

## **Outline of Manufacturing Process and Quality Control Water-<sup>18</sup>O**

### **1. Introduction**

Scopus Research has been appointed as authorized supplier of Water-<sup>18</sup>O manufactured by the Taiyo Nippon Sanso Corporation (TNSC), Japan's largest oxygen manufacturer. Together, we provide Oxygen-<sup>18</sup>O enriched water (Water-<sup>18</sup>O) with the highest quality as a precursor of <sup>18</sup>F labeled compounds for Positron Emission Tomography.

TNSC has developed "Ultra Pure Oxygen Distillation Process" for the separation of Oxygen-<sup>18</sup>O. In this process Oxygen-<sup>18</sup>O gas is separated from ultra high purity Oxygen-<sup>18</sup>O gas by cryogenic distillation, and then this enriched Oxygen-<sup>18</sup>O is converted to water- by hydrogenation with high purity hydrogen. The Water-<sup>18</sup>O is manufactured under strict quality control at TNSC's Chiba factory, ISO9001 certified for Oxygen, Nitrogen and Argon. The following processes were validated through 6 (six) actual production batches based on our GMP established to assure highest quality.

### **2. Production**

#### **2.1. Isotope Separation**

Oxygen gas, a raw material, is separated from air by a large air separation plant and is purified to ultra pure oxygen with the chemical purity of over 99.999999% (eight nines). Oxygen-<sup>18</sup>O is enriched with this ultra pure oxygen to the isotopic purity of over 97atom% by a dedicated plant. All of these processes are performed by cryogenic distillation and monitored with a fully automated system around the clock all the year.

#### **2.2. Hydrogenation**

Enriched Oxygen-<sup>18</sup>O gas is reacted with high purity hydrogen to produce water-<sup>18</sup>O, while monitoring its enrichment of over 97atom% with Q-MS.

#### **2.3. Dispensing**

Water-<sup>18</sup>O obtained in the previous process is dispensed through sterilized filter into cleaned and sterilized bottles with a high-precision syringe pump at a clean bench installed in a clean room. The loaded bottles are sealed with rubber stoppers and aluminum crimp caps.

#### **2.5. Sterilization**

The bottles loaded with water-<sup>18</sup>O is then sterilized by autoclave at 121degree Celsius , for 20 minutes.

#### **2.6. Packaging**

Sterilized products obtained in the previous process are properly labeled and packaged as final products after ensuring that the products conform to the specifications by the following quality analyses.

### **3. Quality Analyses**

#### **3-1. Sampling**

All the analytes are sampled from each production batch of final products in order to verify the quality of the final products.

#### **3.2. Oxygen Isotopes**

Water-18O sampled from final products is electrolyzed in a air-tight cell. The resulting oxygen gas is introduced into Q-MS to measure mass numbers of 32-36 to calculate isotopic enrichment.

(Precision of 0.1%)

#### **3.3. Metals**

With ICP-MS, calibration curve is prepared by measuring blank and standard solution. The sample is diluted by 500 folds before applying.

(Precision : 3%)

#### **3.4. Ions**

With ion chromatography, calibration curve is prepared by measuring blank and standard solution. The sample is diluted by 10 folds before applying.

(Precision: 3%)

#### **3.5. pH**

After calibration with standard solutions of pH 4.01, 7.00 and 9.21, the sample is measured by pH meter under nitrogen environment.

( Precision: 0.01)

#### **3.6. Conductivity**

Conductivity meter is calibrated with blank and standard solutions, the sample is measured.

(Precision: 0.5%)

#### **3.7. TOC**

Calibration curves are prepared by measuring potassium phthalate for total carbon, and sodium carbonate and sodium hydrogen carbonate for inorganic carbon by TOC analyzer. Then the sample is measured and the TOC is calculated according to the calibration curves.

(Precision: 10%)

#### **3.8. Microorganisms**

The sample is passed through 0.22mm filter. The filter is applied onto tryptic soybean agar media. The media are incubated for 5 days then the numbers of colonies are counted.

#### **3.9. Pyrogenicity**

Pyrogenicity is measured using LAL kit.