POSITION PAPER

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Certification by a Qualified Person and Batch Release

Directive 2001/83 EC requires "…the holder of a Manufacturing Authorisation to have permanently and continuously at his disposal the services of at least one Qualified Person (QP)…". This QP takes full and personal responsibility to certify batches of finished products before release and to ensure that the manufacturing conditions adhere to the requirements in the Marketing Authorisation and that there is a compliant Quality Management System implemented.

The industrial gases industry manufactures medicinal gases utilising processes and equipment that are designed to established principles used throughout the world and which have not significantly changed over several decades.

Medicinal gases are either supplied in high pressure gas cylinders or in cryogenic vessels. Due to the size and the weight of these containers, medicinal gases have to be produced on a site that is close to the point of customer use. This means that the medicinal gas industry requires a large number of production sites per country. To comply with the interpretation of Directive 2001/83 by some national Authorities, the medicinal gas industry has to employ a high number of QPs and deputy QPs, which reduces the overall process efficiency without adding any improvements to patient safety. In many countries there are insufficient QPs available, or interested to carry out the task of certifying a single molecule drug.

In order to address these issues and to meet the full intent of the Directive and based on a compliant Quality Management System, EIGA proposes that a QP in the medicinal gas industry should be allowed to certify product remotely and for more than one site.

This could be achieved by making changes to Annex 16, Certification by a Qualified Person and Batch Release of the EU Good Manufacturing Practice Guide.

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1 Introduction

Within the pharmaceutical industry there is a general trend to rationalise the number of sites so that the manufacturing of medicinal products can be more effectively and efficiently managed. This is not possible in the medicinal gases industry due to specific design requirements for the gas packages and the logistics associated with the international transport of dangerous goods. This means the bulk gas production sites and cylinder filling sites have to be located close (within usually three hundred kilometres) to the hospitals, clinics and patients at home. Due to the high costs of the cylinders and liquid containers and cost to transport these containers long distances, our medicinal gases are not subject to the risk of counterfeiting.

Large numbers of cylinders are required to be delivered (and collected for refilling) using specialised vehicles. The logistics associated with the distribution of medicinal gas cylinders and cryogenic liquid containers and the need to minimise its environmental impact, means the number of distribution and manufacturing sites may be orders of magnitude higher than in other parts of the pharmaceutical industry. As a consequence, if a QP and deputy QP is required to be present on every manufacturing site, the medicinal gas industry will have difficulty in providing sufficient numbers of appropriately qualified QPs. In addition, because their role on site is relatively simple, (due to well established manufacturing processes and in-process controls) it will be difficult to keep them motivated, making it extremely difficult to retain these highly qualified people.

Within Europe, Competent Authorities of the Member States have adopted their own requirements for the release of medicinal gases. In some countries, even where there is only a simple transfilling of medicinal liquid oxygen, there is a need for a QP resident on all sites which leads to a need for hundreds of QPs and deputy QPs.

The number of medicinal gas sites in Europe is considerable, typically with up to a hundred production sites for bulk and cylinder gases in a large country and specifically for homecare requirements, more than three hundred (specifically in Italy and in Spain).

The significant differences in the interpretation of the legislative requirements, on the number for QPs required and the restriction to certify on-site, between EU member states is leading to market distortions. As there are currently significant differences in how a national Regulatory Authority requires the medicinal gases to be certified, it is proposed that the QP requirements be standardised in order to provide a common and practical approach within all Member States. Allowing for QPs to be responsible for several sites within the same Marketing Authorisation Holder and permitting remote certification, using standardised procedures, removes the barriers to trade and ensures that all products are supplied to a consistent standard between member states, without any loss of safety for the patients.

2 Medicinal Gases Manufacturing Processes

As the manufacturing and filling processes associated with the medicinal gases are well established, and produce product of a significantly higher purity than specified in Pharmacopoeia monographs', the possibility of product being non-compliant is minimal.

Other differences with medicinal gases are that the:

- bulk products have short shelf lives (i.e. max 6 months);
- cylinder batch sizes are small, but several batches per day are produced (e.g. 80 cylinders per batch and 4 batches per day, per site);
- Distributing gas cylinders and containers more than three hundred kilometres is not an efficient process.

A single Qualified Person can control Good Manufacturing Practice (GMP) compliance on different medicinal gas manufacturing sites effectively and can certify remotely batches. In several countries this is already a common standard.

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It may also be considered that a QP should be allowed to certify product whilst resident in another EU member state because his effective control is not dependant on the distance between locations, or on the possible border between federal states, regions or countries.

Justification for this approach is based on the following:

- The QP can ensure compliance to GMP Annex 16 paragraph 4.3 by having personal involvement and knowledge of
    - all facilities and procedures employed at the individual sites within the same Marketing Authorisation Holder,
    - the expertise of the persons concerned,
    - the Quality Management System used to ensure compliance.
- Production sites have an appointed person with defined responsibilities and authority for Quality Assurance,
- Any system used for release and certification is appropriately validated, e.g. to GMP Annex 11 in case of computerised systems,
- These manufacturing processes involve few production steps of mostly one product component, where the Active Pharmaceutical Ingredient, API, is the same molecule of the finished product, with no excipient and with no chemical or other transformations,
- The use of common and well established manufacturing and filling processes in the different sites, which are fully validated and compliant to GMP Annex 6, Manufacture of Medicinal Gases.

Due to the nature of the products and the type of plant that is used for manufacturing and filling medicinal gases, it is proposed that the qualification requirements for the person who releases batches should be reviewed to allow suitably qualified and competency tested professional engineers to be appointed to the role. As the processes used in the manufacture of medicinal gases are cryogenic distillation and compressed gases filling, it is felt that a professional engineer has a comprehensive understanding, hence control of these processes.

3 Good Distribution Practice

The Guideline on Good Distribution Practice (GDP) of Medicinal Products for Human use – draft for public consultation by 31 December 2011, defines the requirements for a Responsible Person (RP) as follows:

2.1 ... the RP should fulfil his/her responsibilities personally and should be permanently available …", and

2.3. …. the qualification of the Responsible person should meet the conditions provided by national legislation….a degree of pharmacy is desirable ….."

Due to the nature of the packages, medicinal gases are generally transported directly to the customer with few intermediate storage sites. There is no re-packaging or any transformation of these products. The simple processes with few transactions make it possible to ensure GDP compliance without being permanently on site.

The storage and distribution of medicinal gases is regulated by the international regulation of dangerous products 'ADR'. There are also specific storage requirements in GMP Annex 6, which can apply to GDP. Therefore, also intermediate storage locations can fall under the responsibility of a GMP QP, who is then best placed to take the RP role.

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4 Conclusions

It is recognised that it is important to ensure that the QP and deputy QP for the site should be compliant with the requirements in 2001/83 for his duties and that his qualifications could be based on relevant scientific and engineering practices.

Under all circumstances, Quality Management and Risk Management Systems should be in place and self-audited to demonstrate compliance with the requirements of the Marketing Authorisation.

Electronic systems should also be available to allow transfer of sufficient data to allow the QP to confirm compliance with the Marketing Authorisation.

Based on the fact that these requirements are met, EIGA members can ensure product safety and quality and patient safety and therefore propose that for the medicinal gases industry, a QP should be allowed to certify product remotely and for more than one site.

This could be achieved by making to the GMP Annex 16 “Certification by a Qualified Person and Batch Release” either specific changes related to medicinal gases, or general changes applicable to the pharmaceutical industry if based on the complexity of products, production and distribution processes and their effective control.

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