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Manufacturing of Oxygen for Medicinal Use at Healthcare Facilities

EIGA's view regarding the on-site preparation in healthcare facilities

Gaseous substances for inhalation by patients, such as oxygen and air, are usually supplied to healthcare facilities as licensed drugs in defined packages, though technological development also allows their on-site generation at the hospital premises by dedicated devices.

The pharmaceutical legislation defines that the production of a drug is carried out in compliance with a Marketing Authorisation at a manufacturing plant that is authorised by a National Competent Authority (under a Good Manufacturing Practice (GMP) certification), whereby the product batches are released by a Qualified Person. Alternatively, a drug can be produced by the hospital pharmacist, upon a physician's prescription for the needs of a specific patient (or group of patients), typically when the drug is not available on the local market.

The medical device legislation defines three types of devices that are not acting on the human body via a pharmacological, immunological, or metabolic way, covering those,

- that administer to the patient a drug produced elsewhere (*e.g.* syringes, anaesthesia machines); or
- that channels a drug; or
- that do not act as a drug, where the device is a substance itself and is absorbed or locally dispersed.

European Industrial Gases Association Aisbl
30 Avenue de l'Astronomie
B-1210 Brussels – Belgium
+32 2 217 70 98
info@eiga.eu
www.eiga.eu

Both legislations, therefore, do not adequately define drug-generating devices:

- For the medical device legislation, the device is neither composed of substances, nor incorporating a drug when placed on the market. It may be administering a drug, but this drug has not been approved for its quality, safety, and efficacy by the European Medicines Agency or by a National Competent Authority. Moreover, it should be recognised that the main action of the device is the production of a drug, as the substance produced acts on the human body in pharmacological way. Thus, only the on-site drug-generating equipment itself can be declared to conform to the Medical Device Regulation, but this excludes the medicine produced at the healthcare facility.
- For the medicinal product legislation, the rules for drug-device combination cannot be applied since the drug is not placed on the market together with the device and the device is not for single use only.

The primary concern is related to the generation of oxygen produced from a Pressure Swing Adsorption (PSA) plant, though it can also relate to the generation of medical air by compressors.
The on-site production equipment manufacturers declare that the plant can produce 'Oxygen (93 per cent)' according to the European Pharmacopoeia (Ph. Eur.) monograph at a defined flow rate when they place it on the market. Under the current legislation, the only regulatory possibility is that the on-site production falls under the principles of a hospital preparation, *i.e.* 'an extemporaneous pharmaceutical preparation' as defined in Ph. Eur. monograph 2619, where it is more similar to an industrial scale production of a drug.

The prime responsibility for the PSA product preparation lies with the Healthcare Facility Responsible Pharmacist, who is responsible for the following:

- Define the operating procedures and quality controls to ensure compliance to the Ph. Eur.
- Ensure that a risk assessment has been conducted, so that design and capacity of the plant meet the volume and fluctuating demand, under single fault condition and pandemic situations.
- Define the batch management system to document and control the released quality and quantity and the traceability of the gas delivered to the patients.
- Ensure procedures are in place, so that the plant is properly maintained to guarantee the availability and quality of the product.
- Where the PSA plant also fills cylinders, that this process and packages meet all applicable high-pressure regulations & standards and safety & quality standards.
- Include the products in the hospital pharmacovigilance and materiovigilance systems.

In this case, the Healthcare Facility Responsible Pharmacist could refer to:

- The Ph. Eur. monograph 2619 'Pharmaceutical preparations', that defines the quality standards and analytical methods of the different products that could be prepared on-site: 'Oxygen (93 per cent)', 'Air, medicinal', 'Air, synthetic medicinal'.
- The guidelines for the preparation of medicinal products in healthcare facilities and pharmacy.
- Standard EN ISO 7396-1 'Medical gas pipeline systems — Part 1: Pipeline systems for compressed medical gases and vacuum', that also defines the main and back-up sources of oxygen supply.

EIGA's view regarding the on-site preparations in Healthcare Facilities is:

- Where the supply of licensed products is logistically difficult, on-site preparation may be a suitable alternative for Healthcare Facilities, who should carry out a specific risk assessment to ensure patients' safety.

- The plant should be CE-marked to the Medical Device Regulation, based on documented performance data.
- The quality management system for on-site production should be compliant with the EU GMP on medicinal gases or its national equivalent for this type of production.
- The use of oxygen produced on-site needs to be integrated in the existing hospital pharmacovigilance system and medical device vigilance system.
- Precautions should be taken when using the drug for certain indications, such as hyperbaric chamber treatment and carbon monoxide intoxication.
- Ventilators and anaesthesia machines manufacturers should state in their technical file and instruction for use, the suitability of their equipment when also used with 'Oxygen (93 per cent)'.
- There is no need to create another monograph such as "Oxygen 90+" because the current Ph. Eur. monographs, *i.e.* 'Oxygen (93 per cent)', 'Oxygen (98 per cent)', and 'Oxygen' (with minimum O_2 content of 99.5 % V/V), cover all possible ways of oxygen product supply to Healthcare Facilities and the different, specific production processes.

In conclusion,

To ensure patient safety, EIGA requests the competent authorities to provide harmonised guidance on how to apply consistently both the medical device and the medicinal product regulations for on-site medicinal gas extemporaneous preparations.

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Contact:
- Phone: +32 2 217 70 98
- E-Mail: info@eiga.eu

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