Oxygen at atmospheric pressure should be considered no more hazardous to the user than inhaling natural air.

The absence of data relating to carcinogenicity is justified, as mutagenic potential has only been demonstrated under hyperbaric conditions.

Oxygen is ultimately metabolised to carbon dioxide and water. Further safety assessment of metabolites is therefore unnecessary.

Medicinal Oxygen contains carbon dioxide, carbon monoxide and water as impurities. The levels at which these impurities are present in the product are lower than those found in natural air and, therefore, they do not constitute a hazard.

During normal conditions of use of Medicinal Oxygen, it is expected that users would be exposed to oxygen via the inhalation route. However, any release of compressed oxygen into the atmosphere would have a negligible impact on the proportion of oxygen in ambient air. Therefore, such release/exposure would be toxicologically insignificant.

The principle risks associated with the use of this product are related to the physiochemical properties of the product rather than its toxicological properties. Therefore, the user safety precautions relate to the presentation of oxygen as a compressed gas, with associated risks such as inadvertent release of pressurised gas following incorrect use and the increased fire risks associated with localised increased oxygen concentrations. Consequently, appropriate user safety statements have been included in the SPC.

Given the proposed indication, it is reasonable to assume that only trained veterinary professionals and veterinary staff will use the product. Given that the users should be familiar with the use of compressed gases, the user safety statement and the precautions for storage are considered appropriate.

The product is a natural substance, the use of which will not alter the concentration or distribution of the substance in the environment. Use of the product does not pose a potential hazard to the environment.

The proposed disposal advice (‘Unwanted partially full, or empty, Medicinal Oxygen cylinders should be returned to the manufacturer or their authorised distributor’) is considered appropriate for a product of this type.

CLINICAL ASSESSMENT (EFFICACY)

The Applicant presented various published papers describing the causes of oxygen deprivation and the varied effects that hypoxia can have on mammalian tissues, organs and metabolism. Clinical signs of hypoxia include: tachypnoea, tachycardia, cyanosis, cardiac arrhythmia and anxiety. In acute conditions of hypoxia due, for example, to hypoventilation or low inspired oxygen concentration during inhalation anaesthesia, oxygen supplementation is indicated to alleviate the hypoxia. The rate of oxygen supplementation required by a patient varies depending on the route of oxygen administration (e.g. use of an endotracheal tube or mask), breathing circuits used, the conditions for which oxygen is administered, and the variation in oxygen requirement of individual animals (e.g. depending on bodyweight, health status, etc.). Consequently, the determination of the appropriate oxygen 'dose' during anaesthesia for a given patient must be established by the attending veterinarian and the adequacy of that 'dose' must be continually monitored during the anaesthesia.

While oxygen may be considered medicinal in its use and effects in mammals are related to its physiological properties, it does not possess truly pharmacodynamic properties. The physiological effects of oxygen deprivation in mammals and the need for oxygen supplementation in acute conditions of hypoxia are well understood. It is accepted that the amount of oxygen to be supplemented to a patient be determined on a case-by-case basis by a suitably qualified veterinarian.

Molecular oxygen enters the body during inhalation. The gaseous oxygen diffuses into the blood stream via the alveoli. Oxygen is transported around the body, mostly as oxyhaemoglobin in the circulation, to all tissues, where it is metabolised by the cells to produce carbon dioxide and water. The carbon dioxide and water re-enter the blood stream and are eliminated via the lungs, together with any un-metabolised oxygen, during exhalation.

The pharmacokinetics have been adequately described. The Applicant has presented published data in support of the safety and efficacy of the product. Given that the test product is formulated as 100 % oxygen, it can be considered to have the same quantitative and qualitative formulation as, and therefore equivalent to, any other brand of pressurised oxygen used in the studies described in the published literature.

While oxygen supplementation is generally regarded as safe, adverse effects can occur if animals are exposed to excessive levels of oxygen for long periods of time or if high levels of oxygen are administered under hyperbaric conditions. In the dog and cat, administration of 100 % oxygen for longer than 12 hours or of 80-90 % oxygen for longer than 18 hours can contribute to alterations in pulmonary function and signs of oxygen toxicity. Oxygen toxicity is related in part to the production of oxygen free radicals and induced membrane damage. Toxic signs are similar to those seen with hypoxia and therefore may be difficult to recognise. Oxygen toxicity is uncommon; it takes at least 12 hours to occur under normobaric conditions, and is reversible in the early stages if oxygen is discontinued. Animals with pre-existing oxygen radical damage to the lung may have this damage exacerbated by oxygen supplementation.

In support of the safety of the product for the target animal, the Applicant provided published literature to describe the potential toxic effects of the administration of high levels of oxygen. It is accepted that adverse effects can occur if animals are exposed to excessive levels of oxygen for long periods of time or if high levels of oxygen are administered under hyperbaric conditions. Given that toxicity takes at least 12 hours to occur with supplementation of 100 % oxygen under normobaric conditions, the safety profile of the product under normal conditions of use can be considered acceptable.

It was noted that limited clinical data supporting the therapeutic uses of oxygen in small animals have been provided, but that extensive data from the pre-clinical literature illustrate that oxygen is well known for its therapeutic uses and its necessity for use during general anaesthesia and recovery from anaesthesia.

In addition to providing metabolic oxygen requirements, oxygen supply also serves to carry inhalation anaesthetic agents. It is generally accepted that oxygen can be safely administered as a carrier gas for inhalation anaesthetics. In addition, it is clear from the literature that oxygen has been used successfully with a variety of other anaesthetic agents without complication. The SPCs of a number of authorised anaesthetic agents (including thiopental, isoflurane and sevoflurane) include recommendations that, in cases of suspected anaesthetic overdose, 100% oxygen is to be administered at high flow rate.

Based on the data from the published literature provided by the Applicant, the proposed general recommendations for oxygen supplementation, as detailed in the SPC, are accepted. It is, however, recognised that the rate of oxygen supplementation required by an animal patient varies depending on a variety of factors and that the determination of the appropriate oxygen 'dose' during anaesthesia for a given animal patient must be established by the attending veterinarian and that the adequacy of that 'dose' must be continually monitored during the anaesthesia.

BENEFIT RISK ASSESSMENT

The active ingredient, oxygen, is controlled by a monograph in the Ph. Eur. Batch analyses data show that these requirements can be met. There are no excipients in the product. The primary packaging components are made to a high quality standard meeting internationally accepted specifications of the compressed gas industry.

An adequate Finished Product Release Specification (which is also the shelf-life specification) is in place and the analytical results of one batch demonstrates that this specification can be met.

Formal stability testing on the active substance has not been conducted. The basis of this lack of testing is the well-known stability of oxygen in its gaseous state when held in an inert container.

Results of a 5 year finished product stability study conducted on the equivalent human medicinal oxygen product were presented. With regard to the stability of the finished veterinary medicinal product, the Applicant has committed to setting up a proper stability study with a designated number of cylinders of each size from the first 3 production batches filled and test retained samples of each of the 3 batches over regular intervals over the next five years in accordance with the principles in the EMEA guideline CPMP/QWP/1719/00.

Oxygen exposures potentially encountered by the user of Medicinal Oxygen would be no different to inhaling natural air, therefore inadvertent exposure to Medicinal Oxygen at atmospheric pressure should be considered no more hazardous to the user than inhaling natural air. The principle risks associated with the use of this product are related to the physiochemical properties of the product rather than its toxicological properties. Therefore, the user safety precautions relate to the presentation of oxygen as a compressed gas, with associated risks such as inadvertent release of pressurised gas following incorrect use and the increased fire risks associated with localised increased oxygen concentrations.

There is a great deal of variability in the susceptibility of various mammal species to the toxic effects of high FiO_2 oxygen and it recognised that there is a possibility that the earliest stages of toxicity may develop after less than 12 hours administration of 100% oxygen, in some animal species.

Whilst there are serious consequences associated with the advanced stages of oxygen toxicity, veterinarians should never risk exposing an animal to dangerous levels of hypoxia for the fear of inducing oxygen toxicity. Twelve hours of 100% oxygen therapy appears to be a lower limit, across non-human mammal species, at which the first signs of oxygen toxicity may clinically manifest themselves.

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the presentation of oxygen as a compressed gas, with associated risks such as inadvertent release of pressurised gas following incorrect use and the increased fire risks associated with localised increased oxygen concentrations.

While oxygen may be considered medicinal in its use and effects in mammals are related to its physiological properties, it does not possess truly pharmacodynamic properties. The physiological effects of oxygen deprivation in mammals and the need for oxygen supplementation in acute conditions of hypoxia are well understood. The pharmacokinetics have been adequately described.

The literature provided by the Applicant demonstrates the requirement for, and benefits of, oxygen supplementation during anaesthesia and recovery in companion animals. The use of oxygen supplementation during anaesthesia is standard veterinary practice for maintenance of adequate ventilation.

It is, however, recognised that the rate of oxygen supplementation required by a patient varies depending on a variety of factors and that the determination of the appropriate oxygen 'dose' during anaesthesia for a given patient must be established by the attending veterinarian and that the adequacy of that 'dose' must be continually monitored during the anaesthesia.

Based on the original and complementary data presented, the Committee for Medicinal Products for Veterinary Use (CVMP) concluded that the quality, safety and efficacy of Medicinal Oxygen were considered to be in accordance with the requirements of Council Directive 2001/82/EC, as amended.