POSITION PAPER

Position Paper PP-38/11 – December 2011

Manufacturing of Medicinal Gases on Hospital Sites

The European Directive on Medicinal Products for Human Use, (2001/83 EC) requires manufacturers and suppliers of medicinal products to conform to requirements established to ensure patient safety.

This Directive, which requires medicinal products to be manufactured under Good Manufacturing Practice, (GMP) and supplied under a Marketing Authorisation (MA), only applies to medicinal products that are 'placed on the market'. However, medicinal products manufactured by the hospital 'on-site' and used solely by the hospital, are not covered by the European legislation.

The Hospital Pharmacist is responsible for the quality of all medicinal products dispensed to patients within the facility, including those manufactured on-site. This includes medicinal gases manufactured on hospital sites and distributed to patients via a medical gas pipeline system but these are not covered by the present European legislation. It is considered that this could lead to hospital patients being exposed to higher risks due to the difference in the quality control requirements for on-site manufacture and licenced product.

To address these potential issues EIGA proposes that a regulation is developed to ensure GMP principles are also followed for on-site manufacture of medicinal gases for distribution by a hospital pipeline system to ensure that patients' safety is not jeopardised.

The requirement to control the manufacturing of medicinal gases on hospital sites could be achieved by:

- **broadening the scope of Annex 6 of the EU GMP Guide to cover this specific requirement; and**
- **utilising the PIC/S (Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme) guidance note "Guide to good practices for the preparation of medicinal products in healthcare establishments" (n° PE 010-3) to provide guidance on good practice for the manufacture of medicinal products on hospital sites.**

Introduction

The supply of medicinal gases used in hospitals is controlled by the European Directive on Medicinal Products for Human Use, (2001/83 EC).

This legislation requires the suppliers of medicinal gases (either in cylinders or as a bulk gas) to hold a Marketing Authorisation, to demonstrate that the product they supply meets the appropriate safety, efficacy and quality requirements for a medicinal product. In addition, the manufacturers of the gases

EUROPEAN INDUSTRIAL GASES ASSOCIATION *AISBL*
AVENUE DES ARTS 3 – 5 ♦ B-1210 BRUSSELS
PHONE +32 2 217 70 98 ♦ FAX + 32 2 219 85 14 ♦ E-mail : info@eiga.eu - www.eiga.eu

are required to hold a Manufacturing Licence, issued by the national Competent Authority. Licensed sites are routinely audited by the national Competent Authority to demonstrate that the procedures used in the manufacture of the gases are suitably controlled and compliant with the principles of Good Manufacturing Practice (GMP).

This European legislation specifically applies to the manufacturers and suppliers of medicinal products that are 'placed on the market' for administration to patients. The main exception to this is where the hospital[1] manufactures the medicinal gases on-site and the manufacturing plant is managed by the hospital. Having manufactured the gas on-site, it is normally distributed around the hospital by a medical gas pipeline system for immediate administration to patients. As the on-site manufactured gas is not considered to be 'put on the market', it is not covered by the requirements detailed in the European legislation.

Although the Hospital Pharmacist is responsible for the quality of all medicinal products used on site, there is no European requirement for the on-site manufacturing facilities to be routinely inspected by the national Competent Authority. Hence there is no documented evidence to demonstrate that GMP principles have been followed or that the on-site manufactured product is suitable for hospital patient use.

To ensure that hospital patients are not subjected to a potentially higher level of risk, EIGA believes that the on-site manufacture of medicinal gases needs to be subjected to the same type and level of controls as those products supplied under a Marketing Authorisation which are "placed on the market".

On-site Manufacture of Medicinal Gases

Conventionally, medicinal air used by the hospital has been produced on-site, using either oil lubricated air compressors or by mixing oxygen and nitrogen using a blending unit to produce synthetic air. The design and installation of this type of plant needs to comply with the requirements specified in EN ISO 7396-1 (Medical gas pipeline systems – Part 1 Pipeline systems for compressed medical gases and vacuum).

EN ISO 7396-1 only specifies the design and testing requirements for the installation of the plant and that the gas should comply with the relevant European Pharmacopoeia (EP) monograph. There are no mandatory requirements in EN ISO 7396-1 to cover the Quality Management System for the operation and management of the manufacturing equipment or any routine quality control or batch management requirements.

With the introduction of the EP monograph for 93% oxygen (using a plant with design requirements specified by ISO 10083, Oxygen concentrator supply systems for use with medical gas pipeline systems), hospitals can manufacture medicinal oxygen on site. Although the Hospital Pharmacist is responsible for all medicinal products administered to hospital patients, the on-site manufacturing plant is normally managed either by the hospital engineering department or by a subcontracted facility management company. This may lead to the quality of the medicinal gases not being correctly controlled in a pharmaceutical manner and the requirements of GMP, as prescribed in the EU GMP Guide not being fully met.

The potential introduction of oxygen on-site manufacturing plants has heightened the concerns of the gas industry about on-site manufacture. The oxygen, which is administered to hospital patients, will be delivered directly by a pipeline system, with only limited on-line control systems to manage product quality. These controls should be robust to ensure that only medicinal gas of the correct quality is administered to these patients as any failure of the on site production system or its controls, could rapidly lead to patients being adversely affected.

Medicinal Gas Supplies

Unlike the on-site manufacture of medicinal gases, the medicinal gases supplied to hospitals in cylinders or as a "bulk" gas are highly regulated.

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AVENUE DES ARTS 3 – 5 ♦ B-1210 BRUSSELS
PHONE +32 (0)2 217 70 98 ♦ FAX + 32 (0)2 219 85 14 ♦ E-mail : info@eiga.eu - www.eiga.eu

The manufacturer of the medicinal gases is required to hold a Manufacturer's Licence (issued by the National Competent Authority). To obtain the licence, the manufacturer has to operate a Quality Management System that is compliant with the EU GMP Guide. As a part of this requirement, they require a number of named persons who have specific responsibilities related to the production and quality control of the product and a Qualified Person to release every batch to ensure it is suitable for patient use.

The medicinal gas supplier is required to hold a Marketing Authorisation (MA), to demonstrate that the quality of each medicinal gas supplied is suitable for patient use. The MA also provides documented evidence that the product is capable of being produced in compliance with pharmaceutical legislation.

In addition to these requirements, the MA holder also needs to operate a Pharmacovigilance system, where any adverse events are reported to the Authorities and assessments made on a routine basis to ensure that patient safety is maintained. This is completely missing for all the medicinal products that are produced inside a hospital, in particular for 93% Oxygen which has recently been established in the European Pharmacopoeia.

Proposals

The medical gas industry recognises that the use of on-site manufacture could be an appropriate method of supply of medicinal gases, via a pipeline system, to patients where the traditional methods are either not readily available or remote from the hospital.

It is proposed that the on-site manufacturing of medicinal gases on hospital sites should be subjected to the same GMP regulations as those covered by the EU Directive 2001/83/EC[2].

As the manufacture of medicinal gases (including 93% oxygen, medicinal air and synthetic medicinal air) on hospital sites is defined as a medicinal product manufacturing process, it should be required to comply with the general principles of GMP, as specified in the EU GMP Guide and specifically with the requirements detailed in Annex 6 of the GMP.

This would ensure that the quality of the product administered to a patient via a pipeline system would be the same from either on site plants or gas supplied under a MA.

EIGA proposes that a harmonised European regulation is produced to ensure GMP principles are also followed for on-site manufacture of medicinal gases for distribution via hospital pipeline systems to ensure that patients' safety is not jeopardised.

The requirement to control the manufacturing of medicinal gases on hospital sites could be achieved by:

- **broadening the scope of Annex 6 of the EU GMP Guide to cover this specific requirement; and**
- **utilising the PIC/S guidance note "Guide to good practices for the preparation of medicinal products in healthcare establishments" (n° PE 010-3) to provide guidance on good practice for the manufacture of medicinal products on hospital sites**

As the equipment is used to produce product for immediate use the proposed regulations should address:

- The certification of the on-site manufacturing system as a medical device to ensure that it is compliant with the appropriate standards and CE marked to the Medical Device Directive 93/42/EEC.
- The establishment of a GMP Quality Management System to cover the manufacture of medicinal gases on-site, which is compliant with the requirements of the EU GMP Guide.
- The preparation of a pharmaceutical file (approved by the appropriate national Competent

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PHONE +32 (0)2 217 70 98 ♦ FAX + 32 (0)2 219 85 14 ♦ E-mail : info@eiga.eu - www.eiga.eu

Authorities) to cover the :

- manufacturing process, including the basic procedures used within the manufacture;
- product quality control requirements to demonstrate compliance of the product, during continuous production with the relevant EP monograph;
- validation of the process to demonstrate the consistency of the manufacturing process;
- responsibilities for product quality administered to hospital patients; and
- the traceability and definition of batches.

- Where product is filled into a gas reservoir above pipeline pressure, (for means of back-up supply), the principles of batch management (and batch release) shall be applied, with the Hospital Pharmacist responsible for releasing the product.
- A confirmation that the requirements of the EU Directive 2001/83 does apply where a product is filled into cylinders and supplied off site

Note 1: The term hospital refers to hospitals, clinics, care homes and other places where medicinal gases are administered to patients by healthcare professionals. It does not cover the supply of medicinal gases to homecare patients.

Note 2: This excludes the use of oxygen concentrators that are Medical Devices designed, used and prescribed for single patient use.

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