

Aspects of the ICH-compliant Storage

for Stability Tests

Speaker: Dipl.-Ing. Volker Rubarth



- 1** **Product Selection:**
Requirements Specification /
Functional Specification
- 2** **Qualification:**
From the DQ to the PQ
- 3** **Operation:**
Monitoring and Failure Management

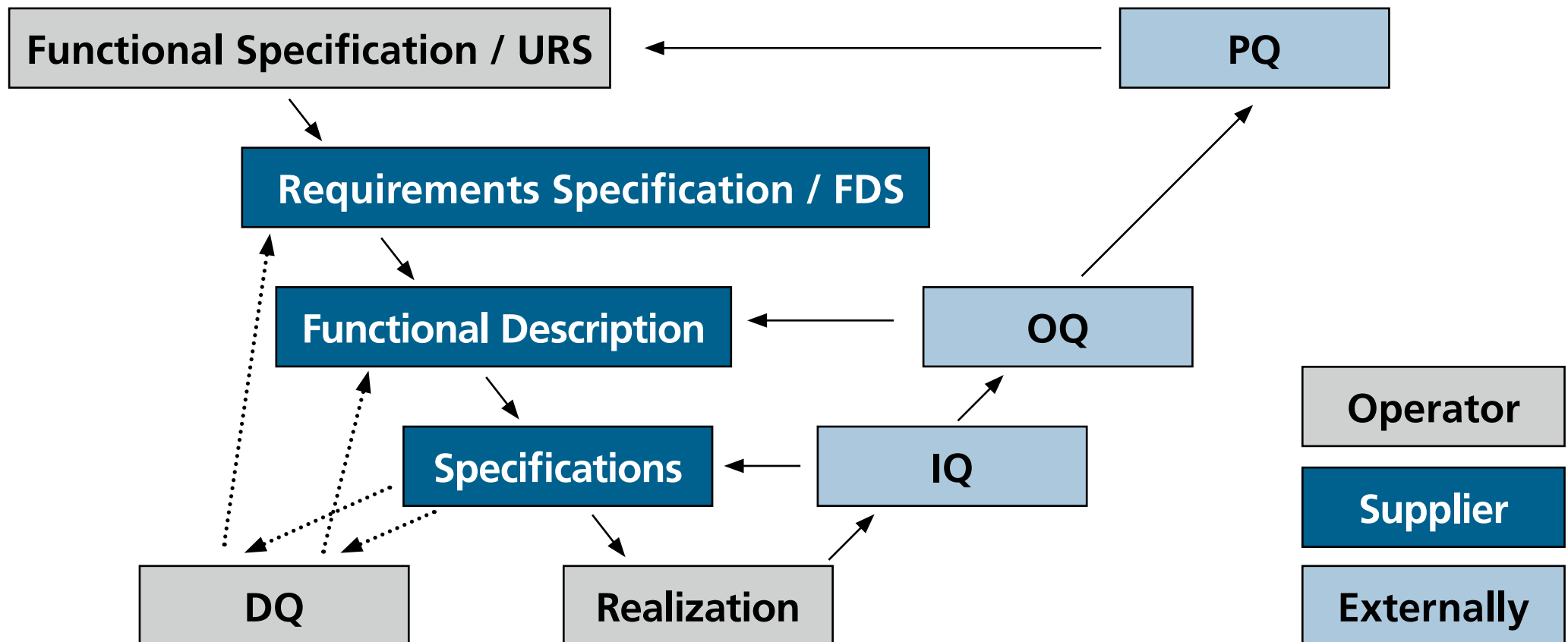
Requirements Specification / Functional Specification

Selection of Suitable Products

- Dualism Requirements Specification- Functional Specification
- The Requirements Specification:
WHAT and **FOR WHAT** shall something be done?
- The Functional Specification:
WHAT and **WITH WHAT** shall something be realized?



Model V



Requirements Specification:

- URS = User Requirements Specification
„...requirements stipulated by the principal concerning the deliveries and performances of a contractor“
- Requirements specification
- Preparation by the principal
- Use for tender and forwarding to possible suppliers
- As general as possible and as restrictive as necessary
- The contractor shall develop optimal solutions – too precise requirements are restrictive
- Verifiable performances for the formal approval

Structure of the Requirements Specification:

- Introduction/General
- Requirement Profile
- Technical Details:
 - Required Volume
 - Maintenance air circulation in loaded condition for temperature distribution and humidity distribution (PQ) in space
 - Dimensions of the samples (important for existing boxes)
 - Consideration of the weights, particularly in case of liquid forms (reinforced shelves)

A bad example for a requirements specification was:

- Please offer a climatic test cabinet for the stability test
- It shall have a big volume

In this case, verifiable data are missing, such as:

- **Maximum dimensions**
- **Volume**
- **Climatic values**
- **Accuracy for the qualification**

Overloaded Cabinet – Fan obstructed



Calculate the size:

- Long-term stability test 25 °C / 60 % rel. humidity (24 months storage)
- Accelerated stability test 40 °C / 75 % rel. humidity (6 months storage)
- Size ratio 4:1

Determination of the size:

- Selection of 6 test room volumes:
from 210 – 1700 litres, otherwise chambers

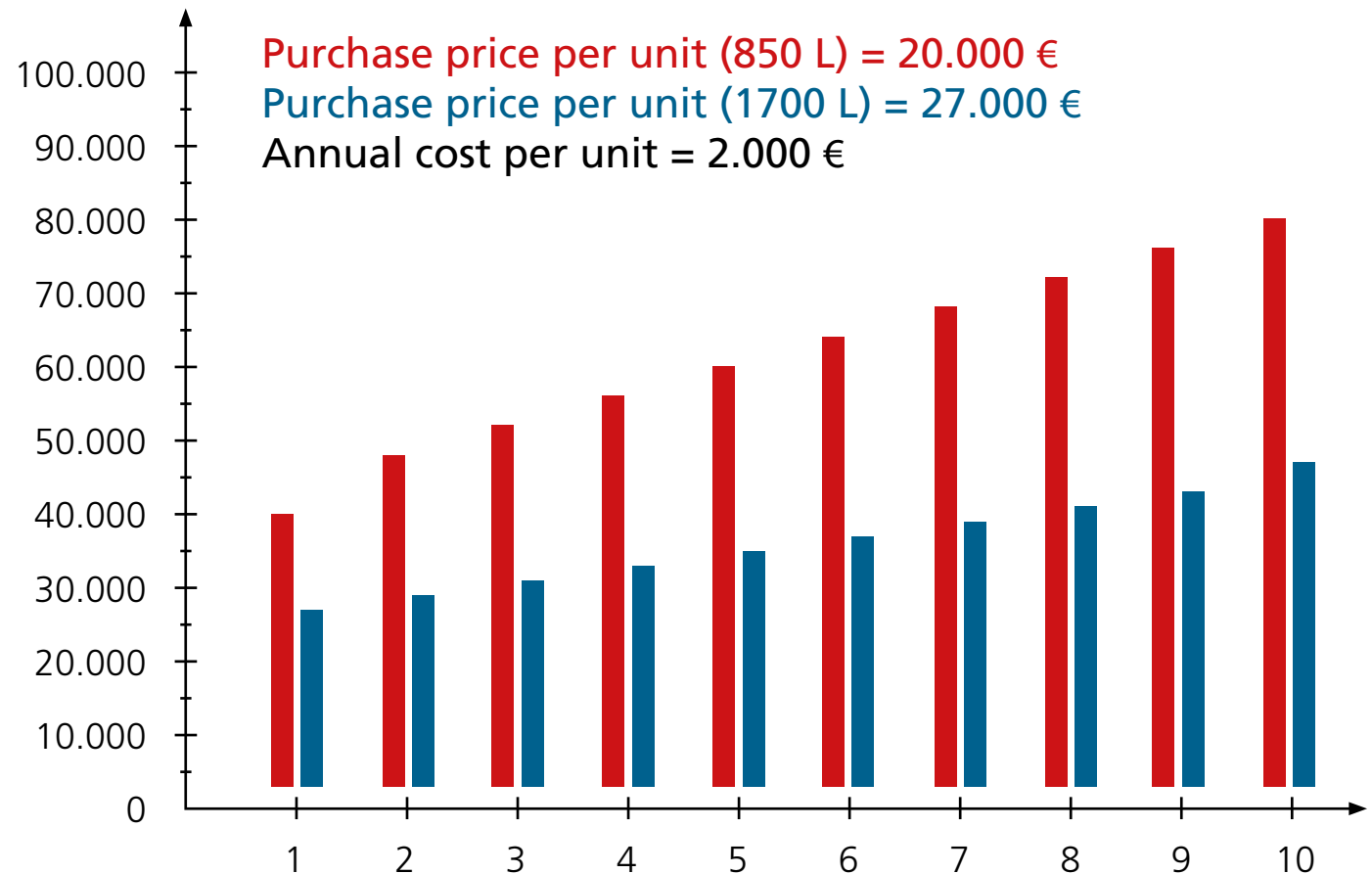


Lifetime costs of ownership:

Comparison of 2 appliances,
850 litres each, with an appliance,
1700 litres

Savings:

- Investment
- Installation
- Qualification
- Monitoring
- Maintenance



Walk-in rooms:

- Small rooms are inefficient
- Optimal solution: Shelves on both sides, if possible, depth 60 cm and aisle width 80 cm
- Shelf width for solids 130 cm and for liquids 90 cm (weight!) because of boxes 60 x 40 cm



Installation in a Clean Room

- Integration of the units in a clean room partition wall
- Operation and charging are done from the clean room
- Service and maintenance from outside the clean room



Installation in a Clean Room

- Direct installation of the equipment in the clean room
- Water-cooled refrigerating machine (no fin heat exchanger with fan because of the particle swirl)



Requirements, Regulations & Documentation:

■ User Requirements:

- Volume
- Geometry
- Equipment
- Materials
- Calibration
- Qualification
- Bringing in

■ Regulations (such as VDE, UVV, CE, Regulation for Workplaces)

■ Documentation

- Qualification File
- Technical Plans
- Bill of Materials of Electrical and Mechanical Components
- Wiring Diagram
- Operating Manuals

■ Deviations

■ If applicable Layout of the installation place

Differentiation in must criteria, target criteria and can criteria

Transport/Placement

- Components can be removed easily for displacement through doors and placement in lifts

Advantage:

- Even larger appliances can be displaced
- Thus, the components are easily accessible for maintenance tasks



Space Saving

- The width of the doors does not exceed the units' width.

Advantage: space-saving side-by-side installation.

- Minimum lateral distance to the wall or distance between the appliances



Media Connections:

- Electricity
- Pure water
- Condensate Drain
- Heat dissipation into the room (not every room is suitable)
- If required, cooling water (water-cooled unit)



Functional Specification

FDS (Functional Design Specification) „realization requirements developed by the contractor for realization of the principal's requirements specification“

Proposed solutions of the supplier using the example of the media connections (water connection):

- Direct connection pure water to the conduit system
- Ion exchanger to the drinking water connection
- Canister for installation places without water connection
- Canister with float switch



Functional Specification

Proposed solutions of the supplier using the example of the media connections (condensate drain):

- Condensate drain fixed pipe connection
- Lifting pump for higher situated sewage pipes
- Heated evaporation pan, if sewage water connection does not exist (automatic emptying)
- Collecting vessel



Waste Heat:

Refrigerating Machine



- Refrigerating machine in the installation room (possibly cooling of the emitted heat is required)

Outdoor Installation



- Outdoor installation of the refrigerating machine (for chambers)

Water Chiller



- Water-cooled unit (cooling water of the customer)

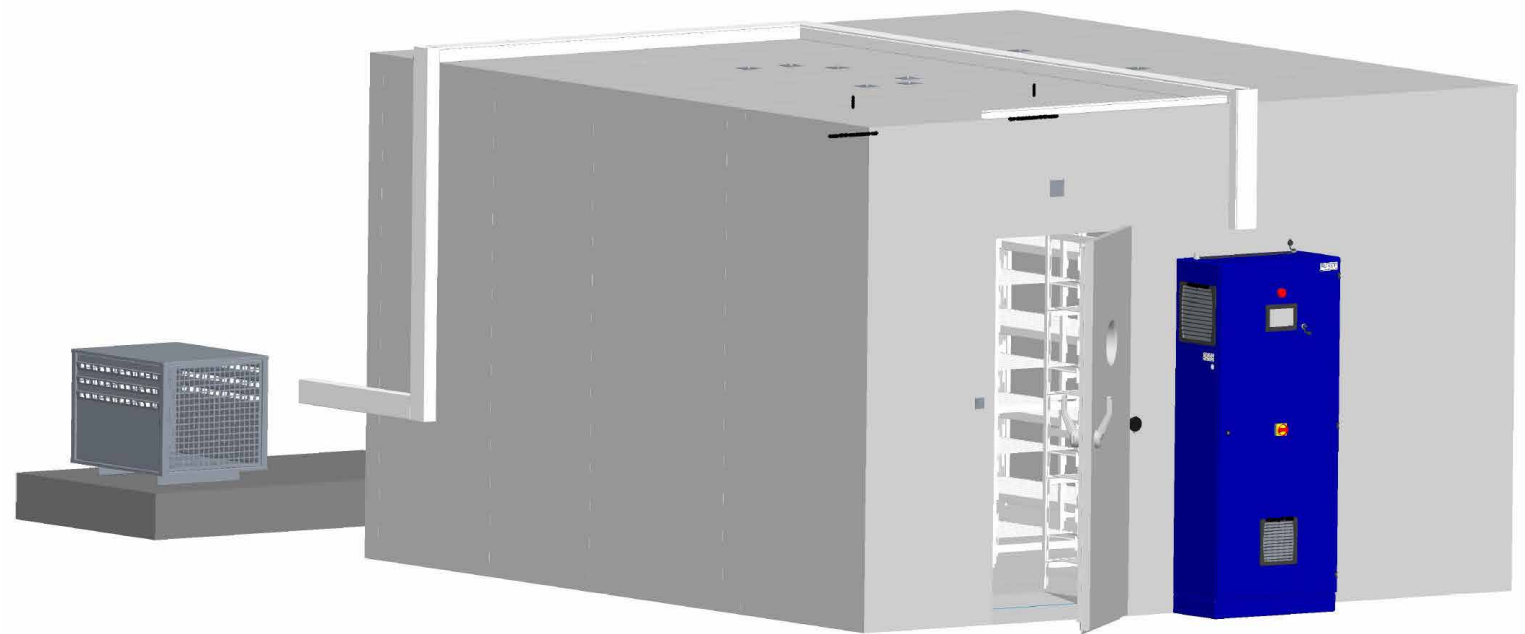


Energy Efficiency

Comparison URS with the Supplier's Offer (FDS) according to the DQ Plan

For Stability Test Chambers:

- Drawing for approval
- Final dimensions
- Required distances
- Media connections (location + dimension)



Preparation of a Time Schedule

- Possibilities of delivery and unloading
- Access authorization of the service technicians
- Working hours



Qualification & Calibration

Traceability guaranteed



From the DQ to the PQ

- Plants / Units for the pharmaceutical industry are subject to the qualification obligation
- Requirements are defined in GLP / GMP / ISO 9000
- Evidence of the suitability for the intended use
- The responsibility is incumbent on the operator

Design Qualification (DQ)



Performance Qualification (PQ)

The Process of Equipment Qualification

- Factory Acceptance Test **(FAT)**
 - Design Qualification **(DQ)**
 - Installation Qualification **(IQ)**
 - Operation Qualification **(OQ)**
 - Performance Qualification **(PQ)**
 - Maintenance Qualification **(MQ)**
- Manufacturer's Site
- On site



Qualification by the Manufacturer

- Reduction of the qualification phase of 3 weeks to 3 days
- Time-saving and cost-efficient due to many years of experience
- Prepared records
- Approved test methods, such as for the alarms
- Device-specific knowledge
- Training certificate for the users
- Test report for the final unit release



Design Qualification

Documented Evidence:

- The appliance complies with the company requirements, and you get exactly what you need
- The functional and operational specifications of the appliance are determined
- The choice of a supplier is explained



Anlagenqualifizierung		
Dokument Design Spezifikation Klimaschrank_Doc	Klimaschrank für Stabilitätsprüfungen	Seite 1 von 9

RUMED[®]
Rubarth Apparate GmbH

Rubarth Apparate GmbH, Mergenthalerstraße 8, 30880 Laatzen

Hermes Arzneimittel GmbH
Herrn Dr. Markus Gutmann
Georg-Kalb-Straße 5-8
82049 Großhesselohe

Angebot

Nummer : AN-201908/025
Datum : 15.08.2019
Kunden-Nr. : 24008
Debitoren-Nr. : 24008
Bearbeiter : V. Rubarth

Mergenthalerstr. 8
D-30880 Laatzen
Germany

Telefon
0511.866.599.80/81
Telefax
0511.866.599.99
e-mail
info@rumed.de
internet
www.rumed.de

Es gelten ausschließlich unsere Allgemeinen Geschäftsbedingungen.
Zu finden im Internet unter: <http://www.rumed.de/agb>
Auf Wunsch senden wir Ihnen diese auch gerne zu.

Ihre Anfrage:
per e-mail gemäß URS vom 05.08.19

Pos	Bezeichnung	Menge	Preis	Gesamt
3	Klima-Prüfschrank (Sonder ohne Kälte)	1,00	22.942,00	22.942,00

Stabilitätstest nach ICH (Accelerated test)

- Prüfraumvolumen 1060 Liter
- Arbeitstemperatur +40°C
- Feuchtebereich 75% bis 95% rel.F. einstellbar bei +40°C
- 2 digitale PID-Regler mit 7-Segment Soll/Ist-Wert-Anzeige
- Pt 100 Temperatursensor Klasse A nach DIN 43760
- kapazitiver Feuchtesensor, wartungsarm und langzeitstabil
- hohe räumliche und zeitliche Temperatur- und Feuchtegenauigkeit durch Umluftsystem (±0,5°C / ±2-3% rel.F. im Leerzustand bei Ausführung mit Kältemaschine)
- Außengehäuse aus Edelstahl mit abschließbarer Tür
- Prüfraum aus Edelstahl, leicht zu reinigen
- 2 x 3 Horden aus Edelstahl, höhenverstellbar
- Über- und Untertemperatur Schutz durch Temperaturwählgrenzer nach DIN 12880, Klasse 3.3
- Übertemperatur Geräteschutz nach DIN 12880, Klasse 2
- Befuchtung durch Ultraschallbefeuchter
- automatische Wasserbefüllung mit demineralisiertem Wasser
- energie- und wassersparend
- CE Zeichen, FCKW-frei, VBG 4 Sicherheitsgeprüft

Techn. Daten des Standardgerätes ohne Optionen:
Prüfraummaße : 1500 x 610 x 585 mm H/B/T (je Prüfraumhälfte)
Außenmaße : 2100 x 1400 x 975 mm H/B/T
Nettogewicht : 260 kg
Elektroanschluss: 230 V, 50 Hz, Absicherung 16 A
Umgebungstemperatur zwischen +10°C und +23°C

"Spezialausführung" ohne Kältemaschine!
Daher keine Kühlung und keine Entfeuchtung.
Die tatsächlich erreichbaren Werte (Temperatur/Feuchte) und die erreichbare Genauigkeit hängen von den Klimabedingungen am Aufstellort ab.

Das Gerät wird mit 1 Jumo Dicon Touch 2-Kanal Regler mit

Übertrag: 22.942,00

AN-201908/025 Seite 1 von 3

Lastenheft

HERMES
ARZNEIMITTEL

Klimaschrank_Klima_1_NEU/Design Spezifikation Klimaschrank.doc, 5.8.2019, MG

Dipl.-Ing. Volker Rubarth | Manager, Rubarth Apparate GmbH

Aspects of the ICH-compliant storage for stability tests 26 / 45

Installation Qualification

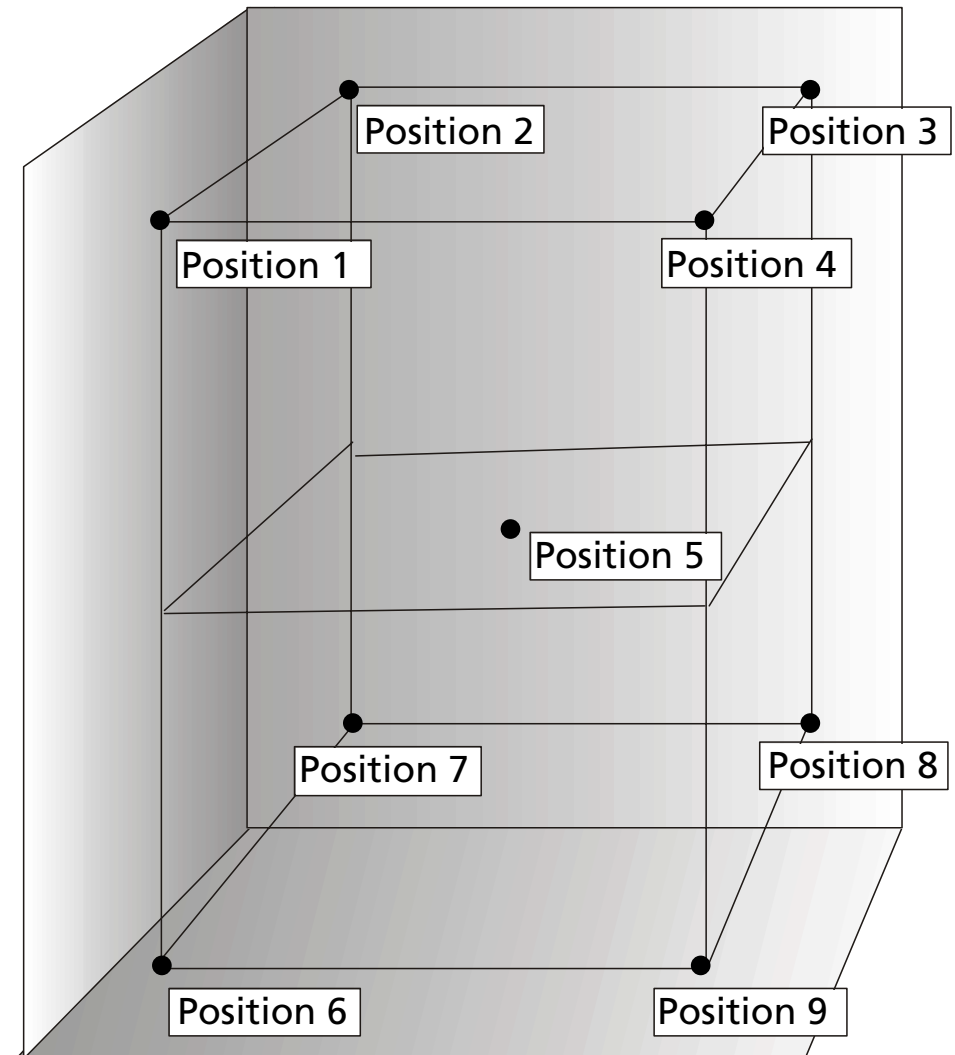
Documented Evidence:

- The delivered appliance complies with the specifications (DQ) of the order
- Complete and undamaged delivery
- Correct execution of the installation at the intended location
- Correct design concerning the environmental conditions at the installation place



Operation Qualification

- Documented evidence, that the installed appliance works according to its specifications
- The appliance works under the companies' environmental conditions at the predetermined location.
- Verification of the distribution in space in the empty appliance
- Mapping in the appliance centre and in the 8 corners of the appliance
- All sensors must be within the range



Performance Qualification

- Documented evidence of constant performance under real operating conditions
- Mapping of the temperature distribution and humidity distribution in space in loaded condition
- Sensors must have a valid certificate and must be traceable to national standards (DKD, SCS, ÖKD)
- Photograph of loading conditions
- Optionally: Open door study

Important: Ensure sufficient loading
for realistic PQ mapping



Maintenance Qualification

- Documented evidence, that the appliance is maintained correctly and according to the specifications to ensure continuous operation
- Determination of cleaning intervals
- Determination of service intervals (maintenance contract)
- Recalibration (PQ)



Monitoring and Failure Management

21CFR part 11 compliant

RCS 4.0 - RUMED Control2015.touch - Übersicht ...

LG 116 - Klimakammer
(25°C / 60%)



LG 186 - Klimaschrank
(30°C / 65%)



LG 187 - Klimaschrank
(30°C / 75%)



LG 198 - Klimaschrank
BTM (25°C / 60%)



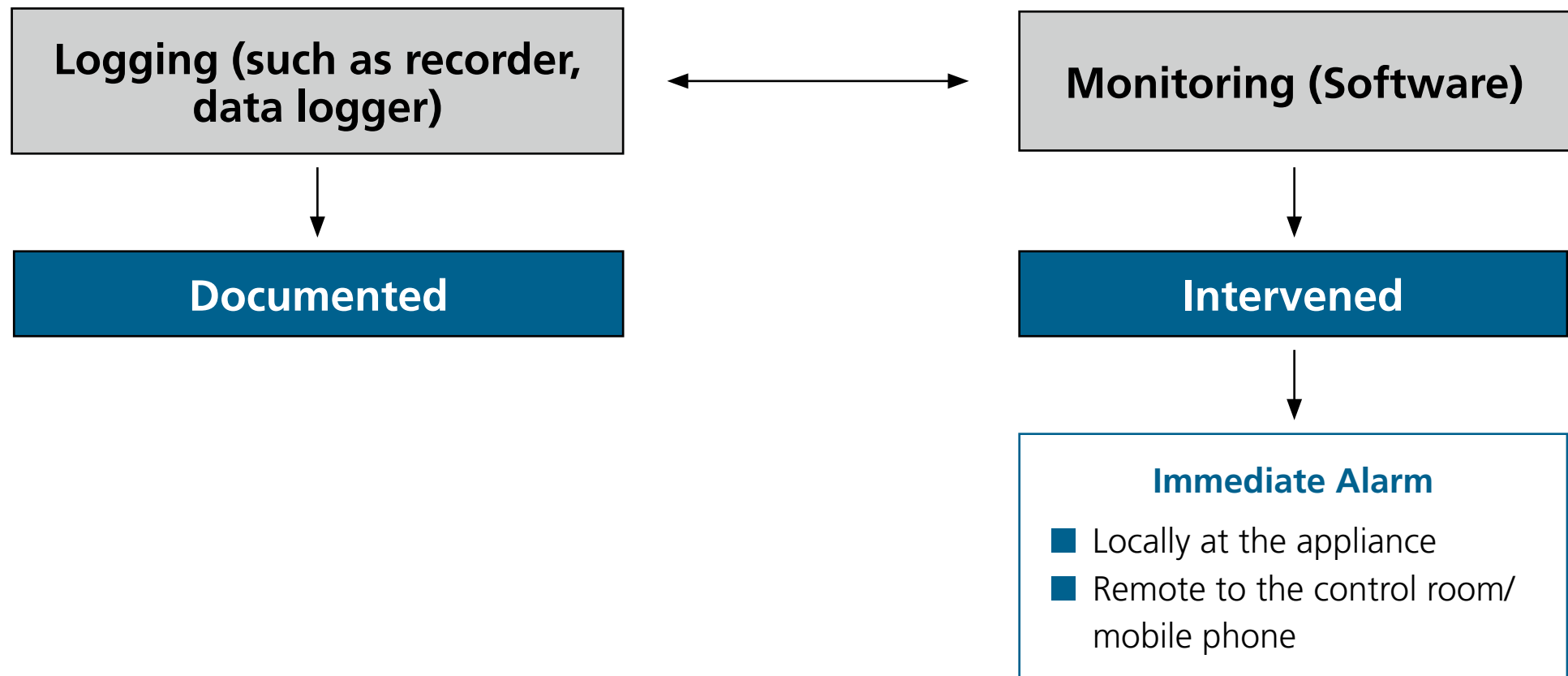
LG 199 - Klimaschrank
BTM (30°C / 65%)

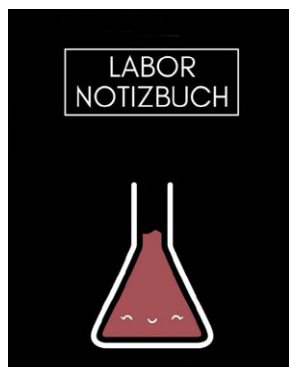


LG 200 - Klimaschrank
BTM (40°C / 75%)



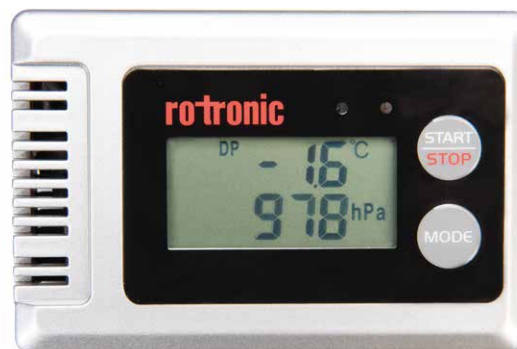
Data Recording + Alarms





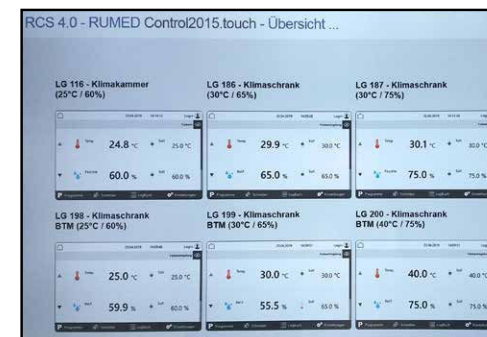
Laboratory Book

- Only 1 working value
- Reading errors and transmission errors are possible
- Time-consuming
- High error rate in reading/transmission



Data Logger

- Subsequent evaluation
- Risk of confusion in case of many measuring points
- Recognition too late



Software

- Raw data are archived
- Current history display by means of graph recorder
- Less manual expenditure
- Digital signature possible
- Logbook firmly linked to graph representation

The following parameters should be recorded during monitoring:

- Temperature
- Profile Humidity
- Profile logbook with:

Messages with time-stamp, such as:

- User Login / Logout
- Changes of Target Values
- Digital Signature
- Door Opening
- Expired Maintenance Interval

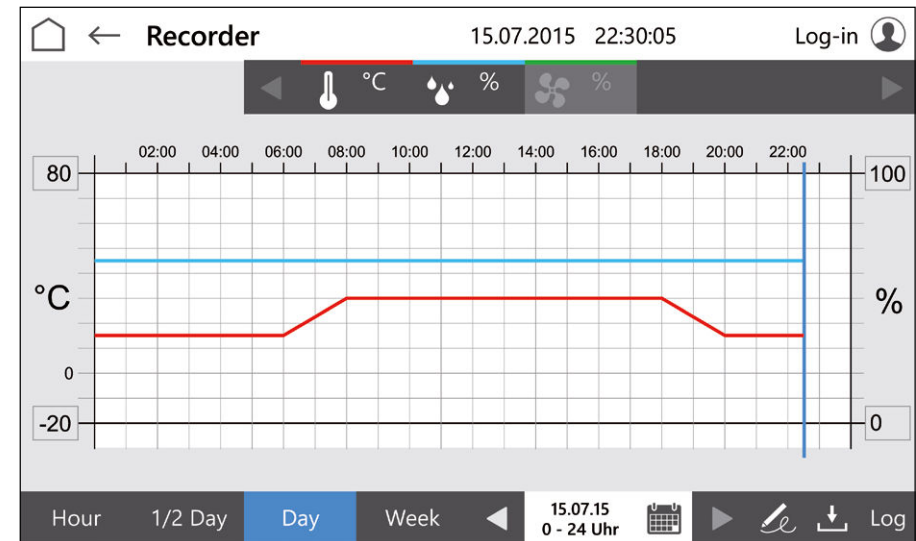
Messages with time-stamp, such as:

- Excess temperature and insufficient temperature
- Humidity value too high or too low
- Conductivity of the humidifier water too high
- Chiller shut-down in case of low pressure or overpressure
- Sensor failure

- Media Outage (Water, Electricity, etc.)

Integrated Screen Recorder

- Recording of actual values of all regulator and control circuits.
- For clearness, all channels can be shown or hidden.
- Past periods can be scrolled conveniently page-by-page.
- Even with power failure, a restricted, battery backed monitoring is effected.



Logbook

- Gapless event documentation in real time, inseparably connected with the recorded data.
- Filter function for the quick, selective display of the events.
- Free comments with login name are possible at any time.

←

Logbook

16.07.2015 17:03:30

frey

Date	Message	All <div></div>
16.07.2015 08:04:23 Uhr	<div></div> Door open	Note
16.07.2015 08:05:34 Uhr	<div></div> Door closed	Note
16.07.2015 08:30:02 Uhr	<div></div> Door open	Note
16.07.2015 08:32:21 Uhr	<div></div> Door closed	Note
▼ 16.07.2015 14:02:45 Uhr	<div></div> Interior had been cleaned (frey)	Comment
16.07.2015 16:59:29 Uhr	<div></div> Door open	Note
16.07.2015 17:00:29 Uhr	<div></div> Door closed	Note

▼

▲

◀

from
21.06.15

▶

◀

to
16.07.15

▶

↓

Comment Entry

- Complete keyboard for entry of comments into the logbook and for entry of individual names for program creation.
- The assignment of the keys is adapted automatically to the selected language.

The screenshot shows a mobile application interface for a logbook. At the top, there is a header bar with a home icon, a back arrow, the title "Logbook", the date and time "16.07.2015 17:06:30", and a user profile icon labeled "frey". Below the header, a text input field contains the comment "Internal Audit successfully completed". To the right of the input field are two buttons: "Save" and "Cancel". Below the input field is a virtual keyboard. The keyboard has a top row with symbols "+%°", numbers "1" through "0", and a delete key with an "X" icon. The second row contains letters "Q", "W", "E", "R", "T", "Z", "U", "I", "O", "P", "Ü", and a backspace key. The third row contains letters "A", "S", "D", "F", "G", "H", "J", "K", "L", "Ö", "Ä", and a return key. The fourth row contains an arrow key, letters "Y", "X", "C", "V", "B", "N", "M", comma, period, hyphen, and another arrow key. The bottom row features a globe icon for language selection, a long empty space, and left and right navigation arrows.

Calendar

- The calendar function allows quick direct access to past recording periods - no matter if to the recorder, to the logbook or for data export.
- All days, for which data have been recorded, are colour-highlighted.

Recorder 16.07.2015 08:58:12 frey

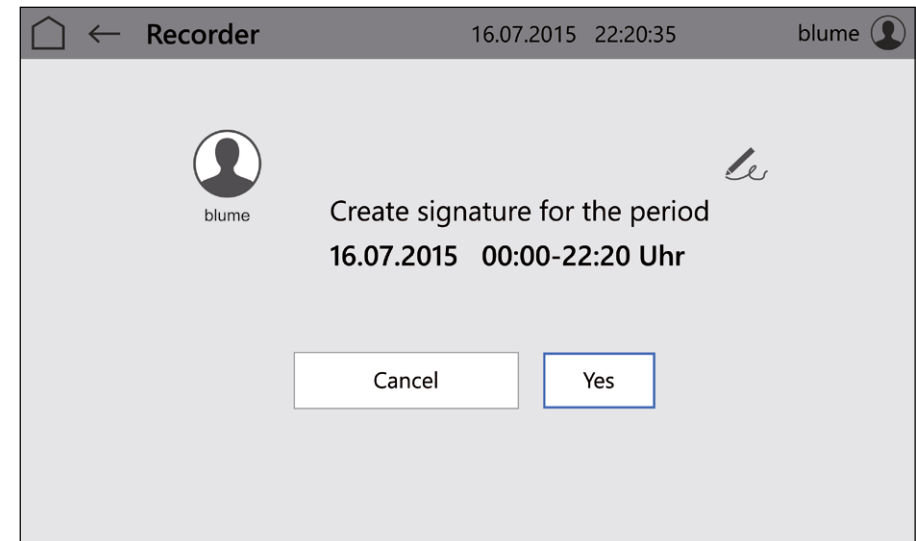
July 2015 Today

Monday	Tuesday	Wednesday	Thursday	Friday	Saturday	Sunday
29	30	31	01	02	03	04
05	06	07	08	09	10	11
12	13	14	15	16	17	18
19	20	21	22	23	24	25
26	27	28	29	30	31	01

Hour 1/2 Day Day Week 10.07.15 16.07.15 Log

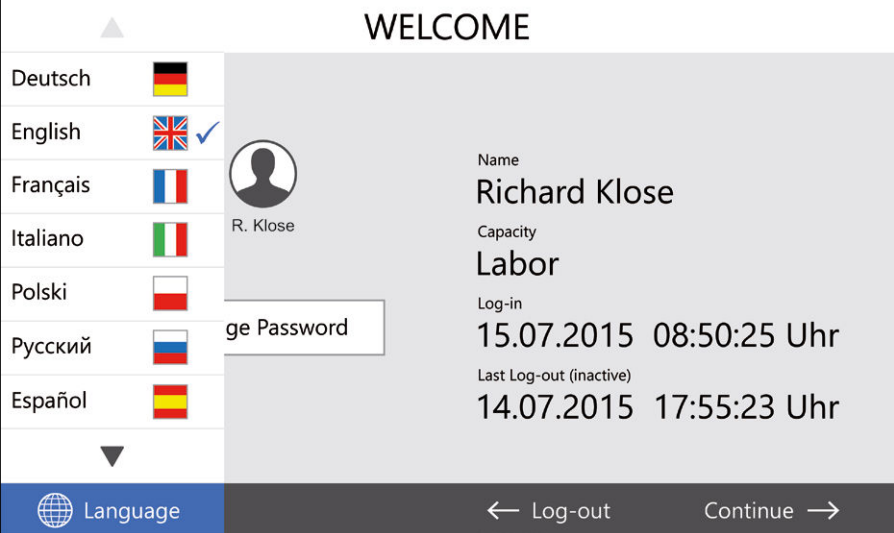
Digital Signature

- Signature of the checked periods directly at the recorder of the control in conformity with 21CFR part 11.
- Undersigned areas are marked correspondingly in the recorder.



User Login

- In the user management, the preferred language can be assigned to the users. A quick change is possible at any time.
- Thanks to the user management, the activities of each user can be traced exactly.
- In connection with the option Electrical Door Release, even the door opening can be allocated to a user.



The screenshot shows a user login interface. On the left, a language selection menu lists: Deutsch (German flag), English (UK flag, selected with a blue checkmark), Français (French flag), Italiano (Italian flag), Polski (Polish flag), Русский (Russian flag), and Español (Spanish flag). Below the list is a 'Language' button with a globe icon. The main area is titled 'WELCOME' and displays user information: a profile icon labeled 'R. Klose', the name 'Richard Klose', the capacity 'Labor', the login time '15.07.2015 08:50:25 Uhr', and the last log-out time '14.07.2015 17:55:23 Uhr'. A password field is labeled 'ge Password'. At the bottom, there are 'Log-out' and 'Continue' buttons with arrows.

User Management

- The user management can be customized: It can be deactivated completely, or different rights can be allocated to the users.
- Passwords can be restricted in time, and the access can be locked after a defined number of failed login attempts.
- The user management allows the use of the appliance in conformity with 21CFR part 11.

User Management					16.07.2015 15:06:40	Log-in 
	User ID	First Name/Name	Capacity	Status	Created on	
	blume	Anna Blume	Laborant	new	01.08.2014	
	fernandez	Sylvia Fernadez	Laborant	blocked	28.08.2014	
	klose	Richard Klose	QT	inactive	02.02.2015	
	wimmer	Erwin Wimmer	Leitung	active	20.05.2015	
	frey	Otto Frey	Laborant	active	19.06.2015	



New

Copy

Edit

The worst that can happen is sample loss

Samples cannot be found
(narcotics)



Access Control



Overheating



Emergency Cooling System
/ Redundancy



Water Damage



Overflow Vessel with
Alarm (Water Stop)



Failure Management

- Early recognition of a failure allows short reaction times of the user
- Redundant chambers
- Rearrangement into a back-up appliance
Service manual + training
- Stockpiling of important spare parts



Possible Measures in Case of Failure

Excess temperature: Emergency cooling with tap water

Humidifier failure: Emergency humidification by evaporation humidifier with hygostat

Power failure: Rechargeable battery for 24 h data recording for retrospective risk assessment (deviation report)

SOP: Action plan for failures



Thank you very much for your attention

Do you have any questions?

www.rumed.de/en/downloads/vortraege

