TECHNICAL BULLETIN

Prepared by WG-7 TB 17/23 – December 2023

Active Substances and Starting Material Used in the Manufacture of Medicinal Gases According to Good Manufacturing Practice Part II

Introduction

This technical bulletin covers the definition and classification of gases used as active pharmaceutical ingredients (API) as specified in the European Guide to Good Manufacturing Practice (GMP).

According to Article 46 (f) of European Directive 2001/83/EC and Article 50 (f) of Directive 2001/82/EC; as amended by Directives 2004/27/EC and 2004/28/EC respectively, the Manufacturing Authorisation Holders (MAH) shall only use active substances that have been manufactured in accordance with the principles of Good Manufacturing Practice as detailed in the EU GMP Guide.

Objective

The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, Guideline Q7, GMP for APIs, do not apply to medicinal gases. This technical bulletin provides guidance regarding the definition and classification of the active substances used in the manufacturing of medicinal gases. It aims at ensuring they meet requirements specified in the Marketing Authorisation (MA).

Scope

This technical bulletin covers the manufacture of all gases used as active substances and starting materials in the manufacture of medicinal gases and is based on the relevant clauses detailed in Part II of the EU GMP Guide

Definitions

Active substance (or Active Pharmaceutical Ingredient)

Any gas or any gas mixture used in the manufacture of a medicinal gas that becomes an active ingredient of the drug product. In the MA, the active substance is classified as the drug substance. In this document the term active pharmaceutical ingredient (API) is equivalent to the term active substance.

Active substance starting material

Raw materials, or intermediates, that are used in the production of an active substance and that are incorporated as a significant structural fragment into the structure of the API. In the case of medicinal gases manufacturing, an active substance starting material is a product manufactured using industrial production processes, under a quality management system (QMS). It can be an article of commerce, a material purchased from one or more suppliers under contract or commercial agreement or produced in-house.

Intermediate

Material produced during the steps of processing an API, that undergoes further changes before it becomes an API.

Intermix gas

Mixture used as an API in medicinal gases manufacturing or as an intermediate in medicinal gases manufacturing.

EUROPEAN INDUSTRIAL GASES ASSOCIATION *AISBL*
AVENUE DE L'ASTRONOMIE 30 • B-1210 BRUSSELS
PHONE +32 2 217 70 98 • E-mail : info@eiga.eu - www.eiga.eu

Manufacture

Medicinal gases are manufactured by cryogenic distillation of ambient air, by chemical synthesis, by fermentation or by recovery from natural resources.

The manufacturer of active substance is responsible for documenting the rationale for the definition of the point at which production of the active substance begins.

For chemical synthesis processes, this is the point at which active substance starting materials enter into the manufacturing process of the API

Table 1 gives guidance on the application of the appropriate quality management system to the manufacturing of active substance starting material, active substance and medicinal finished product

Table 1

Quality Management System			
ISO 9001 (or equivalent)		**GMP Part II**	**GMP Part I**
Industrial manufacturing	Production of API Starting Material	Introduction of API starting material in the API manufacturing process. Production of API and/or intermix	Production of finished product (Pure gas or mixture)
→		→	→
Industrial manufacture		Industrial manufacture	Pharmaceutical manufacture

The requirements specified in Part II of the EU GMP Guide shall be applied when the API starting material is first introduced into the API medicinal gases manufacturing process.

The rational used to identify where Part II of the EU GMP Guide should be applied takes into account the fact that the majority of the gases used as API starting materials are produced in manufacturing plants where most of the product is intended for industrial use, compared to the smaller quantities required for use as API starting material.

As the prime use of the manufacturing plant is for the manufacture of industrial products, for some product (for example, helium, carbon monoxide, acetylene and methane) it is not feasible for the Part II GMP conditions to be applied to the manufacturing process of the API. Under these conditions the manufacturer of the API shall define the acceptable starting point where the GMP Part II Guidelines shall be applied.

The manufacturer of the active substance shall define the transition point between ISO 9001 and GMP Part II to the API starting material manufacturing process based on a risk management system and/or supplier audit.

Risk assessment and/or supplier audit shall be performed by the manufacturer of the finished medicinal product to identify the specific requirement to demonstrate that the API or API starting material is of suitable quality for the production of the finished product.

Table 2 gives guidance on the identification of the active substance starting material for the medicinal gases that are produced as medicinal product.

Table 2

	GMP Part II		GMP Part I
API starting material	**API chemical manufacturing process**	**API/drug substance**	**Manufacturing finished medicinal product**
Industrial ammonium nitrate	Thermal decomposition and purification	Bulk nitrous oxide	Nitrous oxide in cylinders /bulk storage tank
Purified ambient air	Cryogenic distillation	Bulk oxygen	Oxygen in cylinders / mobile cryogenic vessels / bulk storage tank
Purified ambient air	Cryogenic distillation	Bulk nitrogen	Nitrogen in cylinders / mobile cryogenic vessels / bulk storage tank
Purified ambient air	Cryogenic distillation	Bulk argon	Argon in cylinders
Purified ambient air	Cryogenic distillation	Xenon	Xenon in cylinders
Oxygen	Mixing	Synthetic medical air – premixed buffer	Synthetic medical air in cylinders
Oxygen and Argon Mixtures	Cryogenic Distillation	Oxygen Argon	Argon-oxygen mixture in cylinders
Nitrous oxide and Oxygen	Thermal decomposition and purification / Cryogenic Distillation	Nitrous oxide Oxygen	Nitrous oxide–Oxygen mixture in cylinders
Raw CO_2 as a by-product of industrial processes including: • Syngas from steam reforming, • upgrading biogas, raw • CO_2 from natural sources, • neutralization processes, • flue gases, • fermentation	Purification	Carbon dioxide	Carbon dioxide in cylinders
Pure Carbon monoxide	Mixing	Intermix	Gas mixture in cylinders
Carbon Dioxide and Oxygen	Purification / Cryogenic Distillation	Carbon Dioxide Oxygen	Carbon Dioxide - oxygen in cylinders
Industrial carbon monoxide	purification	Carbon monoxide	Gas mixture in cylinders
Sodium nitrite / Sulphuric acid	Chemical reaction and purification	Nitric oxide	Nitric oxide mixture in cylinders
Industrial nitric oxide	Purification	Nitric Oxide	Nitric oxide mixture in cylinders
Pure nitric oxide	Mixing	Intermix	Nitric oxide mixture in cylinders
Industrial acetylene	Purification	Pure acetylene	Gas mixture in cylinders
Pure acetylene	Mixing	Intermix	Gas mixture in cylinders
Liquid helium	Evaporation and compression	Compressed helium	Helium or helium mixture in cylinders
Compressed helium	Mixing	Intermix	Helium or helium mixture in cylinders
Industrial methane	Purification	Pure methane	Gas mixture in cylinders
Pure methane	Mixing	Intermix	Gas mixture in cylinders

EUROPEAN INDUSTRIAL GASES ASSOCIATION *AISBL*
AVENUE DE L'ASTRONOMIE 30 ♦ B-1210 BRUSSELS
PHONE +32 2 217 70 98 E-mail : info@eiga.eu - www.eiga.eu

Recommendations

Most of the gases used as API starting materials are produced in manufacturing plants where the majority of the product is for industrial use, compared to the smaller quantities required for use as API starting material for medicinal use. Where the application of GMP Part II is not possible, it is replaced by the application of another suitable QMS and supplemented by risk management and/or supplier audit. The manufacturer of active substance is responsible for documenting the rationale for the definition of the point at which production of the active substance begins.

EUROPEAN INDUSTRIAL GASES ASSOCIATION *AISBL*
AVENUE DE L'ASTRONOMIE 30 ♦ B-1210 BRUSSELS
PHONE +32 2 217 70 98 E-mail : info@eiga.eu - www.eiga.eu