TECHNICAL BULLETIN

Prepared by WG-7 TB 059/24 – May 2024

Shortage Prevention Plan

Nitric Oxide / Nitric Oxide Mixtures up to 1000ppm in Nitrogen

Introduction:

This document covers the medicinal product Nitric Oxide (NO), with concentrations up to 1000ppm, in Nitrogen (N2). The active substance in these mixtures is Nitric Oxide.

Nitric oxide can be produced from either the reaction of sulfuric acid (diluted 55%) with liquid sodium nitrite, with the resulting gas being counter-current injected in a washing cycle containing sodium hydroxide and then fed into a condenser/decanter, or from the large-scale production as a by-product in the Ostwald process from the synthesis of nitric acid from ammonia.

After both processes the nitric oxide gas is then filled at a defined pressure into aluminum cylinders. Later the nitric oxide active substance is mixed with nitrogen to create a so called intermix of about 1-5% (V/V) Nitric Oxide in Nitrogen. The last step of the manufacturing process is the actual production of the final mixture, where the intermix is further diluted with nitrogen.

This product has had a Ph.Eur. monograph, 1550, for many years and is a commonly used medicinal product worldwide.

Usually, Nitric oxide/Nitrogen mixtures are supplied to healthcare facilities as licensed medicinal products in defined packages of a compressed gaseous mixture in aluminum cylinders.

EIGA emphasizes that in Europe, and as confirmed with the European Medicines Agency (EMA), although there was a significant increase in the use/consumption of nitric oxide/nitrogen medicinal gas products during the COVID-19 pandemic, our member companies confirmed that at no time was there a shortage of these 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

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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.

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 Nitric Oxide/Nitrogen mixtures are:

They are used in conjunction with ventilatory support and other appropriate active substances, as indicated:

- for the treatment of newborn infants ≥ 34 weeks gestation with hypoxic respiratory failure associated with clinical or echocardiographic evidence of pulmonary hypertension, in order to improve oxygenation and to reduce the need for extracorporeal membrane oxygenation.

- as part of the treatment of peri- and post-operative pulmonary hypertension in adults and newborn infants, infants and toddlers, children and adolescents, ages 0-17 years in conjunction to heart surgery, in order to selectively decrease pulmonary arterial pressure and improve right ventricular function and oxygenation.

Therefore, the assessment is that Nitric Oxide/Nitrogen mixtures are for acute short term or chronic long term uses. Furthermore, it should be noted that for inhaled nitric oxide there are other alternatives, such as inhaled prostacyclin and alternative prostaglandin preparations such as inhaled iloprost, treprostinol and beraprost (Lowson SM. Alternatives to nitric oxide. Br Med Bull. 2004 Nov 5; 70:119-31).

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 Nitric Oxide/Nitrogen 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.**

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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:

For Nitric Oxide/Nitrogen mixtures, the drug substance is considered to be Nitric Oxide manufactured either from sulfuric acid (diluted 55%) reaction with liquid sodium nitrite or from production on a large-scale as a by-product in the Ostwald process from the synthesis of nitric acid from ammonia.

There are several manufacturing plants for Nitric Oxide within the European Union that can produce more nitric oxide than is required for patient use across Europe. Although there was a significant increase in the use/consumption of these mixtures (up to 3 times higher use than normal) during the COVID-19 pandemic, at no time was there a shortage of the drug substance.

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, especially in so called intermixes of about 1-5% (V/V) Nitric Oxide in Nitrogen as they are generally stable for a long time.

➔ ***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 and the excipient nitrogen (with the nitrogen also being produced by the finished product manufacturers, usually viaair separation, therefore making it readily available), filled into aluminum cylinders of different sizes, fitted with different valves and transported via road trucks directly to hospitals. The packaging, ie. 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, vessels and valves.

Electricity supply for the manufacturing of nitric oxide, 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 generally manufactured by mixing the nitric oxide with nitrogen and compressed and fillied into cylinders, 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. 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 labeled 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.
The cylinder/vessel or road tanker is the final packaging and no relabeling is done.

- ✓ Simple production process
- ✓ Drug product consist of only the drug substance, drug substance stock (as so called intermixes of about 1-5% (V/V) Nitric Oxide in Nitrogen) 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 Nitric Oxide / Nitrogen mixtures as the distribution is mainly performed directly by the Marketing Authorization Holders/Manufacturer.

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

LOW

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:

LOW

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

Conclusion:
EIGA assessed the medicinal nitric oxide supply chain and all associated risks and concluded that for medicinal nitric oxide/nitrogen mixtures 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 nitric oxide and nitric oxide/nitrogen 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 again wishes to emphasize that in Europe, and as confirmed with the European Medicines Agency (EMA), although there was a significant increase in the use/consumption of nitric oxide/nitrogen medicinal gas products during the COVID-19 pandemic, our member companies confirmed that at no time was there a shortage of these mixtures to patients in healthcare facilities.
EIGA recommends that this SHORTAGE PREVENTION PLAN (SPP) can be used for all EIGA member companies.

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