Humidity measurements in pharmaceutical production

Power engineer Wolfgang Wilde is employed at Pfizer GmbH's Gödecke pharmaceutical plant in Freiburg, Germany, and is responsible for calibrating humidity probes used to regulate and monitor process and room conditions.

Testo: Mr Wilde, strict quality assurance is of great importance in pharmaceuticals production. Why is particular attention paid to humidity in this regard?

Wilde: In our factory we manufacture mainly tablets and capsules. Determining the exact humidity in the product is important for many different reasons. The humidity content needs to be kept as low as possible to prevent the formation of micro-organisms whilst a certain level of humidity is required due to the nature of the process.

Testo: How can one ensure that the humidity or the mass ratio of water in the product is actually correct?

Wilde: From a physical point of view, pharmaceuticals consist mainly of hygroscopic materials. These are substances which absorb, retain or release water and which are continually attempting to achieve a humidity equilibrium with the surrounding air. The individual production processes therefore take place in precisely conditioned process air and sometimes ambient air.

Testo: Do the same conditions apply to all products and production stages?

Wilde: It's no simple process to get from the base material to the formulas to the finished pharmaceutical. The products are run through many different processes where different process conditions may be necessary, depending on the task. For this reason, manufacturing is mainly carried out in enclosed processing stations with precisely controlled process conditions. The range here extends from around 15 to 95 %RH (relative humidity). The humidity value tolerances need to be kept less than ±10 %, and sometimes even under ±5 %. The air conditioned production rooms are also modified according to the procedures in question.

Testo: So the complex manufacturing techniques require the humidity to be measured at many different points?
Wilde: Both the air conditioned rooms and the processing stations have been equipped with integrated humidity sensors for monitoring and regulation purposes.

Testo: How do you ensure the correct functioning of these sensors in terms of quality assurance?
Wilde: For room conditioning we use handheld instruments called thermo-hygrometers testo 615, 625 and 635. These are used in the production rooms on a daily basis to check and document the room humidity produced by the air conditioning system, to an accuracy of ±3 %RH. In accordance with our guidelines on quality assurance these instruments are calibrated every 3 months using a testo 650 reference humidity measuring instrument. This also applies to data loggers used to take and store measurements over extended periods of time, such as for the qualification of new air conditioning systems or in storage or dispatch containers. In addition, the humidity probes which are integrated into the process are regularly calibrated using reference meters.

Testo: This calibration work is carried out using testo 650 reference humidity measuring instruments. Who carries out these calibrations and why do you use this device in particular?

Wilde: All test specimens, i.e. handheld instruments, data loggers and process probes come for calibration to our own calibration laboratory. In this lab we have a humidity generator from Testo. This enables us to set required humidity levels accurately. This means that the humidity measured by the test specimen can be compared to the value measured by the reference instrument. The testo 650 with the patented precision humidity probe provides a sensor accuracy of ±1 %RH. This level of accuracy is required in order to check or tune the process sensors to a tolerance of ±4 %, for example. This is also necessary in order to guarantee the required process tolerance of max. ±10 %.

Testo: How can you be sure that the measurements from the reference instruments are accurate?

Wilde: Reference instruments and probes are sent to Testo at regular intervals and calibrated there in the accredited DKD lab. The calibration results achieved there have a very high level of reliability and international validity. Calibrated testo 650 instruments therefore represent our factory standard. The long-term stability of the probes is also an important factor. This gives us the security of knowing that the measuring accuracy of the probes and therefore the calibration results remain stable.

Testo: The calibration of the mobile and stationary humidity sensors using reference instruments with a DKD certificate ensures a complete and reliable quality control system. Are there any other reasons for using Testo instruments to carry out the humidity measurements?

Wilde: The important factor for us is their high level of precision and reliability, confirmed by international inter-laboratory testing, in particular of the reference instruments. Another benefit is the accreditation of Testo's DKD laboratory, which means that the instrument manufacturer is also the test laboratory. Whenever adjustment and standardisation work are required, we can therefore take advantage of the fast and reliable Testo calibration service.

Testo in discussion with Power Engineer Wolfgang Wilde

Requirements

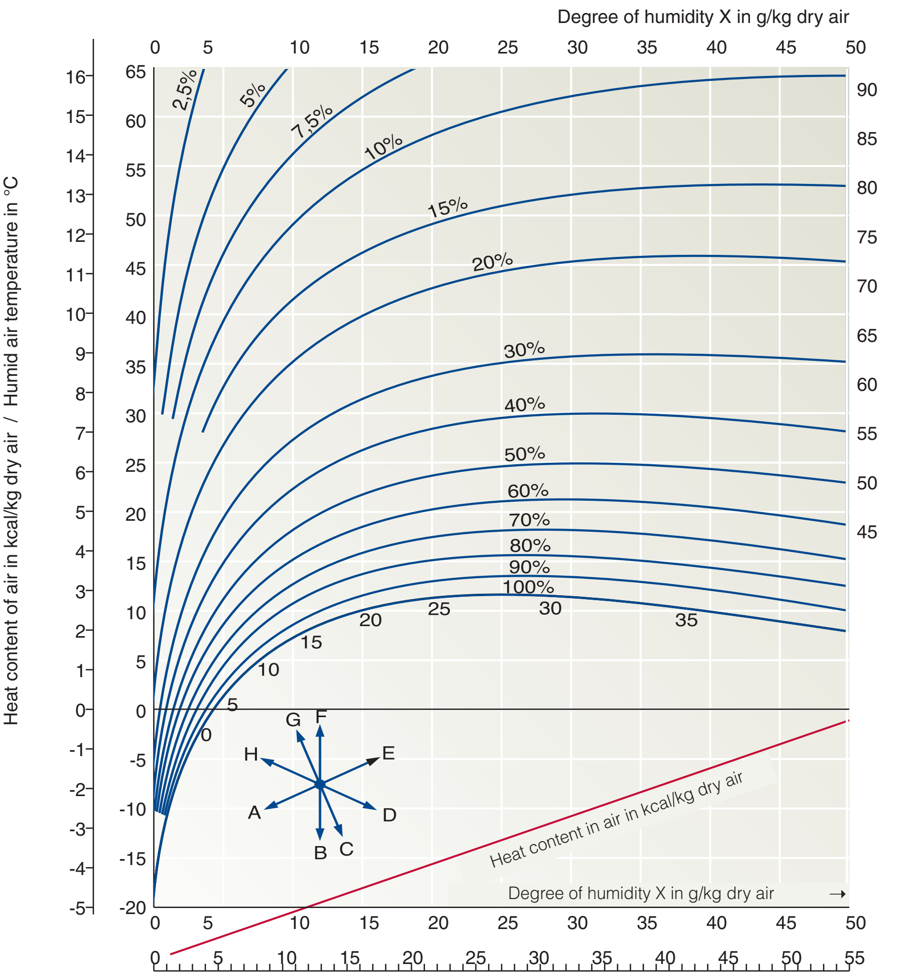
Gas or air humidity measurements are becoming more and more important. Constant improvements to the technical processes, higher demands on quality and energy saving require an accurate, stable and affordable measuring procedure to measure air humidity.

Different measuring methods

Hair hygrometer	Psychrometer	Dew point mirror	Capacitive humidity sensor
The hair hygrometer is one of the oldest methods used to measure humidity. The length of the hairs changes in accordance with the ambient humidity. This change is indicated as relative humidity by mechanical means.	A temperature probe covered with a damp cotton sleeve cools down as a result of evaporation. A second temperature probe measures the ambient temperature. The ambient humidity can be determined from the difference in temperature.	A mirror is cooled until it shows condensation after having reached the dew point temperature. The condensation on the mirror is monitored and the dew point is then measured.	A condensator changes its capacity in accordance with the ambient humidity.
Advantages	**Advantages**	**Advantages**	**Advantages**
– simple to use measuring engineering with low installation costs – Low cost applications	– if used with great care a very accurate measurement of 2 to 3 %RH is possible	– Wide measuring range – Highly accurate	– Affordable, quick-action and accurate measurement (up to ±1%RH) – Wide measuring range (0 to 100 %RH, -40 to +180°C) – Long-term stability – Small and portable
Disadvantages	**Disadvantages**	**Disadvantages**	**Disadvantages**
– High maintenance costs – Frequent regeneration of the hairs – Can be used only from 15 % to 85 %RH and up to max. 50 °C – Highly inaccurate, not definable – Slow measurements	– Cannot be used for multipoint measurements – Time-consuming handling (must be moistened with distilled water before nearly every measurement) – Before every important measurement, the temperature must be adapted to the ambient temperature and the sleeve should be changed	– Time-consuming, expensive method – Not battery-operated – Heavy (non-portable measuring instrument) – Highly accurate temperature measurement required – Slow adaptation time – Large bench-top instruments	**In the past…** capacitive sensors were regarded as unreliable and unstable. **Today…** Testo`s capacitive sensor has been tested worldwide and has established itself in industrial measuring technology (inter-laboratory test, stability test on page 84/85).

Different measuring methods

Mollier diagram



Water vapour pressure in torr

A = Cooling and dehumidification
B = Cooling
C = Cooling and humidification
D = Humidification
E = Heating and humidification
F = Heating
G = Heating and humidification
H = Dehumidification

All of the parameters from the Mollier diagram are automatically shown by testo 650.

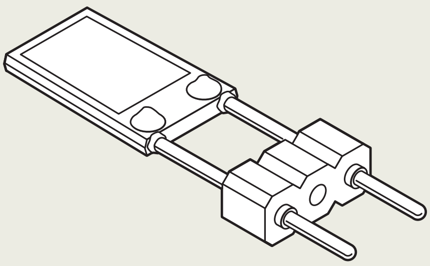
Testo humidity sensor

Testo has succeeded in increasing the range of applications for capacitive sensors with the humidity sensor which it developed:

- Application temperatures to +180 °C
- Dew point measurement from -50 to +100 °C
- Long-term measurement under extreme conditions
- Highly accurate in the high humidity range (>95%RH)

The outstanding characteristics of the Testo humidity sensor are as follows:

- Precision
- Long-term stability
- Temperature resistance
- Robustness



Absolute humidity, g/m^3
Absolute humidity indicates how many grammes of water are in a cubic metre of air or gas.

Relative humidity, %RH
Relative humidity is a % figure indicating how many percent of the maximum amount of water vapour is currently in the air. The maximum possible amount depends mainly on the temperature. Relative humidity always refers to a temperature.

Psychrometer wet-bulb temperature, °C
Evaporation causes cooling. The temperature in a thermometer drops if enclosed in a damp cloth on account of the cold due to evaporation. Evaporation depends on the surrounding relative humidity and air velocity. A second thermometer, stored in a dry place, can measure the difference in temperature. Unit: [°C, °F]

Degree of humidity X
The degree of humidity X is defined as the mass ratio of water to air (dry gas). Unit: [g/kg]

Dew point, td
The dew point is a temperature value given in °C. As the temperature sinks, the ability of the air or gases to hold water is reduced. The dew point is the temperature at which the water is condensed.

Partial pressure in water vapour, pas
Level of overall pressure in a room which can be determined by the water vapour. Unit: [mbar, hPa]

Enthalpy, heat content, i
The heat content is the heat energy which the moist air has saved.
The energy is set to 0 at 0 °C.
Enthalpy is important for calculating cooling and heating capacity. Differential measurements e.g. in front of and behind heat exchangers are of particular interest.

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Stability tests

More than 100 sensors were subjected to the test conditions listed below. Measurements were carried out on the sensors in the climatic test chambers before and after.

Why you should choose humidity measuring instruments from Testo

1. 24 hours in cooled (20 °C) flue gas at 90 %RH:
   The flue gas of an oil burner (O_2 = 5.9 %, CO = 45 ppm, NO_x = 50 ppm, SO_2 = 70 ppm) was extracted from the stack and was submersed in a container with sensors and then automatically cooled
2. 2 hours in the smoke from 3000 cigarettes/m^3
3. 5 minutes in tap water
4. 12 months in a weather house, July ’90 - July ’91
5. 5 minutes submersed in isopropyl alcohol
6. 3 months in silica gel at 20 °C/0.1 %RH
7. 3 months at -25 °C/95 %RH
8. 3 months in 92 %RH (at 20 °C)
9. Shock test:
   16 hours at -20 °C → 10 min boiling water → still wet in -20 °C for 1 hour → forced-air oven at +125 °C for 3 hours → chill in frozen water at +4 °C and leave soaking for 5 min → heat for 5 min at 125 °C
10. 9 months in a cheese dairy: 7 °C/ 70 %RH
11. 9 months in a hen house: 15 °C / 80 %RH
12. 9 months in a pig sty: 17 °C/70 %RH
13. 5 hours in a forced air oven: 150 °C / 10 %RH
14. 30 days at high humidity: 20 °C / 98 %RH
15. 7 days in a wood drying process: 20 to 80 °C/90 to 15 %RH

The stability tests mentioned above did not influence the display by more than -1 %RH.

Applications

Over 100,000 Testo humidity sensors are used throughout the world in portable hand-held instruments, in data loggers and in stationary transducers for the following applications:

- Tobacco industry
- Monitoring conditions in data processing rooms
- Storage of sensitive products
- Gardening shops, greenhouses
- Food sector
- Timber production
- Pharmaceutical industry
- Drying processes and many more

Measuring the dew point td:

- In compressed air
- In CO_2
- In natural gas
- In O_2

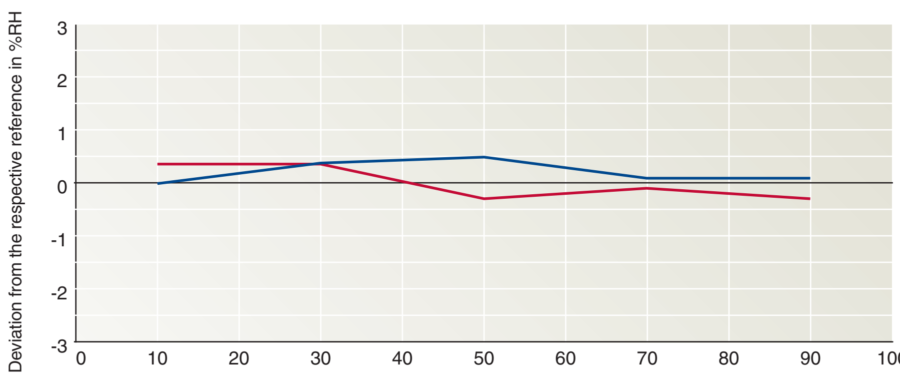
Technical data

Measuring range:	0 to 100 %RH
Temperature range:	-40 to +180 °C
Hysteresis (3 hour cycle 15 to 90 to 15 %RH):	< 1.0 %RH
Response time t90:	< 15 seconds
Temp. dependency:	0.03 %RH/°C
Dew point td	-50 °C to +100 °C
Reproducibility:	< 0.3 %RH

Reference humidity probes for highest precision

- Accuracy ± 1 %RH
- 2 year guaranteed long-term stability under normal conditions

Long-term stability of the Testo humidity sensor



PTB; 04.96 NRCCRM; 10.2000 (see next page)

Inter-laboratory tests

Three precision probes were subjected to extensive inter-laboratory tests by the PTB in Berlin, NIST in the USA, the French national institute CETIAT, the Italian institute IMGC, the English national institute NPL, the Spanish national institute INTA, JQA in Japan, KRISS in Korea, NRCCRM in Peking and in Testo's DKD calibration laboratory. The results confirm an accuracy of ±1 %RH for the probes, as indicated by Testo.

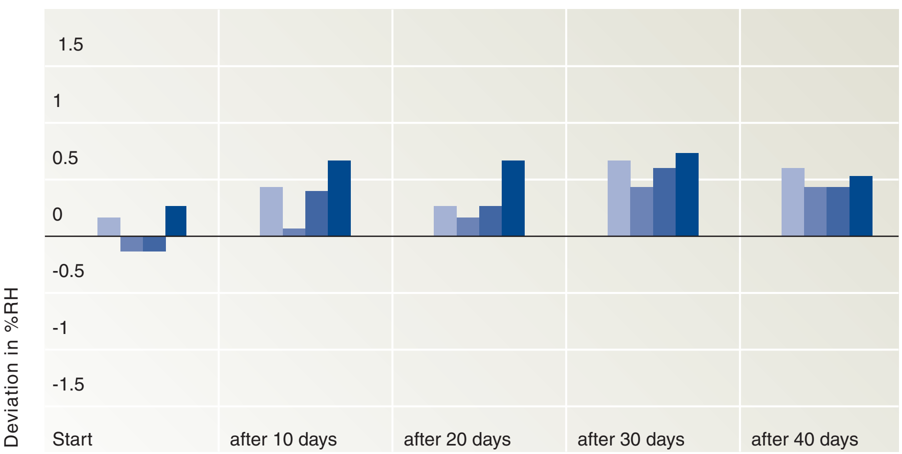
PTB: Physikalisch Technische Bundesanstalt, Berlin, Dr. G. Scholz, Test No. PTB-3.12-1210.96
CETIAT: Centre Technique des Industries Aérauliques et Thermiques, Villeurbanne, B. Cretinon, Test No. 96 1066 1A
NIST: National Institute of Standards and Technology, Gaithersburg, Dr. P. Huang, Test No. H-4608
IMGC: Istituto Di Metrologia „G. Colonetti", Torino, Antonio Actis, Test No. 556/97
NPL: National Physical Laboratory UK, M. Stevens, Test No. 08C043/98020
INTA: Instituto Nacional de Técnica Aeroespacial, Madrid, Dr. R. Benyon, Test No. 0048/0049
JQA: Japan Quality Assurance Organization, Tokyo, Takashi Sugiyama, Test No. 138-0003
KRISS: Korea Research Institute of Standards and Science, Seoul, Dr. H. Nham, Test No. 02491-001
NRCCRM: National Research Center for Certified Reference Materials, Peking, Yi Hong, Test No. 2000-039-292

Reference humidity probes in tests

Reference	Reference	Actual humidity		Actual temperature	
%RH	°C	Probe 1	Probe 2	Probe 1	Probe 2
10.19	25,06	9.8	10.1	25.1	25.0
30.08	25.01	30.0	30.3	25.1	25.0
49.90	25.03	49.9	50.2	25.1	25.0
69.82	25.01	69.7	70.1	25.1	25.0
89.68	25.03	89.8	90.3	25.1	25.0

Extract from the NIST report (National Institute of Standards & Technology, Test No. 4608)

High temperature humidity probes in long-term tests

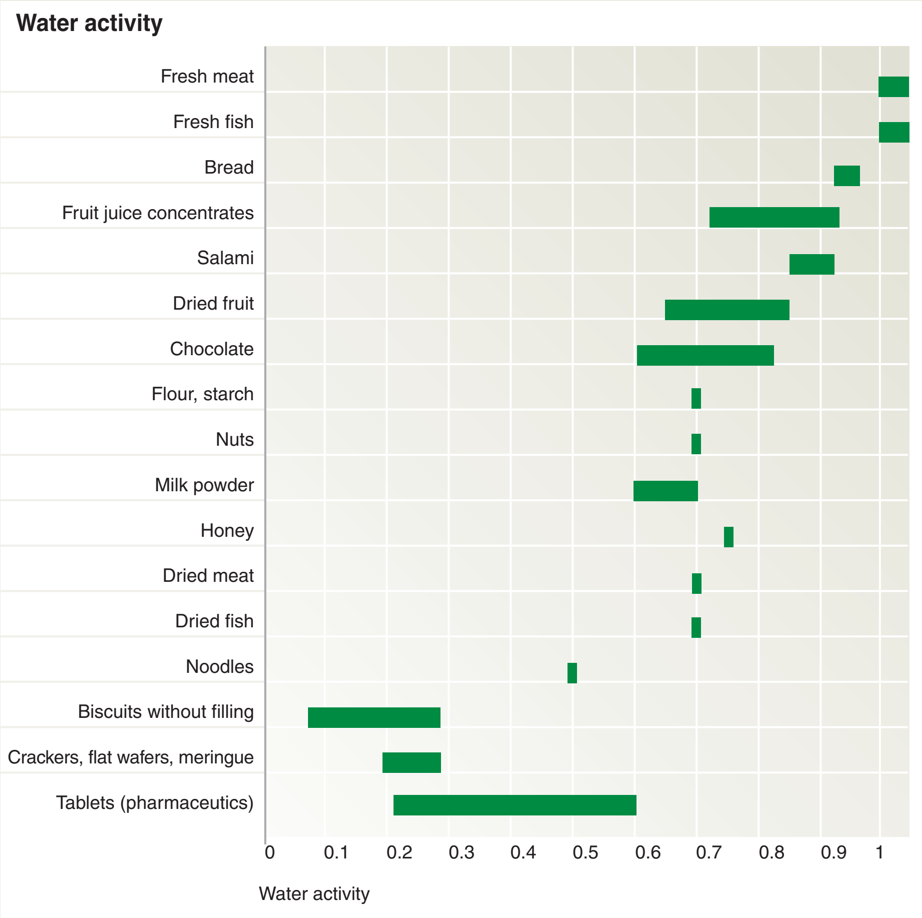


Four high temperature humidity probes in long-term test at +80 °C and 90 %RH
Test result after 10 days´ respective long-term use: maximum deviation < 1%RH!

aw value (water activity)
The aw value contains information on chemically non-bonded water. Measurement is based on the equilibrium moisture content. In a closed room where there is a proportionally lower amount of air than solid matter, the free water contained in the solid matter determines the relative moisture of the ambient air. The water activity (aw value) is practically the same as the equilibrium moisture in a closed room. However, it is not given in the ranges 0 to 100 %RH, instead it is expressed as 0 to 1 aw. aw = 0 applies to anhydrous substances, aw = 1 applies to pure water. Since water activity depends on temperature, the reference temperature must always be given.

Equilibrium moisture
Substances which take in and retain or release water are termed hygroscopic. Hygroscopic substances always try to establish an equilibrium moisture content with the ambient air. The water in a hygroscopic substance causes an increase in the vapour pressure on the surface of the substance. If the water vapour pressure on the surface of the substance is the same as that of the ambient atmosphere, this is known as equilibrium moisture. Any difference in these two pressures results in the exchange of water.

Water content
Water content is the amount of water in a substance in relation to its solid matter. The unit is given in weight per cent. The water content is only of interest if a certain substance is sold according to weight.



Water activity of different products

The reference measurement system, setting new standards in the measurement of aw
Accuracy of measurement ± 0.01 aw. Reproducibility of the measurement ± 0.003 aw.
The accuracy of the precision sensor has been proven in international interlaboratory tests!

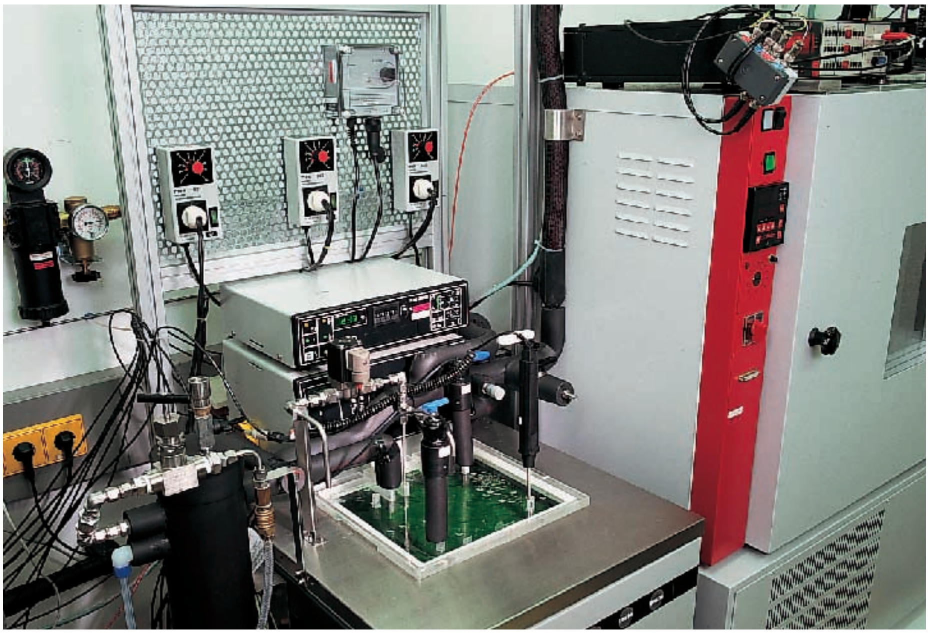
- Long-term stability of the measurement for years, i.e. frequent, time-consuming readjustments are no longer necessary.
- Measuring system traceable to national standards. Supplied with DKD calibration certificate if required. This also gives assurance in legal questions.
- Uncomplicated and reliable documentation of the measured results via attachable printer or on PC.

Two-pressure humidity generator

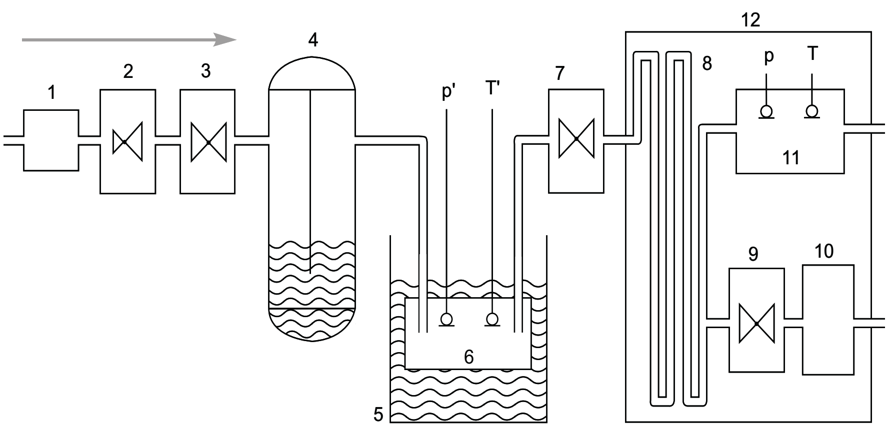
The generator is divided into a high-pressure part (up to 8 bar) and a low-pressure part (atmospheric pressure). The compressed, dry air flows into a humidifier and is saturated up to 100 percent with water. Excess water is then removed from the air in the saturator at precisely determined temperature and pressure values. The water content of the air can then be ascertained or set accurately. The compressed air with the precisely determined quantity of water is then returned to atmospheric pressure and proceeds to a measuring chamber. The relative humidity drops significantly during this process, as the water molecules are distributed across a larger volume. In other words, the higher the pressure in the high-pressure part of the generator, the lower the humidity levels which can be set in the measurement box. The humid air adopts precisely the temperature of the heat chamber as it passes through a long pipe system. This temperature determines the value of the relative humidity in the measurement box. The relative humidity is therefore determined by the pressure and the temperature in the saturator and the measurement box.

Comparative measurements in the conditioning cabinet

An appropriate conditioning cabinet provides any temperature/humidity combination with high stability. The test object to be calibrated is exposed to this temperature and air humidity. At the same time, a factory or working standard measures the actual conditions in the conditioning cabinet. This means that many different kinds of humidity testing objects, just as with temperature calibration in a liquid, can be calibrated according to customer specifications.



The two-pressure humidity generator - An overview



1 Filter	5 Thermostat pan	9 Regulating valve	12 Thermal cylinder
2 Pressure reducer	6 Saturator	10 Condensation level hygrometer transfer standard	p Pressure
3 Pressure regulator	7 Regulating valve		T Temperature
4 Humidifier	8 Pipe register	11 Measurement box for test specimens	

Excerpt from the accreditation notes for DKD laboratory 11201

Measurements or object to be calibrated	Measuring range	Meas. conditions	Meas. uncertainty
Dew point temperature hygrometer with direct measurement of dew point temperature	-20 °C to +70 °C	2-pressure/2-temp. generator	0.05 K
Relative humidity Hygrometer, No psychrometers	5 % to 40 % < 40 % to 80 % < 80 % to 95 %	2-pressure/2-temp. generator Temperature range: 5 °C to 70 °C	0.2 % 0.3 % 0.4 %
Fixed point cell	According to manufacturer specs	In temperature chamber	1.0 %
Hygrometer	5 % to 30 % < 30 % to 60 % < 60 % to 95 %	In conditioning cabinet temperature range: < 25 °C to 50 °C	0.6 % 1.1 % 1.8 %