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BHUTAN STANDARD

Bhutan Standard for Medical Nitrogen

ICS 11.040.10

BHUTAN STANDARDS BUREAU

The National Standards Body of Bhutan

THIMPHU 11001

….., 2021

Price group B

(སྨན་བཅོས་རླུང་སྤྲའི་ཉོ་ཚེན་གྱི་གནད་ཚད།)

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FOREWORD

This Bhutan Standard for Medical Nitrogen was developed by Bhutan Standards Bureau after the draft was finalized by the Pharmaceuticals and Traditional Medicines Technical Committee (TC 05) and approved by the Bhutan Standards Bureau Board (BSB Board) on ….. 2021.

This standard is subject to systematic review after five years to keep pace with the market trends, industrial and technological developments. Any suggestions and further information may be directed to the concerned Technical Committee.

BTS 361: 2021

BHUTAN STANDARD FOR MEDICAL NITROGEN

1 Scope

This standard shall apply to Nitrogen gas manufactured in Bhutan for Medical purpose only.

2 Normative References

There are no normative references in these documents.

3 Terms and Definition

BP : British Pharmacopeia

N_2 : Nitrogen

NLT : Not Less Than

NMT : Not More Than

PPM : Parts per million

V/V : Volume by Volume

4 Content

Minimum 99.5 per cent V/V of N_2, calculated by deduction of the sum of impurities found while performing the test for impurities.

5 Characteristics

Nitrogen is a colourless and odourless gas

6 Impurities Permissible Limits

a) Carbon Dioxide –Maximum 300 ppm V/V
b) Carbon Monoxide –Maximum 5 ppm V/V
c) Oxygen –Maximum 50 ppm V/V
d) Nitrogen Monoxide and Nitrogen Dioxide – Not more than 0.5 ppm V/V (15% RSD)
e) Water –Maximum 67 ppm V/V

7 Identification Test

First Identification 7.1

Second Identification 7.2 and 7.3

7.1 Examine the chromatograms obtained in the assay.

Results: The principal peak in the chromatogram obtained with the gas to be examined is similar in retention time to the principal peak in the chromatogram obtained with reference gas (Nitrogen R1 gas).

7.2 In a 250 ml conical flask replace the air by the substance to be examined. Place a burning or glowing splinter of wood in the flask. The splinter is extinguished.

7.3 In a suitable test tube, place 0.1 g of Magnesium in turnings. Close the tube with a two-hole stopper fitted with a glass tube reaching about 1cm above the turnings. Pass the gas to be examined through glass tube for 1 minute without heating, then for 15 minutes while heating the test tube to a red glow. After cooling, add 5ml of dilute sodium hydroxide solution. The evolving vapours change the colour of moistened red litmus paper to blue.

8 Other Physico-chemical Test

8.1 Assay: Gas Chromatography

Gas to be examined: The substance to be examined.

Reference gas (a): Ambient Air

Reference gas (b): Nitrogen R_1.

Column:

- Material: stainless steel
- Size: l= 2m, Ø = 2mm
- Stationary phase: molecular sieve for chromatography (0.5 nm).

Carrier gas: helium for chromatography.

Flow rate: 40ml/min

Temperature:

- Column- 50° C
- Detection: 130° C

Detection: Thermal conductivity

Injection: Loop injector.

Inject reference gas (a). Adjust the injected volumes and operating conditions so that the height of the peak due to nitrogen in the chromatogram obtained with the reference gas is at least 35 per cent of the full scale of the recorder.

System Suitability:

- The chromatograms obtained show a clear separation of oxygen and nitrogen.
- Calculate the content of N2 in the gas to be examined.

8.2 Carbon Dioxide

Maximum 300 ppm V/V, determined using an infrared analyser.

Gas to be examined: The substance to be examined must be filtered to avoid stray light phenomena.

Reference gas (a): Nitrogen R1

Reference gas (b): Mixture containing 300 ppm V/V of carbon dioxide in nitrogen R1.

Calibrate the apparatus and set the sensitivity using reference gases (a) and (b). Measure the content of carbon dioxide in the gas to be examined.

8.3 Carbon Monoxide

Maximum 5 ppm V/V, determined using an infrared analyser.

Gas to be examined: The substance to be examined must be filtered to avoid stray light phenomena.

Reference gas (a): Nitrogen R1

Reference gas (b): Mixture containing 5 ppm V/V of carbon monoxide in nitrogen R1.

Calibrate the apparatus and set the sensitivity using reference gases (a) and (b). Measure the content of carbon monoxide in the gas to be examined.

8.4 Oxygen

Maximum 50 ppm V/V determined using an oxygen analyser with a detector scale ranging from 0-100 ppm V/V and equipped with an electrochemical cell.

The gas to be examined passes through a detection cell containing an aqueous solution of an electrolyte, generally potassium hydroxide. The presence of oxygen in the gas to be examined produces variation in the electric signal recorded at the outlet of the cell that is proportional to the oxygen content.

Calibrate the analyser according to the instructions of the manufacturer. Pass the gas to be examined through the analyser using a suitable pressure regulator and airtight metal tubes. The process should be operated at the prescribed flow-rates until constant readings are obtained.

8.5 Nitrogen monoxide and Nitrogen dioxide

Not more than 0.5 ppm V/V (15% RSD) determined using a chemiluminescence analyzer.

8.6 Water

Maximum 67 ppm V/V determined using electrolytic hygrometer.

9 Packaging

As per the BP, nitrogen should be kept in approved metal cylinders.

10 Marking and Labelling

Each cylinder shall be marked and labelled with the following:

- **a)** Name of the product (Trade name, Trade mark or Identification mark)
- **b)** Composition
- **c)** Net Weight
- **d)** Batch number
- **e)** Price
- **f)** Manufacturing date
- **g)** Use by date/expiry date
- **h)** Full address of the Manufacturer
- **i)** Use and Handling Instructions
- **j)** Hazard Warnings
- **k)** Disclaimer if any

11 Storage conditions

Store as a compressed gas or liquid in appropriate containers complying with the legal regulations.

Annex A

Test Methods for Medicinal Gases

1. Limit test for Carbon Dioxide in Medicinal Gases

Gases absorb light at one or more specific wavelengths. This property is widely used to allow highly selective measurement of their concentrations. The concentration of carbon dioxide in other gases can be determined by infrared analyzer.

Description and principle of measurement

The infrared analyzer generally consists of a light source emitting broadband infrared radiation, an optical device, a sample cell and a detector. The optical device may be positioned either before or after the sample cell and it consists of one or several optical filters, through which the broadband radiation is passed. The optical device in this case is selected for carbon dioxide. The measurement light beam passes through the sample cell and may also pass through a reference cell if the analyzer integrates such a feature (some use electronic system instead of a reference cell).

When carbon dioxide is present in the sample cell, absorption of energy in the measurement light beam will occur according to the Beer-Lambert Law and this produces a change in the detector signal. This measurement signal is compared to the reference signal to generate an output related to the concentration of carbon dioxide. The generated signal is linearised in order to obtain the carbon dioxide concentration. To prevent the entry of particles into the sensors, which could cause stray-light phenomena, the apparatus is fitted with a suitable filter.

Required Technical specifications

When used for a limit test, the infrared analyzer meets the following technical specifications:

- limit of detection: (generally defined as a signal to noise ratio of 2) maximum 20 % of the maximum admissible concentration;
- repeatability: maximum relative standard deviation of 10 % of the maximum admissible concentration, determined on 6 measurements;
- Linearity: maximum 10 % of the maximum admissible concentration.

The technical specifications must be met in the presence of the other gas impurities in the sample.

2. Limit test for Carbon Monoxide in Medicinal Gases

2.1 Method I

Apparatus: The apparatus (Figure 1) consists of the following parts connected in series:

- a U-tube (U_1) containing anhydrous silica gel impregnated with chromium trioxide;
- a wash bottle (F_1) containing 100 ml of a 400 g/L solution of potassium hydroxide;
- a U-tube (U_2) containing pellets of potassium hydroxide;
- a U-tube (U_3) containing diphosphorus pentoxide dispersed on previously granulated, fused pumice;
- a U-tube (U_4) containing 40 g of recrystallized iodine pentoxide in granules, previously dried at 200°C and kept at temperature of 120°C during the test; the iodine pentoxide is packed in the tube in 1 cm columns separated by 1 cm columns of glass wool to give an effective length of 5 cm;
- a reaction tube (F_2) containing 2ml of potassium iodide solution and 0.15 ml of starch solution.

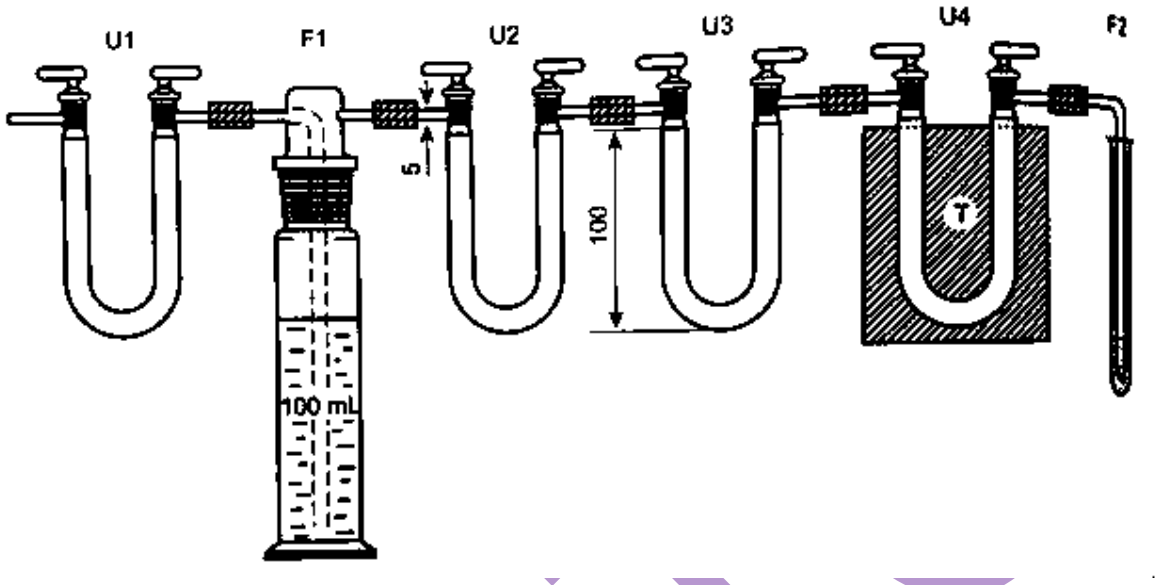

Figure 1: Apparatus for the determination of Carbon Monoxide (Dimensions in Millimeters)

Procedure: Flush the apparatus with 5.0 L of argon R and if necessary, discharge the blue color in the iodide solution by adding the smallest necessary quantity of freshly prepared 0.002 M sodium thiosulfate. Continue flushing until not more than 0.045 ml of 0.002 M sodium thiosulfate is required after passage of 5ml of argon R. Pass the gas to be examined from the cylinder through the apparatus, using the prescribed volume and the flow rate. Flush the last traces of liberated iodine into the reaction tube by passing through the apparatus 1 L of argon R. Titrate the liberated iodine with 0.002 M sodium thiosulfate. Carry out the blank test, using the prescribed volume of argon R. The difference between the volumes of 0.002 M sodium thiosulfate used in the titrations is not greater than the prescribed limit.

2.2 Method II

The concentration of carbon monoxide in other gases can be determined using an infrared analyzer.

Description and principle of measurement

The infrared analyzer generally consists of a light source emitting broadband infrared radiation, an optical device, a sample cell and a detector. The optical device may be positioned either before or after the sample cell; it consists of one or several optical filters, through which the broadband radiation is passed. The optical device in this case is selected for carbon monoxide. The measurement light beam passes through the sample cell and may also pass through a reference cell if the analyzer integrates such a feature (some use electronic system instead of reference cell).

When carbon monoxide is present in the sample cell, absorption of energy in the measurement light beam will occur according to the Beer-Lambert Law and this produces a change in the detector signal. This measurement signal is compared to the reference signal to generate an output related to the concentration of carbon monoxide. The generated signal is linearised in order to obtain the carbon monoxide concentration. To prevent the entry of particles into the sensors, which could cause stray-light phenomena, the apparatus is fitted with a suitable filter.

Required Technical specifications

When used for a limit test, the carbon monoxide infrared analyzer meets the following technical specifications:

- limit of detection: (generally defined as a signal to noise ratio of 2) maximum 20 % of the maximum admissible concentration;
- repeatability: maximum relative standard deviation of 10 % of the maximum admissible concentration, determined on 6 measurements;
- Linearity: maximum 10 % of the maximum admissible concentration.

The technical specifications must be met in the presence of the other gas impurities in the sample.

3. Determination of Oxygen in Medicinal Gases

Oxygen in gases is determined using a paramagnetic analyzer.

Description and principle of measurement

The principle of the method is based on the high paramagnetic sensitivity of the oxygen molecule. Oxygen exerts strong interaction on magnetic fields, which is measured electronically, amplified and converted to a reading of oxygen concentration. The measurement of oxygen concentration is dependent upon the pressure and temperature and, if the analyzer is not automatically compensated for variations in temperature and pressure, it must be calibrated immediately prior to use. As the paramagnetic field of oxygen is linear, the instrument must have a suitable range with a readability of 0.1 % or better.

Required Technical specifications

Calibration of the instrument: Make the setting in the following manner:

- Set the zero by passing nitrogen R1 through the instrument until a constant reading is obtained.
- Set the scale to 100% by passing oxygen R through the instrument at the same flow rate as for nitrogen R1 until a constant reading is obtained.

Assay: Pass the gas to be examined through the instrument at a constant flow rate until a constant reading is obtained. Record the concentration of oxygen in the gas to be examined.

4. Limit test for Nitrogen Monoxide and Nitrogen Dioxide in Medicinal Gases

Nitrogen monoxide and nitrogen dioxide in gases are determined using a chemiluminescence analyzer (figure 2)

The apparatus consists of the following:

- a device for filtering, checking and controlling the flow of the gas to be examined,
- a converter that reduces nitrogen dioxide to nitrogen monoxide, to determine the combined content of nitrogen monoxide and nitrogen dioxide. The efficiency of the converter has to be verified prior to use.
- A controlled flow rate of ozone generator: the ozone is produced by high voltage electric discharges across two electrodes. The ozone generator is supplied with pure oxygen or with

dehydrated ambient air and the concentration of ozone obtained must greatly exceed the maximum content of any detectable nitrogen oxides,

- A chamber in which nitrogen monoxide and ozone can react,
- A system for detecting light radiation emitted at a wavelength of 1.2 µm, consisting of a selective optical filter and a photomultiplier tube.

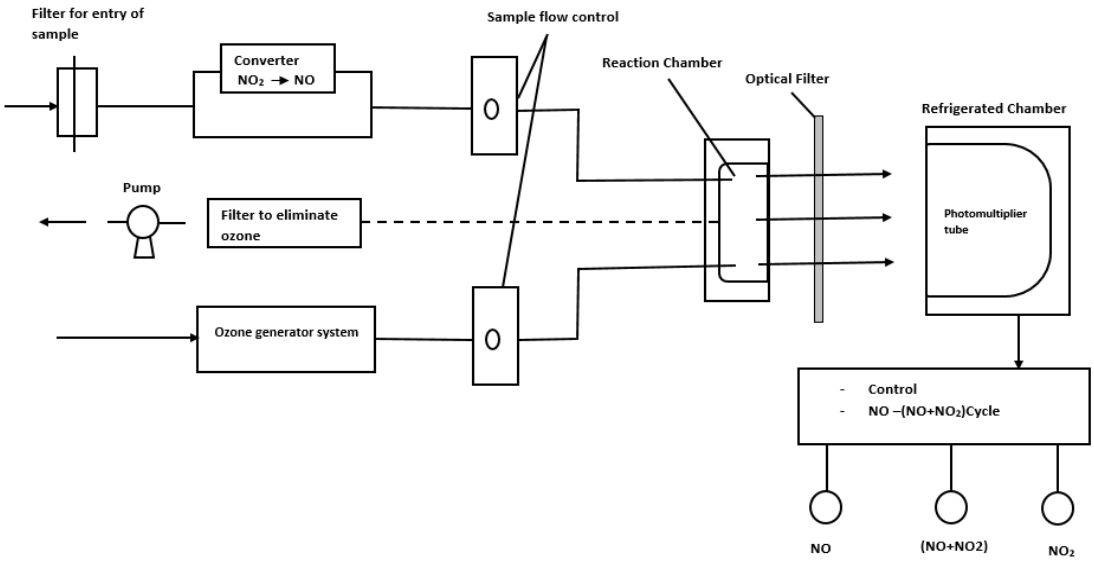

Figure 2: Chemiluminescence Analyzer

5. Determination of Water in Medicinal Gases

Water in gases is determined using an electrolytic hygrometer.

Description and principle of measurement

The measuring cell consists of a thin film of diphosphorous pentoxide, between 2 coiled platinum wires which act as electrodes. The water vapour in the gas to be examined is absorbed by the diphosphorous pentoxide, which is transformed to phosphoric acid, an electrical conductor. A continuous voltage applied across the electrodes produces electrolysis of the water and the regeneration of the diphosphorous pentoxide. The resulting electric current, which is proportional to the water content in the gas to be examined, is measured. This system is self-calibrating since it obeys Faraday's Law.

Take a sample of the gas to be examined. Allow the gas to stabilize at room temperature. Purge the cell continuously until a table reading is obtained. Measure the water content in the gas to be examined; making sure that the temperature is constant throughout the device used to introduce the gas into the apparatus.

The electrolytic hygrometer achieves accurate sample flows by using a mass flow controller to deliver a constant volumetric flow rate to ensure that the water content is determined accurately. The calibration of the mass flow controller is normally performed using nitrogen. When using gases other than nitrogen for calibration, consult the manufacturer's instructions for the appropriate conversion factors and ensure that the correct cell is used for the type of gas to be examined.

6. Gas Detector Tubes (Alternate Test Methods)

Gas detector tubes are cylindrical, sealed tubes consisting of an inert transparent material and are constructed to allow the passage of gas. They contain reagents adsorbed onto inert substrates that are suitable for the visualization of the substance to be detected and, if necessary, they also contain preliminary layers and/or adsorbent filters to eliminate substances that interfere with the substance to be detected. The layer of indicator contains either a single reagent for the detection of a given impurity or several reagents for the detection of several substances (monolayer tube or multilayer tube).

The test is carried out by passing the required volume of the gas to be examined through the indicator tube. The length of the colored layer or the intensity of a color change on a graduated scale gives an indication of the impurities present.

The calibration of the detector tubes is verified according to the manufacturer's instructions.

Procedure: Examine according to the manufacturer's instruction or proceed as follows:

The gas supply is connected to a suitable pressure regulator and needle valve. Connect the flexible tube fitted with a Y-piece to the valve and adjust the flow of gas to be examined to purge the tubing in order to obtain an appropriate flow (Figure 3). Prepare the indicator tube and fit to the metering, following the manufacturer's instructions. Connect the open end of the indicator tube to the short leg of the tubing and operate the pump by the appropriate number of strokes to pass a suitable volume of gas to be examined through the tube. Read the value corresponding to the length of the colored layer or the intensity of the color on the graduated scale. If negative result is achieved, indicator tubes can be verified with a calibration gas containing the appropriate impurity.

In view of the wide variety of available compressor oils, it is necessary to verify the reactivity of the oil detector tubes for the oil used. Information on the reactivity for various oils is given in the leaflet; the tube manufacturer must verify the reactivity and if necessary, provide a tube specific for this oil.

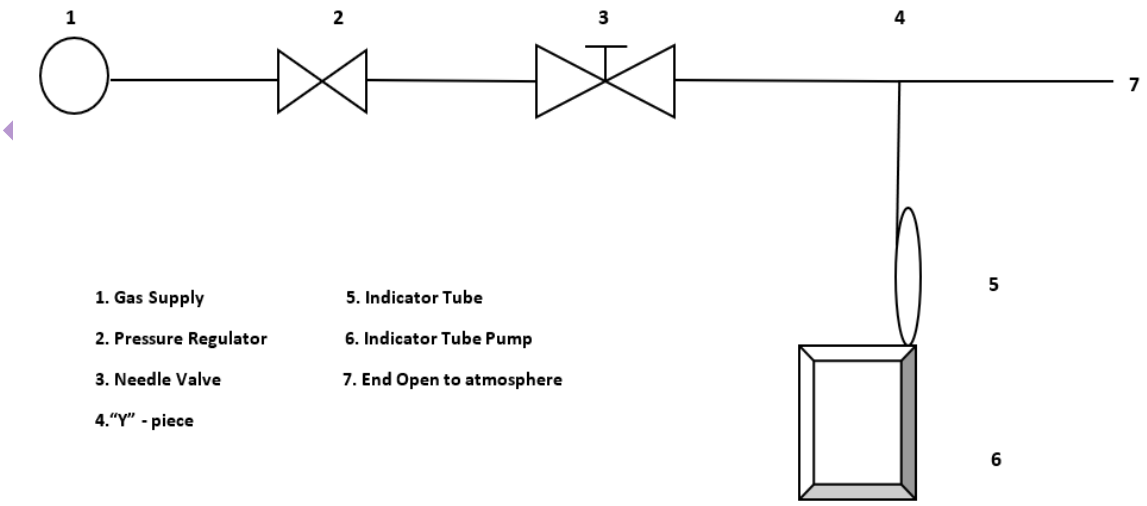

Figure 3: Apparatus for gas detector tube

Arsine detector tube

Sealed glass tube containing adsorbent filters and suitable supports for the gold salt or other appropriate indicator. The minimum value indicated is 0.25 ppm or less with a relative standard deviation of at most 20 percent.

Carbon Dioxide Detector Tube

Sealed glass tube containing adsorbent filters and suitable supports for hydrazine and crystal violet indicators. The minimum value indicated is 100 ppm with a relative standard deviation of at most 15 per cent.

Carbon Monoxide Detector Tube

Sealed glass tube containing adsorbent filters and suitable supports for di-iodine pentoxide, selenium dioxide and fuming sulfuric acid indicators. The minimum value indicated is 5 ppm or less, with a relative standard deviation of at most 15 per cent.

Hydrogen sulfide detector tube

Sealed glass tube containing absorbent filters and suitable supports for an appropriate lead salt indicator. The minimum value indicated is 0.2 ppm or less, with a relative standard deviation of at most 10 per cent.

Nitrogen Monoxide and Nitrogen Dioxide Detector Tube

Sealed glass tube containing adsorbent filters and suitable supports for an oxidizing layer [Cr(VI) salt] and the diphenylbenzidine indicator. The minimum value indicated is 0.5 ppm with a relative standard deviation of at most 15 per cent.

Oil Detector Tube

Sealed glass tube containing adsorbent filters and suitable supports for the sulfuric acid indicator. The minimum value indicated is 0.1 mg/m3 with a relative standard deviation of at most 30 percent.

Phosphine detector tube

Sealed glass tube containing absorbent filters and suitable supports for the gold salt or other appropriate indicator. The minimum value indicated is 0.2 ppm or less, with a relative standard deviation of at most 20 per cent.

Sulfur Dioxide Detector Tube

Sealed glass tube containing adsorbent filters and suitable supports for the iodine and starch indicator. The minimum value indicated is 0.5 ppm with a relative standard deviation of at most 15 per cent.

Water Vapour Detector Tube

Sealed glass tube containing adsorbent filters and suitable supports for the magnesium perchlorate indicators. The minimum value indicated is 67 ppm or less, with a relative standard deviation of at most 20 per cent.

Annex B

R Values

SL NO	GAS	MOLECULAR WEIGHT	CONTENT	REFERENCE
1	Argon R	Ar=39.95	Minimum 99.995% v/v	BP 2019 (Appendix IA, V-A36)
2	Argon R1	Ar=39.95	Minimum 99.99990% v/v	BP 2019 (Appendix IA, V-A36)
3	Nitrogen R1	N2=28.01	Minimum 99.999%v/v Carbon monoxide less than 5ppm Oxygen less than 5ppm	BP 2019 (Appendix IA, V-A108)
4	Oxygen R	O2=32.00	Minimum 99.99% v/v Nitrogen and Argon: less than 100ppm Carbon dioxide: less than 10ppm Carbon monoxide: less than 5 ppm	BP 2019 (Appendix IA, V-A111)
5	Oxygen R1	O2=32.00	Minimum 99% v/v	BP 2019 (Appendix IA, V-A111

BIBLIOGRAPHY

[1] British Pharmacopeia 2019

[2] European Pharmacopeia

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