NOTE ON THE MONOGRAPH

The European Pharmacopoeia (Ph. Eur.) currently includes two monographs on oxygen: Oxygen (0417) and Oxygen (93 per cent) (2455). Oxygen (0417) was drafted over 50 years ago and while various methods of manufacture were feasible when it was first introduced, recent revisions have restricted it specifically to oxygen produced by cryogenic distillation, with an O_2 content specification of minimum 99.5%.

The second monograph, Oxygen (93 per cent) (2455), was first published in the Ph. Eur. in 2010. This monograph covers oxygen produced by a concentrator that removes the nitrogen from ambient air using a pressure swing adsorption plant (PSA). At the time of publication, the plants available on the market utilised a single-stage adsorption process which did not remove any argon from the air being processed.

The tests described in this monograph are basically the same as those in monograph 0417, but with the addition of supplementary tests for impurities to address the risk of other atmospheric pollutants being present in the ambient air used.

In part, the elaboration of Oxygen (93 per cent) arose from the need to cover an additional source of oxygen for healthcare facilities which did not have access to oxygen produced from cryogenic distillation of air, e.g. field hospitals.

It is important to note that oxygen 93 per cent produced by oxygen concentrators differs from other medicinal gases and indeed from other medicines since, while the equipment itself is a medical device, the product obtained is a medicine that does not require a marketing authorisation and is not packaged and authorised in its final container. GMP is therefore not applicable and the quality of the gas is very much dependent upon the performance of the equipment that produces it.

Oxygen (93 per cent) was elaborated to cover this somewhat unique situation, to provide a pharmacopoeial standard to control the quality of the oxygen produced. It was based on the monograph on Medicinal air (1238), as the composition of the gas produced was much closer to that of air than to oxygen 99.5 per cent. Argon, as the other most abundant constituent, had not been considered an impurity in oxygen 93 per cent since it is a natural constituent of air. Clinical data for argon had been reviewed to confirm this.

Advances have since been made in the design of PSA oxygen concentrators and two-stage PSA plants capable of producing oxygen with a nominal content of 98.0 per cent are now available. This prompted the decision to elaborate a new monograph, Oxygen (98 per cent) (3098).

It is generally recognised that the ongoing COVID-19 pandemic has increased the demand for oxygen worldwide (by as much as a factor of 10), but the main issue appears to be the distribution systems in place within healthcare facilities rather than the actual availability of oxygen supplies. Recourse to a PSA plant as a source of oxygen is still only necessary when bulk liquid medical oxygen distribution systems are unavailable: healthcare facilities with existing distribution networks need only acquire additional supplies and use their medical oxygen pipeline networks to full capacity.

In view of the urgency of the situation and the need to significantly increase the supply of oxygen to healthcare facilities to treat infected patients, the Ph. Eur. Commission is launching an extraordinary public consultation on the most appropriate way of including oxygen obtained via two-stage concentrators in the Ph. Eur.:

A. either by publishing a new monograph on oxygen 98 per cent (see draft below);

B. or by revising the monograph on Oxygen (93 per cent) to cover the wider potential range of oxygen contents produced by pressure swing adsorption.

Your views on which of these two alternatives is the most appropriate are requested by 3 May 2020. Your response must be accompanied by concrete supporting data to be considered by the Ph. Eur. Commission.

XXXX:3098

OXYGEN (98 PER CENT)

Oxygenium 98 per centum

O_2 M_r 32.00

DEFINITION

Content: 96.0 per cent *V/V* to 99.5 per cent *V/V* of O_2, the remainder mainly consisting of argon and nitrogen.

This monograph applies to oxygen (98 per cent) for medicinal use. It does not apply to gas produced using individual concentrators for domiciliary use.

PRODUCTION

Oxygen (98 per cent) is produced in double-stage concentrators by two successive modules of adsorption purification of ambient air using zeolites. During production, the oxygen content is continuously monitored by means of a paramagnetic analyser (*2.5.27*). Following the design and installation of the concentrator, and after any modification or significant intervention, the gas produced complies with the following requirements.

Carbon dioxide: maximum 300 ppm *V/V*, determined using an infrared analyser (*2.5.24*).

Gas to be examined. The substance to be examined. It must be filtered to avoid stray light phenomena.

Reference gas (a). Oxygen R.

Reference gas (b). A mixture of 2 per cent *V/V* of *nitrogen R1* and 98 per cent *V/V* of *oxygen R*, containing 300 ppm *V/V* of *carbon dioxide R1*.

Calibrate the apparatus and set the sensitivity using reference gases (a) and (b). Measure the content of carbon dioxide in the gas to be examined.

Carbon monoxide: maximum 5 ppm *V/V*, determined using an infrared analyser (*2.5.25*).

Gas to be examined. The substance to be examined. It must be filtered to avoid stray light phenomena.

Reference gas (a). Oxygen R.

Reference gas (b). A mixture containing 5 ppm *V/V* of *carbon monoxide R* in *nitrogen R1*.

Calibrate the apparatus and set the sensitivity using reference gases (a) and (b). Measure the content of carbon monoxide in the gas to be examined.

Nitrogen monoxide and nitrogen dioxide: maximum 2 ppm *V/V* in total, determined using a chemiluminescence analyser (*2.5.26*).

Gas to be examined. The substance to be examined.

Reference gas (a). A mixture of 21 per cent *V/V* of *oxygen R* and 79 per cent *V/V* of *nitrogen R1*, containing less than 0.05 ppm *V/V* of nitrogen monoxide and nitrogen dioxide.

Reference gas (b). A mixture containing 2 ppm *V/V* of *nitrogen dioxide R* in *nitrogen R1*.

Calibrate the apparatus and set the sensitivity using reference gases (a) and (b). Measure the content of nitrogen monoxide and nitrogen dioxide in the gas to be examined.

Sulfur dioxide: maximum 1 ppm *V/V*, determined using an ultraviolet fluorescence analyser (Figure 3098.-1.).

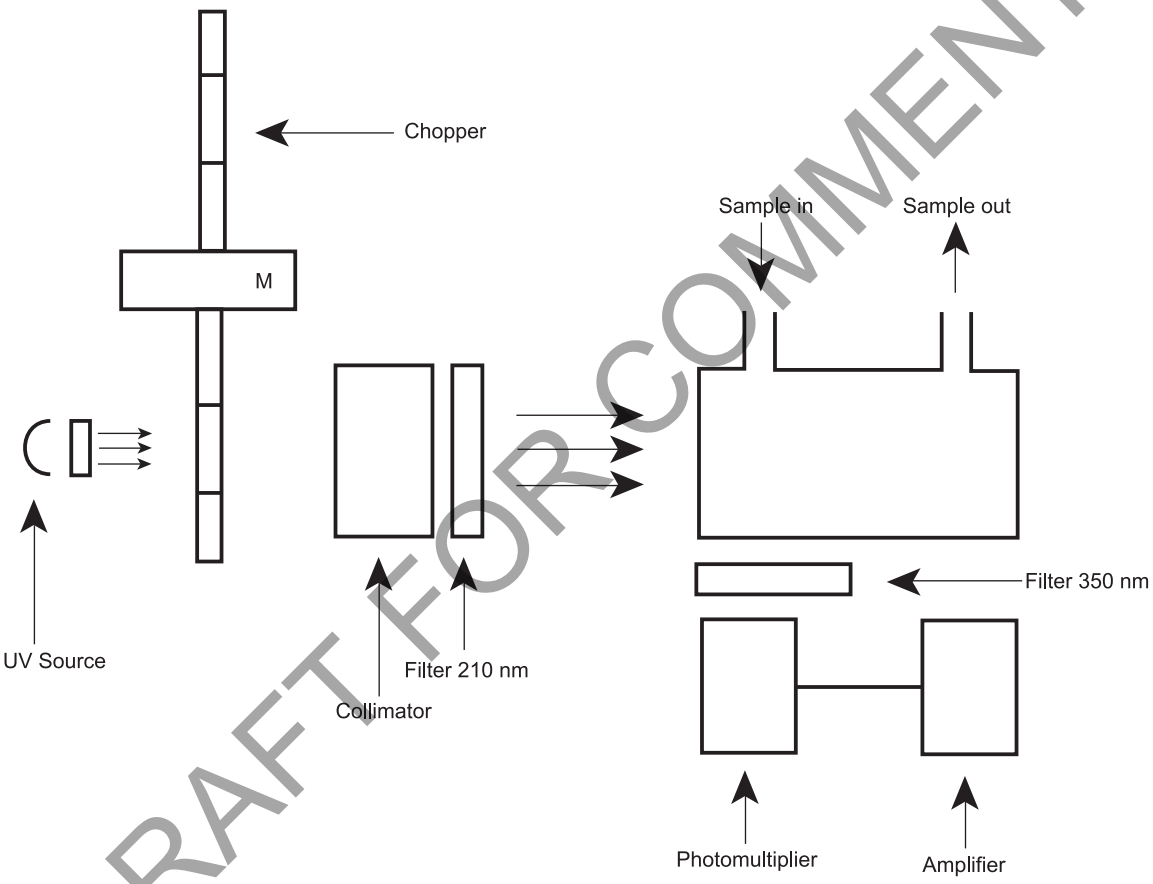

Figure 3098.-1. – *UV fluorescence analyser*

The apparatus consists of the following:

- a system generating ultraviolet radiation with a wavelength of 210 nm, made up of an ultraviolet lamp, a collimator, and a selective filter; the beam is blocked periodically by a chopper rotating at high speeds;
- a reaction chamber, through which flows the gas to be examined;
- a system that detects radiation emitted at a wavelength of 350 nm, made up of a selective filter, a photomultiplier tube and an amplifier.

Gas to be examined. The substance to be examined. It must be filtered.

Reference gas (a). A mixture of 2 per cent *V/V* of *nitrogen R1* and 98 per cent *V/V* of *oxygen R*.

Reference gas (b). A mixture of 2 per cent *V/V* of *nitrogen R1* and 98 per cent *V/V* of *oxygen R*, containing 0.5 ppm *V/V* to 2 ppm *V/V* of *sulfur dioxide R1*.

Calibrate the apparatus and set the sensitivity using reference gases (a) and (b). Measure the content of sulfur dioxide in the gas to be examined.

Oil: maximum 0.1 mg/m^3, determined using an oil detector tube (*2.1.6*).

Water: maximum 67 ppm *V/V*, determined using an electrolytic hygrometer (*2.5.28*).

Assay. Determine the concentration of oxygen using a paramagnetic analyser (*2.5.27*).

CHARACTERS

Appearance: colourless gas.

IDENTIFICATION

It complies with the limits of the assay.

TESTS

Carbon dioxide: maximum 300 ppm *V/V*, determined using a carbon dioxide detector tube (*2.1.6*).

Carbon monoxide: maximum 5 ppm *V/V*, determined using a carbon monoxide detector tube (*2.1.6*).

Nitrogen monoxide and nitrogen dioxide: maximum 2 ppm *V/V* in total, determined using a nitrogen monoxide and nitrogen dioxide detector tube (*2.1.6*).

Sulfur dioxide: maximum 1 ppm *V/V*, determined using a sulfur dioxide detector tube (*2.1.6*).

Oil: maximum 0.1 mg/m^3, determined using an oil detector tube (*2.1.6*).

Water vapour: maximum 67 ppm *V/V*, determined using a water vapour detector tube (*2.1.6*).

ASSAY

Determine the content of oxygen using a paramagnetic analyser (*2.5.27*).

STORAGE

Oxygen 98 per cent obtained from an oxygen concentrator is normally used on the site where it is produced. It is fed directly into a medicinal gas pipeline or administration system. Where authorised by the competent authority, it may be stored in suitable containers complying with the legal regulations. Oils and grease are not to be used unless they are oxygen-compatible.

IMPURITIES

A. CO_2: carbon dioxide,

B. CO: carbon monoxide,

C. SO_2: sulfur dioxide,

D. NO and NO_2: nitrogen monoxide and nitrogen dioxide,

E. oil,

F. H_2O: water.