DELEGATED ACT ON THE PRINCIPLES AND GUIDELINES OF GOOD MANUFACTURING PRACTICE FOR ACTIVE SUBSTANCES IN MEDICINAL PRODUCTS FOR HUMAN USE
CONCEPT PAPER SUBMITTED FOR PUBLIC CONSULTATION

1. Extension of the Directive on GMP for medicinal products to active substances

Consultation item No 1: Do you agree with this appraisal and approach? Please comment.

EIGA basically agrees with the principle of the extension of the Directive on GMP for medicinal products to active substances. However, we would like to underline some specifications connected to the medicinal gas sector.
In the field of medicinal gases, an Active Substance is any gas or any gas mixture used in the manufacturing of a medicinal product
An "Active Substance Starting Material" is a raw material or intermediate that is used in the production of a gas active substance. In the case of medicinal gases the Active Substance Starting material is a product manufactured in industrial production under a Quality Management System, but not under GMP.
Table 1 gives guidance on the identification of the Active Substance Starting Material for the medicinal gases that are produced as medicinal product.
At the point the API Starting Material enters into the medicinal gases manufacturing process, from then on GMP should be applied to further manufacturing steps.
An industrial production, i.e. a large scale continuous production of industrial products, even from which only a very small fraction is used for ultimate medicinal product manufacturing , cannot conform to GMP as these principles have no relevance to these types of industrial processes

			GMP part I
API Starting Material	**Typical Chemical Manufacturing Process – Industrial Quality Management System**	**API/drug substance GMP part II**	**Typical Manufacturing Finished medicinal product**
Industrial Ammonium Nitrate	Thermal Decomposition and purification or similar	Bulk Nitrous oxide	Nitrous Oxide in cylinder/tank
Purified Ambient Air	Cryogenic distillation	Bulk Oxygen	Oxygen in cylinder /tank
Purified Ambient Air	Cryogenic distillation	Bulk Nitrogen	Nitrogen excipient in cylinder /tank
Oxygen	Mixing	Synthetic medical air –premixed buffer	Synthetic medical air in cylinder
Crude / Tall Oil from steam reforming or natural source or fermentation	Purification or similar	Carbon Dioxide	Carbon dioxide in cylinder , mixture
Pure Carbon monoxide	Mixing	Intermix	Lung function mixture
Crude / Tall Oil from steam reforming or catalytic partial oxidation	Purification	Carbon Monoxide	Lung function mixture
Sodium Nitrite / Sulphuric Acid	Chemical reaction and purification or similar	Nitric oxide	Nitric oxide mixture
Pure Nitric oxide	Mixing	Intermix	Nitric oxide mixture
Industrial Acetylene	Purification or similar	Pure acetylene	Lung function mixture
Pure acetylene	Mixing	Intermix	Lung function mixture
Liquid Helium	Gasification	Compressed Helium	Helium mixture
Compressed Helium	Mixing	Intermix	Lung function mixture
Industrial Methane	Purification or similar	Pure methane	Lung function mixture
Pure Methane	Mixing	Intermix	Lung function mixture

2. Adaptation of regulatory requirements of Directive 2003/94/EC to active substances

2.1. Provisions in Directive 2003/94/EC that would not apply to active substances

Consultation item No 2: Are there other aspects which should be considered? Please comment.

EIGA proposes to add that the manufacturing of an Active Ingredient should follow a quality management system which is "GMP equivalent" such as ISO 9000 plus relevant standard operating procedures to cover the pharmaceutical aspects of the API production.

2.2. Provisions in Directive 2003/94/EC that would need to be amended

Consultation item No 3: Do you consider this list complete? Please comment.

EIGA proposes to add a definition of "GMP equivalent" quality management system:
Quality management system is where the documentation demonstrate that each production batch has been manufactured in conditions at least equivalent to the standards of good manufacturing practice

2.3. Other provisions on active substances that could be added to Directive 2003/94/EC

Consultation item No 4: Do you agree with this specific point? Do you consider that other provisions specific to active substances should be added?

According to the GMP part II (point 7.3), it is not the obligation of the manufacturer of API to control the premises of the manufacturer of the starting material, as these can be industrial production sites. Consequently, EIGA proposes the following:
"*An obligation should be placed on the manufacturer of the active substance to perform a Risk Assessment in order to define the necessary controls required on the incoming starting materials* "

3. Other issues

3.1. Date of transposition of the delegated act

3.2. Date of application of the delegated act

Consultation item No 5: Please comment on section 3. Please raise any other issues or add any other comments you wish to make which have not been addressed in the consultation items set out above.

See point n° 1 above