# OBTAINING A MARKETING AUTHORISATION FOR NITROUS OXIDE

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## ABSTRACT

**OBJECTIVE** To prepare a Common Technical Document for nitrous oxide (NO) in accordance to European Guidelines, for submission to the Medicine's Authority to obtain a Marketing Authorisation (MA) and to carry out a project feasibility study.

**METHOD** Directives and guidelines issued by the European Commission were followed to compile a dossier for NO in the Common Technical Document (CTD) format, in preparation of an abridged application.

**KEY FINDINGS** The Common Technical Document gave details on the Administrative Information (Module 1), Summaries (Module 2), Quality (Module 3) and Non-Clinical Studies (Module 4) consisting of a detailed scientific bibliography. The active substance manufacturer was inspected and accepted as an approved supplier. A feasibility study which was conducted proved the project feasible.

**CONCLUSION** The whole manufacturing process of nitrous oxide is well controlled and batches can be produced with a constant level of quality. NO has been used for 150 years for analgesia and anesthesia and has proven safe and effective. Even though its administration is not without risks, it currently has a niche role as an inhalational analgesic and sedative.

**KEYWORDS** Nitrous oxide, Common Technical Document, Marketing Authorisation

## INTRODUCTION

No medicinal product may be placed on the market in Malta unless there is with respect to the product a valid marketing authorisation (MA) issued by the Licensing Authority[1] in accordance with EC Directive 726/2004. The key requirement of an application for a MA is the submission of a dossier.

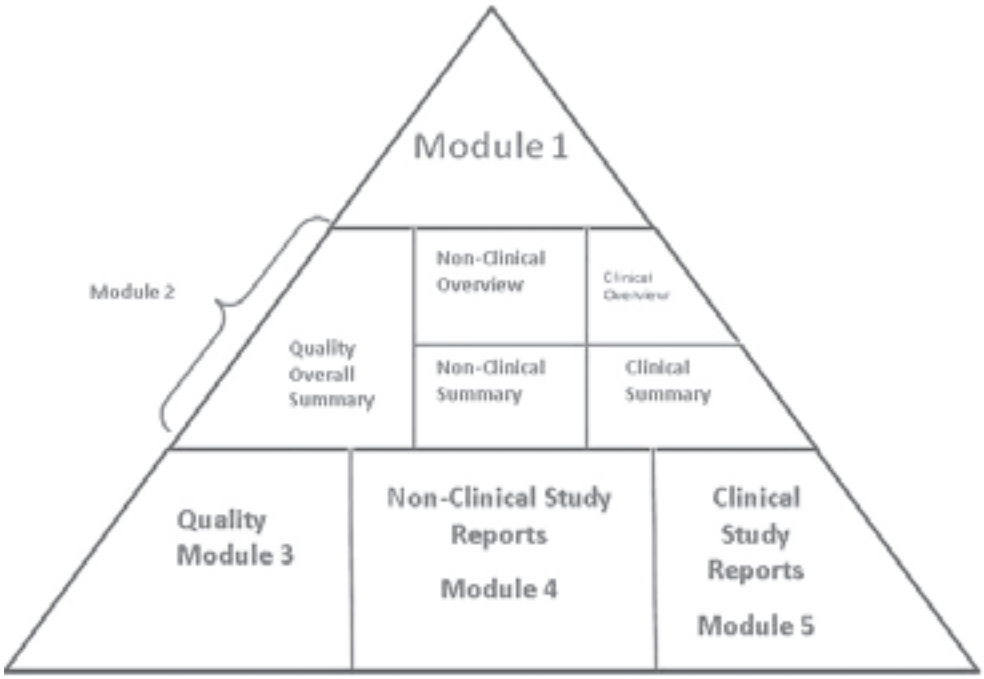


**Figure 1** - Common Technical Document format as issued by the ICH

Taken from:
ICH. M4: The Common Technical Document 2004 (cited 2014 Feb 19). Available from: www.ich.org/fileadmin/Public_Web_Site/ICH_Products/CTD/M4_R3_Organisation/M4_R3_organisation.pdf

The application must be presented in an agreed common format known as the Common Technical Document (CTD), as implemented in July 2003 by the International Conference on Harmonisation (ICH) (Figure 1). Since NO has been widely used in therapeutic practice for several decades and has recognised efficacy and an acceptable level of safety, this medicinal product is defined as having a 'well-established medicinal use' within Article 10(1)(a)(ii) of Directive 2001/83/EC.[2] During initial meetings it was established that the company's intention was to import NO in bulk as the active substance. The NO will be stored at the company's premises in cryogenic tanks and will eventually be used for filling cylinders. Batch release of the finished products will be carried out by the company's Qualified Person after batch analysis. This project aimed at auditing the active ingredient manufacturer and preparing a CTD for an application to obtain a marketing authorisation through a decentralised procedure. Project feasibility was also studied.

## METHOD

The official audit of the active ingredient manufacturer consisted of sending an Approval of Suppliers Questionnaire to the potential supplier. The questionnaire was divided into six sections including Personnel, Premises and Equipment, Documentation, Quality Control/Validation, Batch Release, Production/Operation Activities and Maintenance. This was followed by a visit to the manufacturer's premises. An official audit report detailing findings was compiled.

The first undertaking in producing the dossier entailed an exhaustive literature review in which an insight was gathered on different characteristics of NO. The Common Technical Document was compiled according to Notice to Applicants Volume 2B – Medicinal Products for human use as issued by the European Commission in order to fulfil the Commission's obligations with respect to article 6 of Regulation (EC) No. 726/2004[3], and with respect to Annex I of Directive 2001/83/EC.[2] Module 1 included administrative information. Information from the recurrent literature review was used to assemble the Summary of Product Characteristics and Labelling and Patient Information Leaflet. Notice to Applicants – A Guideline on Summary of Product Characteristics issued by the European Commission[4] was used to compile the Summary of Product Characteristics. Guidelines issued by the European Commission - Guideline on the readability of the labeling of and package leaflet of medicinal products for human use, were followed for the compilation of the labeling while guidelines issued by the European Medicines Agency were followed to produce the Patient Information Leaflet.

In accordance with Articles 59(3) and 61(1) of Directive 2001/83/EC[2], a readability study was conducted to ensure the safe use of the medicinal gas. A set of 14 multiple choice questions were compiled. The Patient Information Leaflet and the readability questionnaire were handed to ten participants and the collected data was reviewed. After satisfactory data was obtained a further ten participants were also given the readability questionnaire. Forty percent of the participants were healthcare professionals, 30% were university students and 30% were laypersons. As indicated in Article 56a of Directive 2001/83/EC[2] the name of the medicinal product on the packaging was also expressed in Braille format.

The marketing authorisation for NO will be applied for by an abridged dossier under Article 10a of Directive 2001/83/EC[2] relating to the marketing authorisation of medicinal products with a well established use. In order to demonstrate that NO is a medicinal with a well established use, a literature review was undertaken with respect to the first uses of NO in sedation and anaesthesia. In accordance with Article 8 (ca) and (g) of Directive 2001/83/EC[2] an application for marketing authorisation should be accompanied by an environmental risk assessment, evaluating any potential risks of the medicinal product to the environment. Since NO is a greenhouse gas with tremendous global warming potential, literature sources were evaluated and results were drawn up in a report.

A detailed description of the Pharmacovigilance System (DDPS) and an EU Risk Management Plan (EU-RMP) were compiled as outlined in Eudralex Volume 9A.

| Test | Specification | Analytical Method |
|---|---|---|
| **Purity** | ≥ 98.0% V / V | Infrared |
| **Carbon dioxide** | ≤ 300 ppm V / V | Gas chromatography |
| **Carbon monoxide** | ≤ 5 ppm V / V | Gas chromatography |
| **NO + $NO_2$** | ≤ 2 ppm | Chemiluminescence |
| **Water** | ≤ 67 ppm V / V | Electrolytic |

**Table 1** - Specifications and Analytical Procedures of Nitrous oxide

Taken from:
European Pharmacopoeia version 7.3, Volume 2, Directorate of the Quality of Medicinesof the Council of Europe, 2012. Medicines Conmel Agency

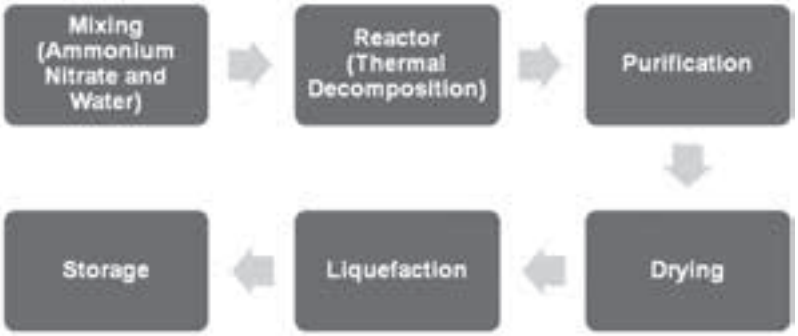


**Figure 2**: Manufacturing Process of Nitrous oxide

Module 3 – Quality, detailed the quality of the manufacturing process for the active substance and the finished product, including information about the chemical structure, composition, manufacture, quality control, process validation and stability, to demonstrate drug manufacture control and reproducibility.

A retrospective validation study of the production process was carried out by analysing 20 consecutive batches manufactured in 2011. Since nitrous oxide has a 'well-established medicinal use', nonclinical studies (Module 4) consisted of a detailed scientific bibliography giving details on pharmacokinetic, pharmacodynamic and toxicological studies. No clinical trials were carried out hence there was no further information to be presented in module 5. Module 2 contained summaries and overviews of the information presented in detail in the other modules. A market analysis was carried out to establish consumption figures as part of the project's feasibility study. Costs were calculated and the profit and loss schedule was presented. By calculating the return on investment after the first 5 years one was able to determine the feasibility of this project.

## RESULTS

The quality system of the Italian manufacturer was deemed acceptable and therefore it was accepted as an approved supplier. In the patient information leaflet readability study, all twelve questions obtained at least sixteen correct answers. Eleven participants rated the length as adequate, thirteen thought the layout is attractive and eighteen considered the letter size acceptable. Nine participants rated the information conveyed as excellent. The well-established use of NO was proven through literature. The environmental risk assessment concluded that the emission levels for NO are very limited and amount to an average of 1.3% of the overall greenhouse gas emissions. Concerns about the environmental impact of the anesthetic use of NO are unfounded as anesthesia accounts for <1% of total NO emissions. The nitrous oxide produced meets the specifications required by the European Pharmacopoeia (Table 1).

The manufacturing process of NO is based on the thermal decomposition of ammonium nitrate through a pyrolysis reaction. The flowchart in Figure 2 shows the main stages of the process. The analytical methods used are those indicated in the European Pharmacopoeia (Table 1). In the manufacturing process validation studies, all batches conformed to the European Pharmacopoeia specifications shown. The minimum and maximum purity results were 99.7% and 99.9% respectively, with a median of 99.97%. The standard deviation values (Table 2) were very minimal. NO is packaged in high pressure cylinders of various sizes, contained at a pressure of approximately 60 bar at 25°C. The different cylinders are identified by their liquid volume ranging from 5 liters or less to 50 liters. Cylinders are made from suitable materials (carbon steel, Cr-Mo steel, stainless steel and aluminum alloys, composite type). Stamp markings as required by European Directives[6] and ISO standards are applied on the cylinders' shoulder.

| Parameter | Minimum | Maximum | Median | Std. Dev. | RSD |
|---|---|---|---|---|---|
| **Purity** | 99.70 % | 99.99 % | 99.97 % | 0.00064 | 0.00064 % |
| **$CO_2$** | 3 ppm | 6 ppm | 4.05 ppm | 0.94451 | 23.32 % |
| **CO** | 1 ppm | 1 ppm | 1 ppm | 0 | 0 % |
| **NO + $NO_2$** | 0.1 ppm | 0.2 ppm | 0.165 ppm | 0.04894 | 29.66 % |
| **Water** | 1.1 ppm | 3.22 ppm | 2.0125 ppm | 0.53866 | 26.77 % |

**Table 2:** Manufacturing Process Validation Statistical Results

The cylinders are fully painted in white with a blue shoulder as per standards and are supplied with two main types of valves; the pin-index valve or the pressure residual valves.

The non-clinical studies included the mechanisms of action of nitrous oxide both as an anesthetic and an analgesic together with its effect on the cardiovascular system, respiratory system, central nervous system, muscle, kidneys, liver and gastrointestinal tract. The known and proposed adverse effects of NO include postoperative nausea and vomiting, megaloblastic anaemia, possible immunosuppression, myocardial ischaemia, increased risk of hypoxia, neural toxicity, possible teratogenicity, expansion of air spaces and increased intracranial pressure. Attention to occupation exposure limits (OELs) is important. Facilities to ensure adequate scavenging and ventilation are imperative to ensure the occupational health of medical staff. Even though, the administration of NO is not without risks, it was proven to be safe and effective through its use throughout the years.

The five year feasibility study proved the project feasible.

## DISCUSSION

The audit ensured that the product obtained from that particular site is up to the required quality standard. The visit to the Italian manufacturer also served for training purposes. Training was provided in different aspects of production of NO. This visit took place at an early stage of this project and served as a good introduction to the production process of this medicinal gas. Further training sessions are planned for other company personnel including operators and senior operators.

The readability study concluded that the Product Information presented is legible, clear and easy to use. Through ongoing literature searches and pharmacovigilance activities, new information available will be evaluated and Product Information updated.

Drug manufacture control and reproducibility are essential requirements in Module 3 for reviewers of the Common Technical Document to conclude that the product merits a marketing authorisation. By defining the safety parameters and the critical control steps of both the manufacturing process of the active substance and the manufacturing process of the finished product one ensured that the whole process is well controlled and that the next batch produced is essentially the same as the last batch i.e. batches can be produced with a constant level of quality.

Statistical analysis of data recorded confirms that the process of production of NO is considered to be validated. This feasibility study was conducted by taking into consideration the Maltese market only, which is relatively small and mainly limited to the government sector through a tendering process. Since the company is applying for a decentralised procedure, consumption figures will rise considerably if the company manages to penetrate foreign markets. This will possibly make the project even more feasible.

## CONCLUSION

The whole manufacturing process of NO is well controlled and batches can be produced with a constant level of quality.

Nitrous oxide has been used for 150 years for analgesia and anesthesia and has proven safe and effective. Even though its administration is not without risks, it currently has a niche role as an inhalational analgesic and sedative.

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