# TECHNICAL BULLETIN

Prepared by WG-7 TB 060/24 – May 2024

# Shortage Prevention Plan

# Nitrous Oxide / Nitrous Oxide – Oxygen Mixtures

**Introduction:**

This document covers the medicinal product Nitrous Oxide ($N_2O$), as well as its mixtures with oxygen, usually at a concentration of 50%.

Nitrous oxide has a Ph.Eur. monograph, 0416, for many years and is one commonly used medicinal gas.

Nitrous oxide is produced by the thermal decomposition of ammonium nitrate, with the resulting gas being counter-current washed with water and with a solution containing sodium hydroxide and potassium permanganate and then compressed, dried and liquefied before being fed to a cryogenic storage working at about 20 bar.

While in the case of nitrous oxide the medicinal product coincides with the active substance, in the mixtures both nitrous oxide and oxygen are considered active substances.

Usually, medicinal nitrous oxide is supplied to healthcare facilities as a licensed medicinal gas liquefied under pressure in gas cylinders or cylinder bundles. Some large healthcare facilities are supplied with liquid nitrous oxide as a liquid product stored at the healthcare facility site in insulated storage tanks.

Nitrous oxide – oxygen mixtures is obtained either pre-mixing the two ingredients before transferring the mixture in the licenced package or introducing them in sequence in the final package.

EIGA emphasizes that in Europe at no time was there a shortage of nitrous oxide and his mixtures to patients in healthcare facilities.

EIGA has used Technical Report No. 68, “Risk-Based Approach for Prevention and Management of Drug Shortages”, as prepared by the Parenteral Drug Association (PDA) in 2014 as part of the inter-association collaborative contribution to the EMA (European Medicines Agency) Initiative on medicinal product shortages caused by manufacturing and GMP compliance issues. The document can be freely downloaded from the PDA website.
The risk triage method is a simple four-step process that uses a preliminary hazards analysis approach to evaluate the risk of a drug shortage by considering the therapeutic use of a product, availability of alternatives, and likelihood of occurrence. The process assigns a risk priority level based on a combination of the potential impact to the patient and likelihood of a drug shortage, and then recommends risk controls for the assessed product. The method uses discrete information and key words to assign a priority level for each element, making the assessment focus on product information and avoiding discussions on general subjective terms.



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**The steps in the triage process are as follows:**

1. Identify risk level (impact to patient) based on therapeutic use and availability of alternatives.
2. Determine the likelihood of a drug shortage for the product.
3. Determine the risk priority level based on a combination of impact to patient and likelihood of a drug shortage for the product.
4. Plan and implement the suggested risk controls for the assessed product based on the risk priority level.

**Step 1:**

| | | | Availability of Alternatives | | |
|---|---|---|---|---|---|
| | | | No Alternatives Available | Alternative Products Available: Similar Therapy | Exact Product Available but in Other Presentations |
| Therapeutic Use & Consequences if Product is not Available | Medically necessary product, life supporting or life sustaining | Fatal or severe irreversible harm if the patient is not treated with the product | Risk Level A | Risk Level A | Risk Level B |
| | Acute short term or chronic long term | Severe harm but reversible if patient is not treated with the product | Risk Level A | Risk Level B | Risk Level C |
| | Other indications | inconvenience if patient is not treated with the product | Risk Level B | Risk Level C | Risk Level C |

Typical Indications of Nitrous Oxide and Nitrous oxide/Oxygen mixtures are:

Nitrous oxide is used as a basic anaesthetic in combination with inhalation anaesthetics or intravenous anaesthetics in adults and children from the age of 1 month. Medical oxygen is added at a concentration of at least 21% v/v.

Nitrous oxide in equimolar concentration with oxygen (50% v/v nitrous oxide and 50% v/v oxygen) is indicated for the treatment of short-term pain conditions of mild to moderate intensity when rapid analgesic onset and offset effects are required, in adults and in children older than 1 month.

Therefore, the assessment is that Nitrous Oxide and its mixtures are for acute short term uses. Furthermore, it should be noted that for nitrous oxide there are other alternatives, like Desflurane, Sevoflurane or Ketamine and Propofol.

In the assessment of alternatives, the outcome is that there are many “Exact products available” as there are many Marketing Authorisation Holders (MAHs) within each EU member state having authorisations for Nitrous Oxide and Nitrous Oxide/Oxygen mixtures. It should also be noted that these products are present in the exact same presentation, therefore lowering the risk even further.

With the assessment of “Therapeutic Use & Consequences if Product is not Available” as “Acute short term or chronic long term uses” and “Availability of Alternatives” as “Exact Product Available” – it is classed as **RISK LEVEL C**.

**Step 2:**

For the likelihood analysis, the following main sources of hazards were assessed:


according to the following criteria:

**LOW:** Robust controls exist for a hazard

**MODERATE:** Limited controls exist for a hazard

**HIGH:** No controls exist for a hazard

**Drug Substance:**

Nitrous oxide is produced by the thermal decomposition of ammonium nitrate. There are several manufacturing plants for nitrous oxide within the European Union producing nitrous oxide for medical, food and industrial use.
The industrial / food use of nitrous oxide is far larger than the medical one.
Moreover, ammonium nitrate is a commonly produced base chemical. The amount of ammonium nitrate required by the production of nitrous oxide is very small fraction of the nitrate used for the production of fertilisers.
In the case of Nitrous oxide/Oxygen mixtures, both $N_2O$ and $O_2$ are drug substances.
Oxygen is produced from ambient air in Air Separation Plants (ASU). There are many ASUs within each member state that can produce significantly more oxygen than is required for medical use across Europe, with only a negligible percentage of oxygen produced at an ASU being used for the manufacturing of nitrous oxide / oxygen mixtures.
For both nitrous oxide and its mixtures with oxygen the manufacturing is performed directly within the EU with short delivery times and stable production in accordance with GMP requirements. Transportation of the drug substance is performed either directly on the site where the finished product is manufactured, or in cylinders loaded onto trucks and transported by road. Drug substance manufacturers are normally located within a few hours from the finished product manufacturing site.

- ✓ Back up available
- ✓ Production already located within European Union
- ✓ low possibility of shortage of starting materials (commodity products)
- ✓ Short transport routes if not onsite
- ✓ Well established and highly reliable process producing high quality products
- ✓ Sufficient minimum stocks of drug substance at the manufacturing site

➔ ***The resulting risk of failure of Drug Substance supply is considered:***

**LOW**

**Step 2 - continued:**

**Drug Product & Packaging:**

The drug product consists of the drug substance (drug substances in the case of the mixture), filled into gas cylinders of different sizes, fitted with different valves and transported via road trucks directly to hospitals. The packaging, i.e.. cylinder and valve combination, used for medicinal gases are unique, in that they are reused when the cylinders are returned to the finished product manufacturer for refilling. Generally, the cylinders and valves are in use for at least 10 years, sometimes much longer. The supply of these packaging materials can be considered highly reliable as there are several manufacturers within the EU for cylinders and valves.
Electricity supply for the manufacturing of nitrous oxide, oxygen, as well as for the drug product filling equipment, has historically been extremely reliable, and is therefore not considered to be a significant contributory factor to the risk of product shortage. The finished product is stored at ambient temperature, rendering stocks independent from electricity supply as the product is stored as a compressed gas in cylinders.
The drug product is obtained by means of a mere transfer of gas from a cryogenic storage (a sequential transfer or blending and compression in the case of the mixture), making the manufacturing process extremely stable and consistent.
The equipment for manufacturing is relatively simple, consisting of mainly reservoirs, piping, valves and filling hoses, with the aging of equipment therefore not considered a potential reason for product shortages. The quality control is carried out with since long time known methods, implemented on reliable instrumentation of simple use for the operators.

Quality defects are rare (< 1%) due to batch sizes generally being relatively small, resulting in closely managed quality control processes. This also means that any rejected batch only affects a relatively small quantity of cylinders. The cylinders are labelled with an outer label, batch label, and in some regions, a patient information leaflet. Stocks of pre-printed packaging material are usually kept at the manufacturing site and can be readily obtained from local suppliers; batch labels are printed in-house.

- ✓ Simple production process
- ✓ Simple and reliable quality control equipment
- ✓ Drug product consists of only the drug substance (or drug substances in the case of mixtures), drug substance(s) stock(s) are quite large
- ✓ Simple drug substance made from commodity starting materials – readily available
- ✓ Reusable packages (min. 10 years) and reliable packaging manufacturers
- ✓ Aging of equipment negligible
- ✓ High quality products, < 1% OOS, additional small batch sizes with short lead times and large number of quality controls

➔ ***The resulting risk of failure of Drug Product manufacturing and packaging is:***

**LOW**

**Step 2 - continued:**

**Warehouse Distribution & Affiliates:**

In the vast majority of cases the Marketing Authorisation Holder (MAH) is also the manufacturer, with transportation of the finished product often being directly managed to the end user/customer. There can be minimum stocks for certain sizes, however, to trace them in national databases or the EMA is not necessary as package sizes are exchangeable, as generally they are intended to be multi-dose, multi-patient packages.

➔ ***The resulting risk of failure of Warehouse Distribution & Affiliates is:***

**LOW**

**Wholesaler & Pharmacy:**

Wholesaler and Pharmacies are not commonly used in the supply chain of Nitrous oxide and its mixtures as the distribution is mainly performed directly by the Marketing Authorization Holders/Manufacturer.

➔ ***The resulting risk of failure of Wholesaler & Pharmacy is:***


**Conclusion for the Likelihood of Shortage:**
As all parts of the supply chain “Drug Substance”, “Drug Product & Packaging”, “Warehouse Distribution & Affiliates” and “Wholesaler & Pharmacy” are considered to be low risk, the overall resulting risk is considered:




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**Step 3 - Determine the risk priority level based on a combination of impact to patient and likelihood of a drug shortage for the product:**

| Therapeutic Use & Consequneces if Product is not Available | | Likelihood of Shortage | | |
|---|---|---|---|---|
| | | High | Moderate | Low |
| | Risk Level A | Risk Priority Level 1 | Risk Priority Level 1 | Risk Priority Level 2 |
| | Risk Level B | Risk Priority Level 1 | Risk Priority Level 2 | Risk Priority Level 3 |
| | Risk Level C | Risk Priority Level 2 | Risk Priority Level 3 | Risk Priority Level 3 |

With the assessment of “Therapeutic Use & Consequences if Product is not Available” as “**RISK LEVEL C** and the assessment “Likelihood of Shortage” as **LOW** the outcome is **RISK PRIORITY LEVEL 3**.



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**Step 4 - Plan and implement the suggested risk controls based on the risk priority level:**
Depending on the risk level the following controls are suggested by the PDA document, see table:

| Risk Priority | Suggested Controls |
|---|---|
| Level-1 | • Appropriate inventory and safety stock management<br>• Multisite sourcing with higher manufacturing capacity reserves<br>• Supplier management controls (see **sec. 5.4** of TR54)<br>• Supply chain/transportation line security, business continuity and communication plan<br>• Extended Value Stream Mapping (VSM) |
| Level-2 | • Consider multisite sourcing<br>• Value Stream Mapping (VSM)<br>• Proactive inventory management<br>• Process capability and robustness exercised (with Quality Metrics) |
| Level-3 | • Generally accepted risk level |

**Conclusion:**
EIGA assessed the medicinal nitrous oxide and nitrous oxide / oxygen mixtures supply chains and all associated risks and concluded that for both products the **RISK PRIORITY LEVEL 3** is appropriate, with the residual risk of a drug shortage being generally accepted.
Therefore, it is proposed that there is no necessity to prepare additional SHORTAGE MITIGATION PLAN (SMP) as the risk of drug shortage can be generally accepted.
EIGA also recommends that nitrous oxide and nitrous oxide/oxygen mixtures should be assessed as **not** required to be included in the "Union list of critical medicines" as the security in the supply and prevention of shortages is assured.
EIGA recommends that this SHORTAGE PREVENTION PLAN (SPP) can be used for all EIGA member companies.



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