TECHNICAL BULLETIN

Prepared by WG-7 TB 061/24 – May 2024

Shortage Prevention Plan

Xenon

Introduction:

This document covers the medicinal product Xenon, which is a pure liquefied gas (100% v/v) for inhalation, belonging to the class of "general anesthetics".

Xenon is produced in air separation units (ASU), the manufacturing principle being based on the purification of ambient air, followed by liquefaction of this purified air and fractional distillation of the liquefied air into its various components, including xenon, which represents a very small fraction of the rare gases contained in air.

Medicinal Xenon is indicated for the maintenance of general anesthesia in adults ASA I-II, in combination with other volatile anesthetics and/or opioids as part of a balanced anesthetic regimen in adults. Xenon should not be used as the sole anesthetic agent. With xenon alone it is not possible to achieve anesthesia with adequate oxygenation in all patients under normal atmospheric pressure conditions. For this reason, xenon is often combined with opioids such as morphine.

Xenon is administered to the patient using an approved anesthetic delivery system, which must ensure patient ventilation and control of the inhaled gas mixture. The delivery system must provide the desired dose of xenon, regardless of machine settings. Xenon should only be used in a gas mixture containing at least 30% oxygen, otherwise there is a risk of asphyxiation. The duration of administration depends on the duration of anesthesia.

EIGA emphasizes that in Europe at no time was there a shortage of xenon 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.

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.

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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**

Table 1

Typical Indications of medicinal xenon are:
Xenon, used in combination with other medical devices for the following purposes:

- Xenon is intended for maintaining anaesthesia in combination with other volatile anaesthetics and/or opioids as part of a balanced anaesthetic regimen in adults of ASA class I-II.

Therefore, after the assessment, xenon fits into the category of 'other indications' (see table 1).

In evaluating alternatives to xenon, there are "Alternative products available: Similar Therapy". It is a product that despite having a wide experience, is not widely marketed in Europe due to the costs of its manufacturing process and the existence of various alternative and more economical therapies such as N2O and other anesthesia inducers.

With the assessment of "Therapeutic Use & Consequences if Product is not Available" as "Other indications" and "Availability of Alternatives" as "Alternative Products Available: Similar Therapy" – 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:

Pure Xe is obtained as a by-product of cryogenic fractional distillation of air. In a typical large-scale industrial facility, air is liquefied and subjected to fractional distillation in a set of distillation columns at different temperatures to obtain different gases as different terminals, finally ending up with a mixture of approximately 20/80 v/v of noble gases Xe and Kr, respectively. Given their difference in boiling point and other physical properties (-108.1°C and -153.2°C for Xe and Kr, respectively), efficient fractional distillation can be achieved.
The price of obtaining Xe is high, mainly due to its rarity in air and partly due to the number of additional distillation steps required to obtain high purity Xe gas (>99.99%). Moreover, as Xe production is complementary to O2 and N2 production, and there is no industrial cryogenic unit dedicated to Xe production in operation in Europe.
However, there are no SHORTAGE records for the drug substance.

- ✓ Production already located within European Union
- ✓ Well established and highly reliable process producing high quality products
- ✓ Sufficient minimum stocks of drug substance at the manufacturing site stable for a very long time.

- → Costly manufacturing process
- → Few manufacturing sites

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

MODERATE

Step 2 - continued:

Drug Product & Packaging:

The medicinal product consists solely of the drug substance, filled in aluminum cylinders, assembled with different valves and transported by road trucks directly to the hospitals. The containers, i.e. the cylinder and valve

combination, used for medical gases are unique in that they are reused when the cylinders are returned to the manufacturer of the finished product for refilling. Typically, cylinders and valves are used for at least 10 years, sometimes much longer. The supply of these packaging materials can be considered very reliable, as there are several manufacturers of cylinders, containers and valves in the EU.
The supply of electricity for the manufacture of the drug substance, as well as for the drug product filling equipment, has historically been reliable and is therefore not considered a significant contributing factor to the risk of product shortages. The finished product is stored at ambient temperature, so stocks are independent of the power supply, as the product is stored as compressed gas in cylinders.
The pharmaceutical product is generally manufactured by filling the drug substance into cylinders, which makes the manufacturing process extremely stable and consistent.

- ✓ Simple production process
- ✓ Drug product consist of only the drug substance, drug substance stock usually sufficient
- ✓ 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 Xenon 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:

Considering that, all parts of the supply chain: “Pharmaceutical product and packaging”, “Warehouse distribution and subsidiaries” and “Wholesaler and pharmacy” are considered low risk, with the exception of Drug substance being classified as moderate; we could consider the resulting overall risk as:

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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 **MODERATE** 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 xenon supply chain and all associated risks and concluded that for medicinal Xenon 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 xenon 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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