Sublimation

Georg Frinke - *Process Engineer*

Volunteer for PDA

Overview

- Theory of Sublimation
- Practical aspects of Suplimation
- PAT
- Recipe & Transfer Parameters
- Hands-On: Barometric / Manometric Temperature Measurement

Theory of Sublimation

General Equation for Heat Transfer

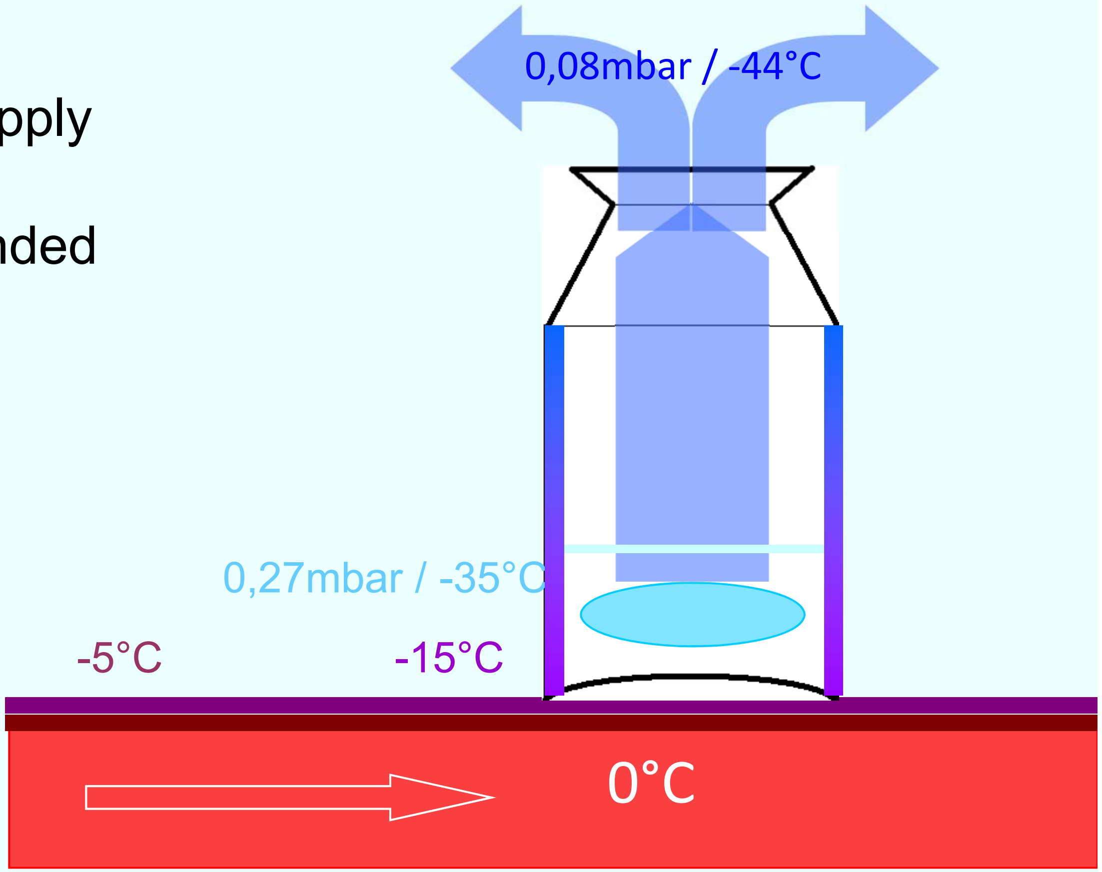
$$dQ_{Cond} + dQ_{Rad} + dQ_{Conv} = dQ_{comp}$$

$$\frac{dQ_{comp}}{dt} = k_V \cdot A_H \cdot [T_{Siliconeoil} - T_{Product}]$$

k_V	Very simplified Heat Transfer Coefficient
A_H	Vial Bottom Area
$T_{Product}$	Product at the Sublimation front

Sublimation – Thermic & Pressure profile

- Frozen water evaporates
- Process requires high energy supply
- Steady conditions are recommended



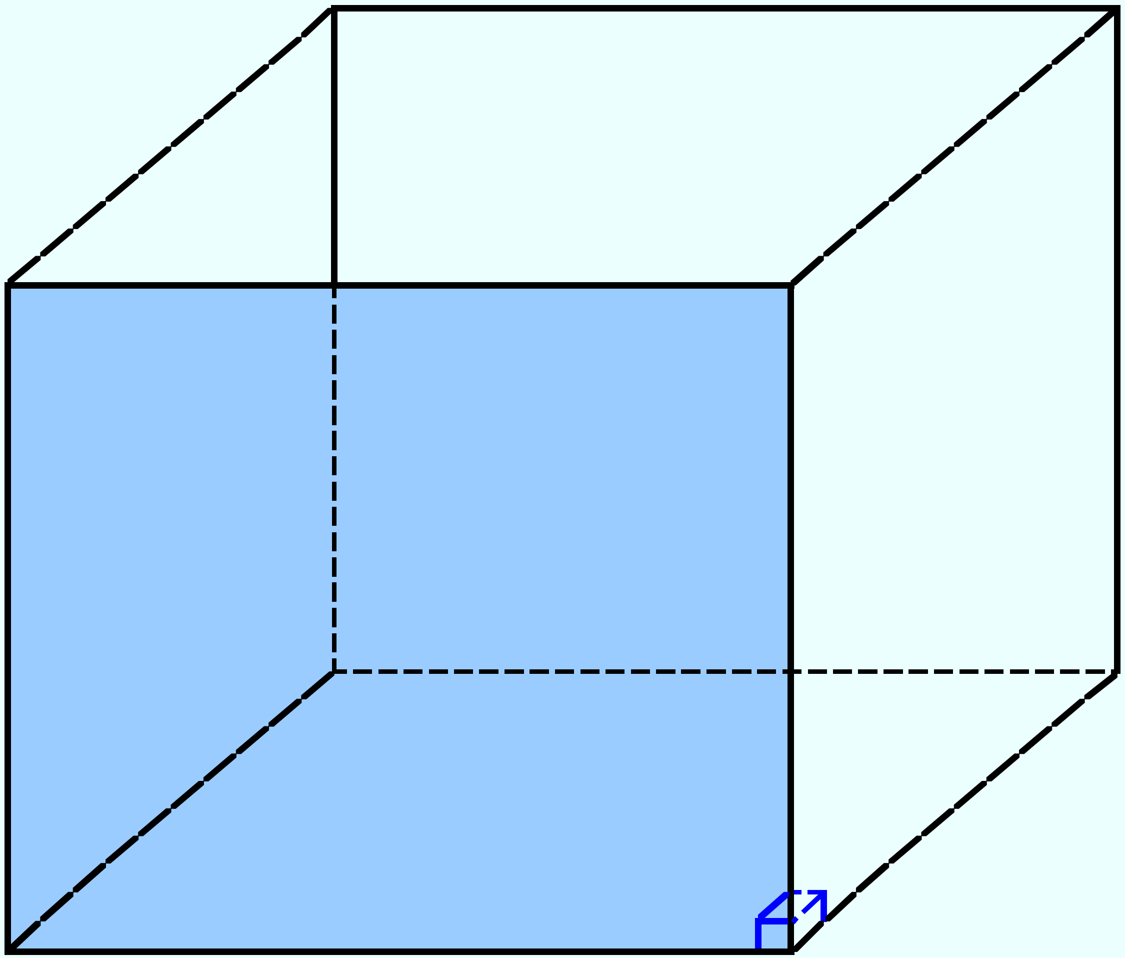
Heat Flux is stationary

- Each step of energy transfer transfers same amount of energy
- Temperature difference and thermal resistance are proportional
- Temperature gradient in vial is changing during sublimation

$$\frac{1}{K_V} = \sum^{i} \left[\frac{1}{K_i}\right] \Leftrightarrow K_V = \frac{1}{\sum^{i} \left[\frac{1}{K_i}\right]}$$

Partial Heat Transfer	Coefficient [W / m² K]
Silicone Oil => Shelf Surface	40…250
Shelf Surface => Vial Bottom	8…20
Vial Bottom => Sublimation Front	100…1000

Theory of Sublimation



Comparison of liquid and gazeous volume of same mass

Gas production due to sublimation

- Sublimation provides tremendous gas volume
- e.g. 1 kg of ice sublimes into 13.220m³ (-44°C / 8Pa)

General Equation for Mass and Heat balance of the vial

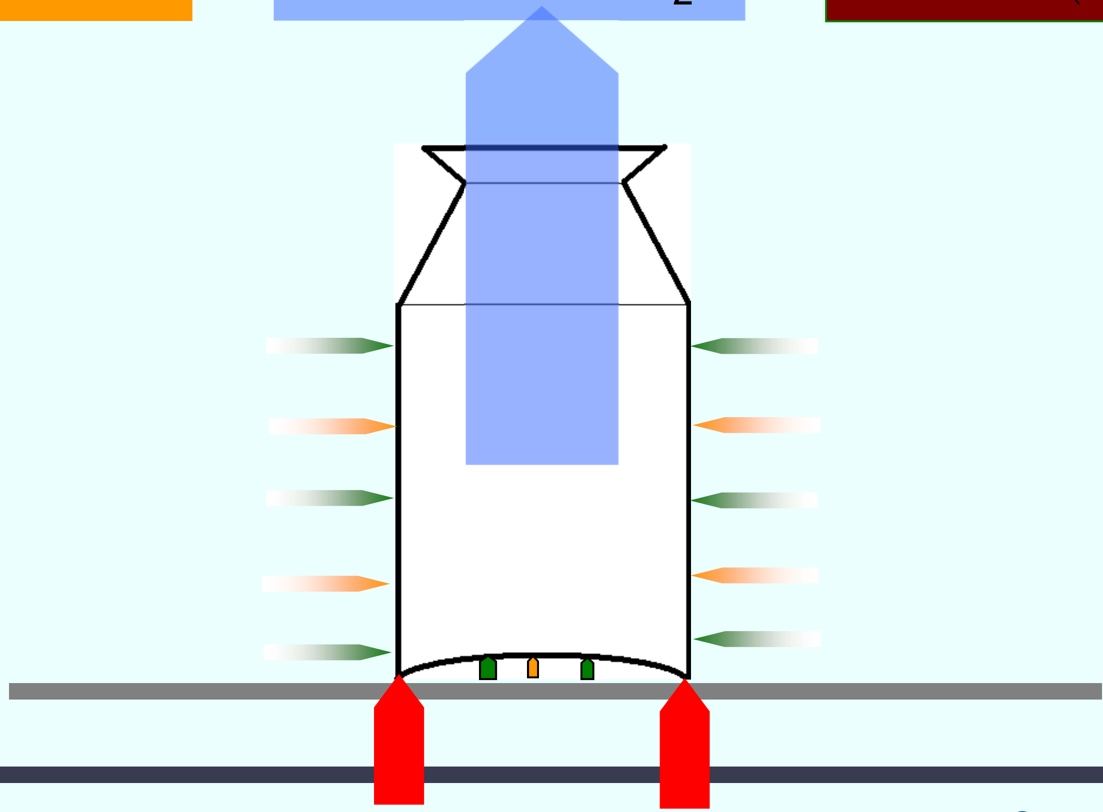
$$dQ_{Cond} + dQ_{Rad} + dQ_{Conv} = h_{Subl} \cdot dm_{H_2O} + d\vartheta \cdot C_{(\vartheta)}$$

Heat conduction

Heat radiation

Heat convection

Sublimation



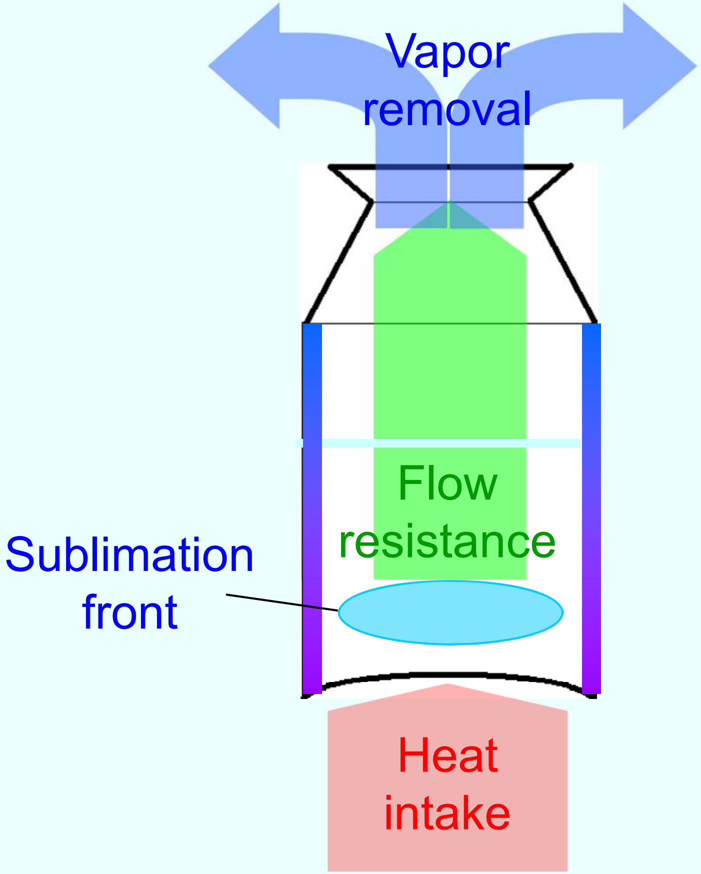
Sublimation at the front

- Heat intake equilibrates with heat consumption by ice sublimation

- Driving force for mass flow is pressure difference

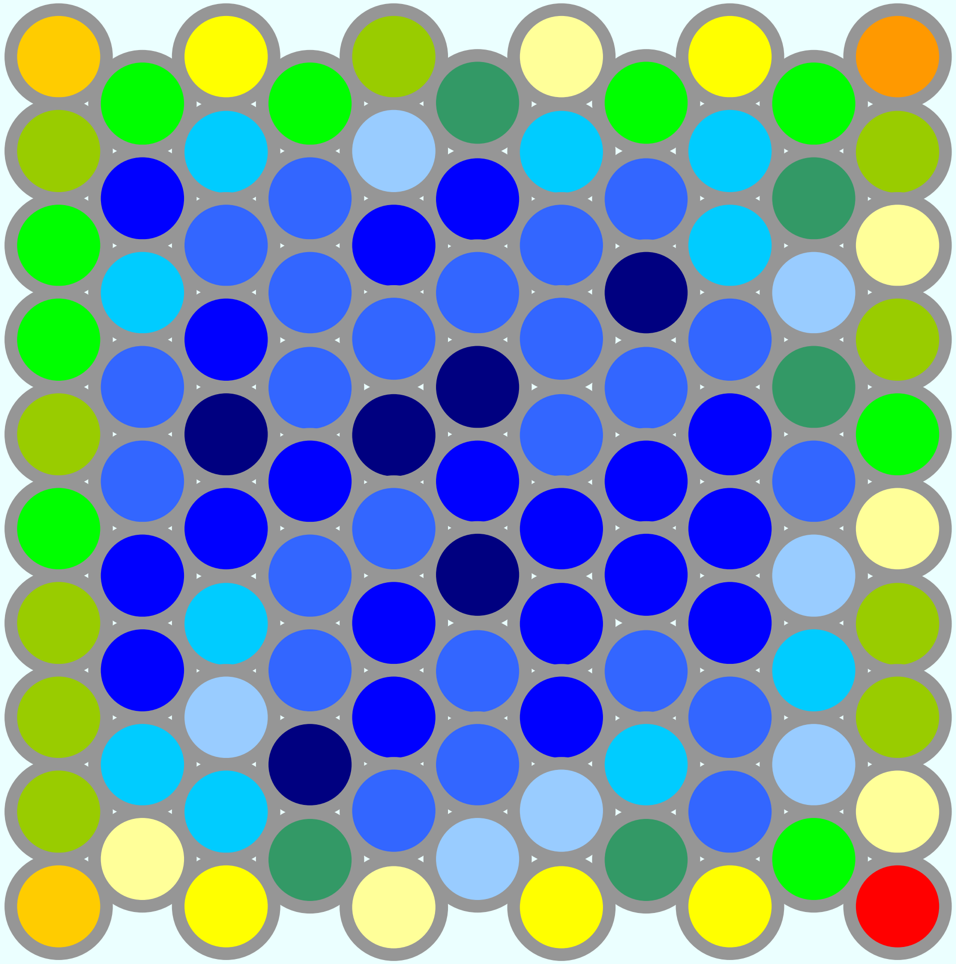
- Driving force for heat flux is temperature difference

$$\frac{dm}{dt} = \frac{A_P}{R_{PS}} \cdot (P_i - P_C) = \frac{dQ_{subl}}{h_{subl}}$$



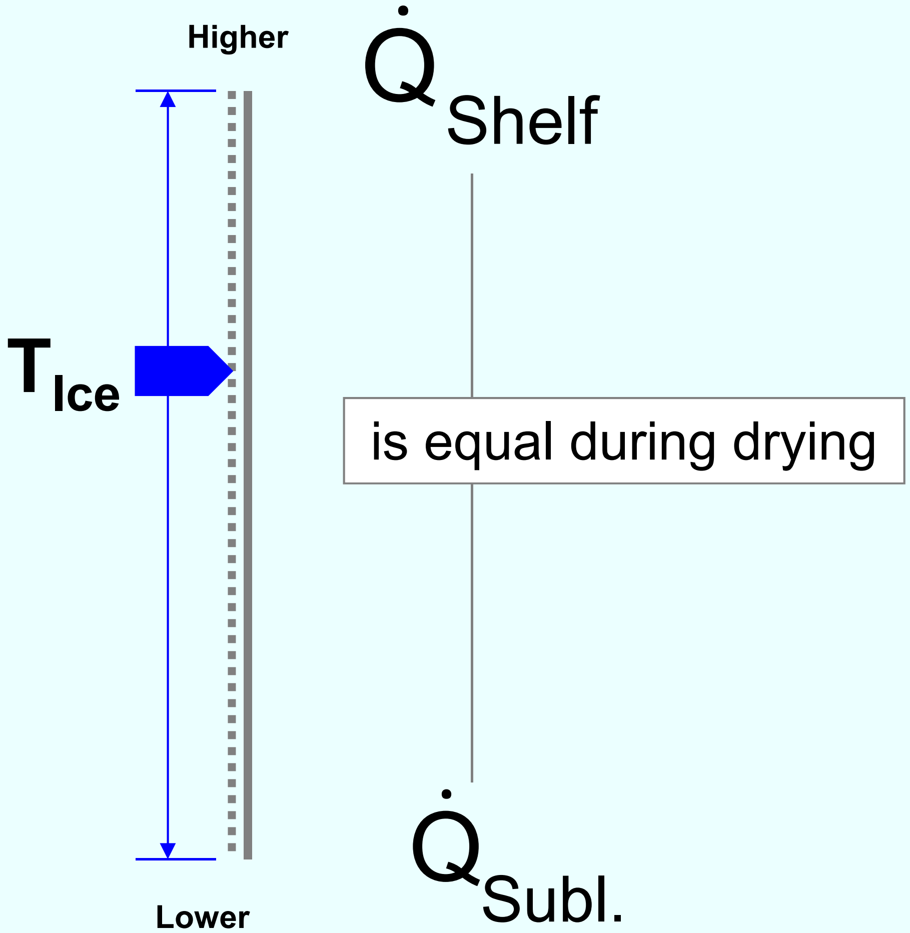
Impact of different Heat intake on Homogeneity

Vialtype:	10ml Vial
Filling:	5ml
Layer:	8mm
T_{Sh}:	0°C
T_{Rad}:	0°C
p_{ch}:	80µbar
t_{End}:	8h
m_{min}:	1,88g; 0,24g/h
m_{max}:	3,64g; 0,45g/h
Base:	3 runs aver.



	min	max
	1,85g	1,98g
	1,98g	2,10g
	2,10g	2,23g
	2,23g	2,35g
	2,35g	2,48g
	2,48g	2,60g
	2,60g	2,73g
	2,73g	2,85g
	2,85g	2,98g
	2,98g	3,10g
	3,10g	3,23g
	3,23g	3,35g
	3,35g	3,48g
	3,48g	5,00g

Equilibrium of T_{Ice}



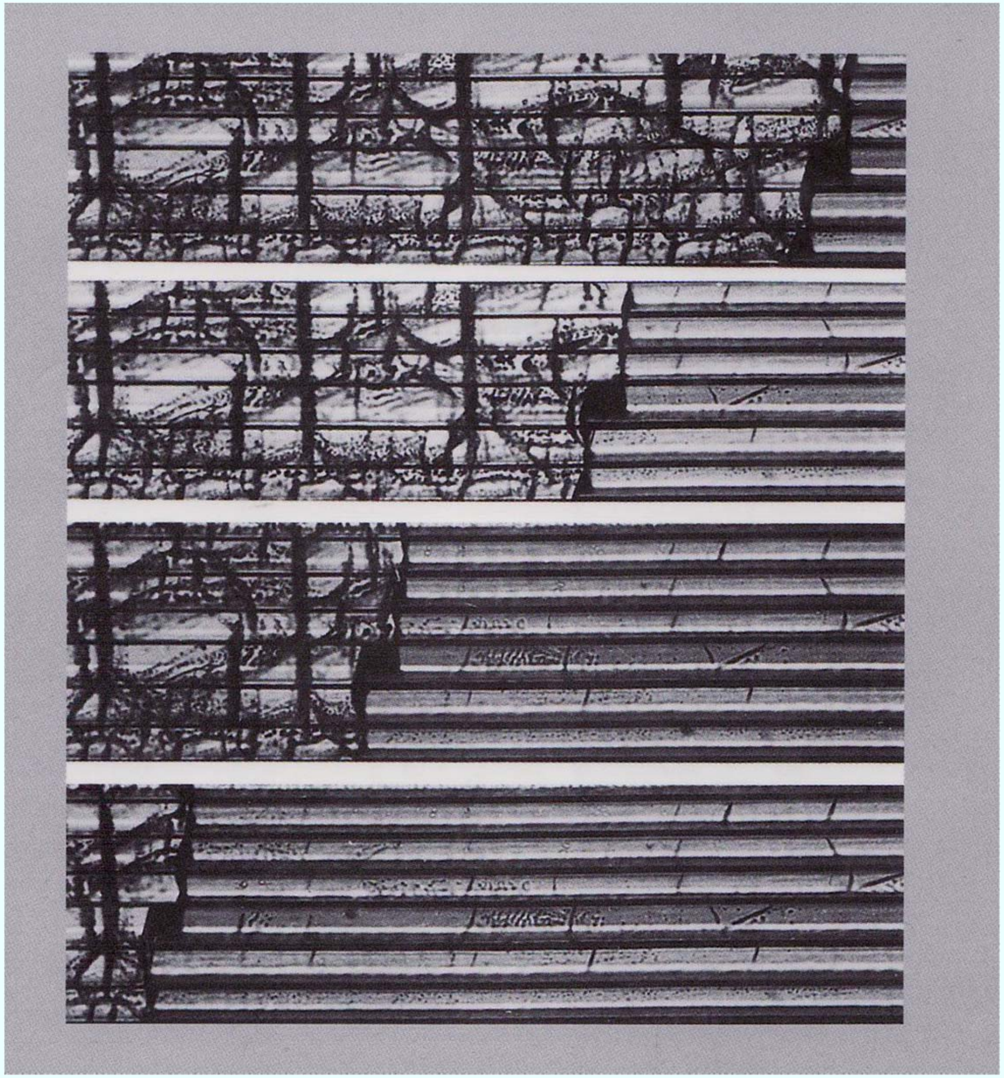
Limitations of Heat supply

- Heat transfer coefficient in the shelf
- Heat transfer coefficient between shelf surface and sublimation front
- Difference between T_{Ice} and $T_{Silicone\ oil}$

Limitations of Sublimation Rate

- Cooling capacity of ice condenser
- Flow resistance of Freeze Dryer
- Vapor transport in product

Theory of Sublimation



Course of Freeze Drying at FD-Microscope (Bookcover, Oetjen/Haseley)

Sublimation progress

- 90s
- 180s
- 270s
- 360s

At the end of sublimation all ice is removed

Questions?

Practical Aspects of Sublimation

Sublimation phase – Hints for a first run (I)

When process vacuum is reached the shelves should be heated up...
...Sublimation starts

- As shown before, the temperature at the sublimation front (T_{ice}) depends on the equilibrium of shelf temperature and chamber vacuum

- T_{ice} must never exceed the critical temperature investigated with one of the previously described instruments

- A proper process vacuum could be the vapor pressure of (T_{crit} - 5...10°C)

Sublimation phase – Hints for a first run (II)

When process vacuum is reached the shelves should be heated up...
...Sublimation starts

- A first estimation for step duration could be calculated based on sublimation progress of 0,5mm_{Layer}/hour

- Due to variations in Drying Progress over time, changes in Shelf Temperature or Process Vacuum during Sublimation should be avoided

- For a first guess, a conservative Temperature difference between t_{crit} and t_{shelf} of 15°C can be assumed

Optimization of Sublimation phase (I)

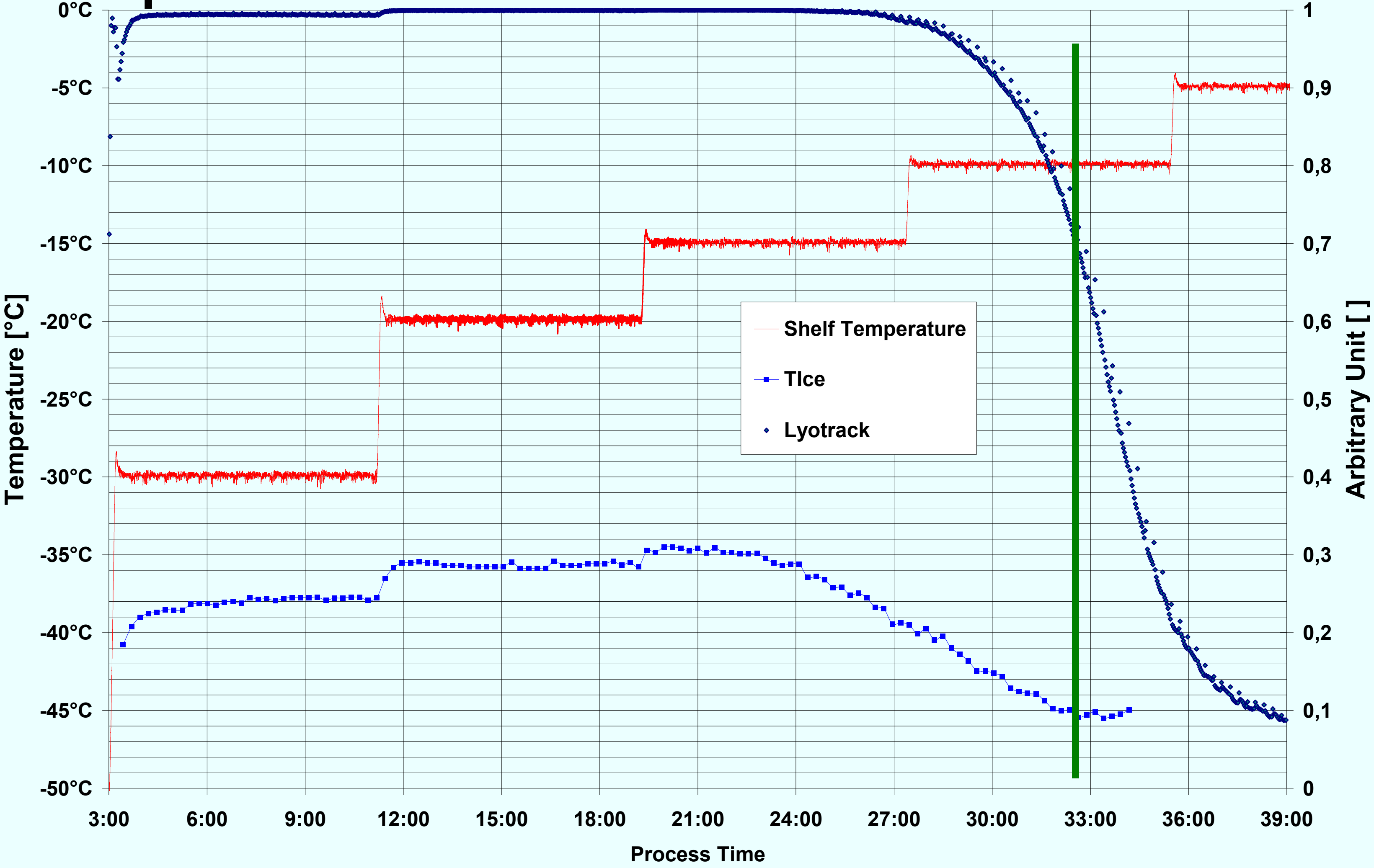
- Every raise of T_{ice} by +1°C increases process speed by 10...15%
- Frequently performed Pressure Rise Analysis enable safe monitoring of right T_{ice}
- The average T_{ice} can be also calculated based on TDLAS results

Optimization of Sublimation phase (II)

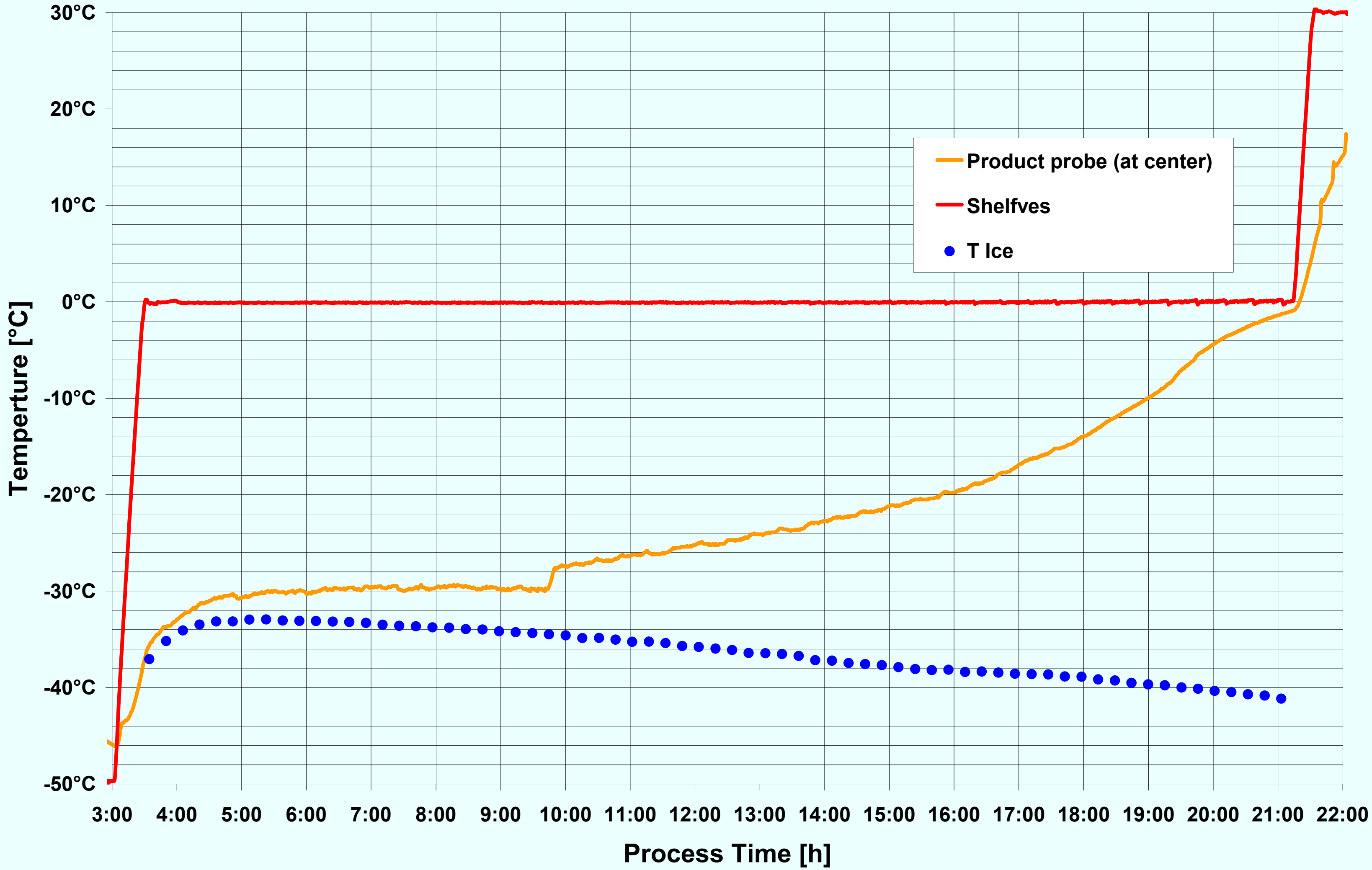
- The use of PAT Tools allows the safe control of the right step time

- The ice is safely removed, when
  1. the Temperature probes are above the shelf temperature *(requires time margin and right positioning of the temperature sensors*)
  2. T_{ice} has reached the equivalent vapor temperature of the chamber vacuum
  3. the Pirani Vacuum converges to the capacitive vacuum closer than 5%
  4. the indicated Lyotrack value has reduced below 0,4
  5. the Sublimation Rate has reduced to some percents of its maximum value

Sublimation phase



Sublimation phase



Temperature Measurement during Sublimation phase

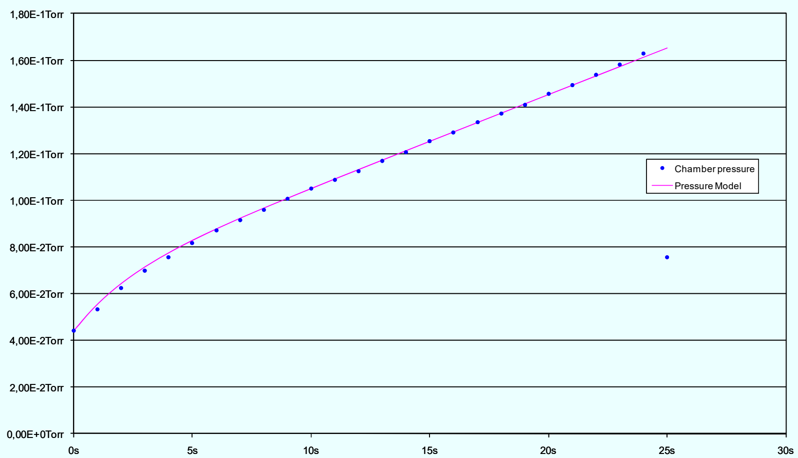
Procedure	Temp. Probes	Manometric / Barometric Temperature measurement	Temperature Calculation by TDLAS
Aseptic Handling	If wireless	yes	yes
Process impact	no	Yes	no
Main Valve close time	No process impact, always open	3...25s	No process impact, always open
Measuring scope	Indefinable position at vial	Full load	Full load
Other Considerations	Monitoring of some Samples only, Comparability of Samples with Cycle	Detects always the most critical vials in the process	Calculates the general average of t_{ice}

PAT

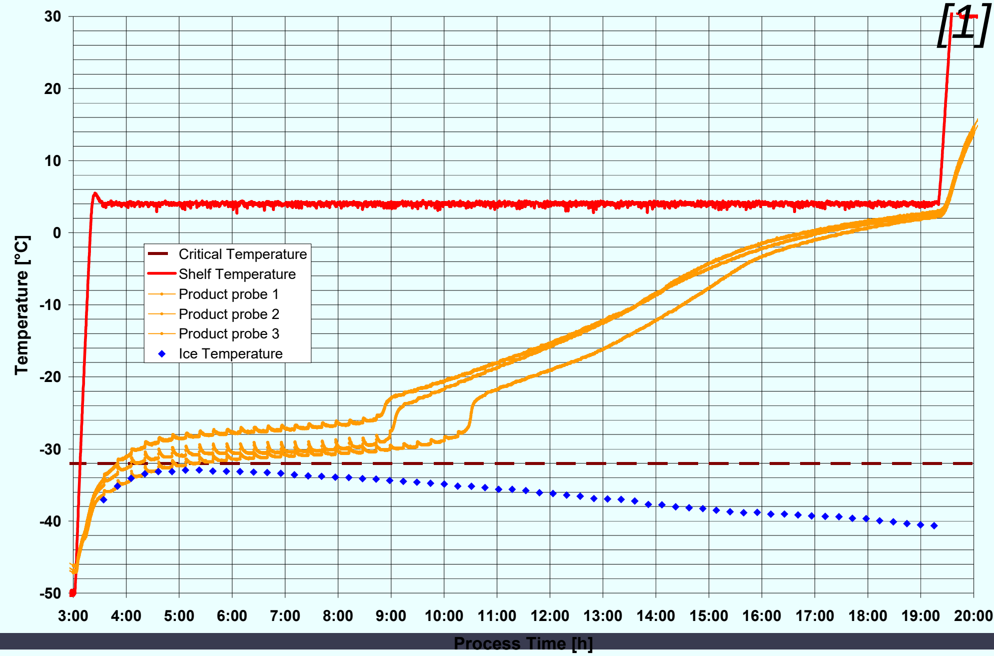
PAT @ Sublimation:

Process Feedback for Sublimation

- Ice Temperature (Frozen Product / sublimation Front)
  - Conventional Sensors (PT100 / TC / Wireless)
  - Barometric / Manometric Temperature Detection
  - Analysis of TDLAS results



[1]



PAT @ Sublimation:

Process Feedback for Sublimation

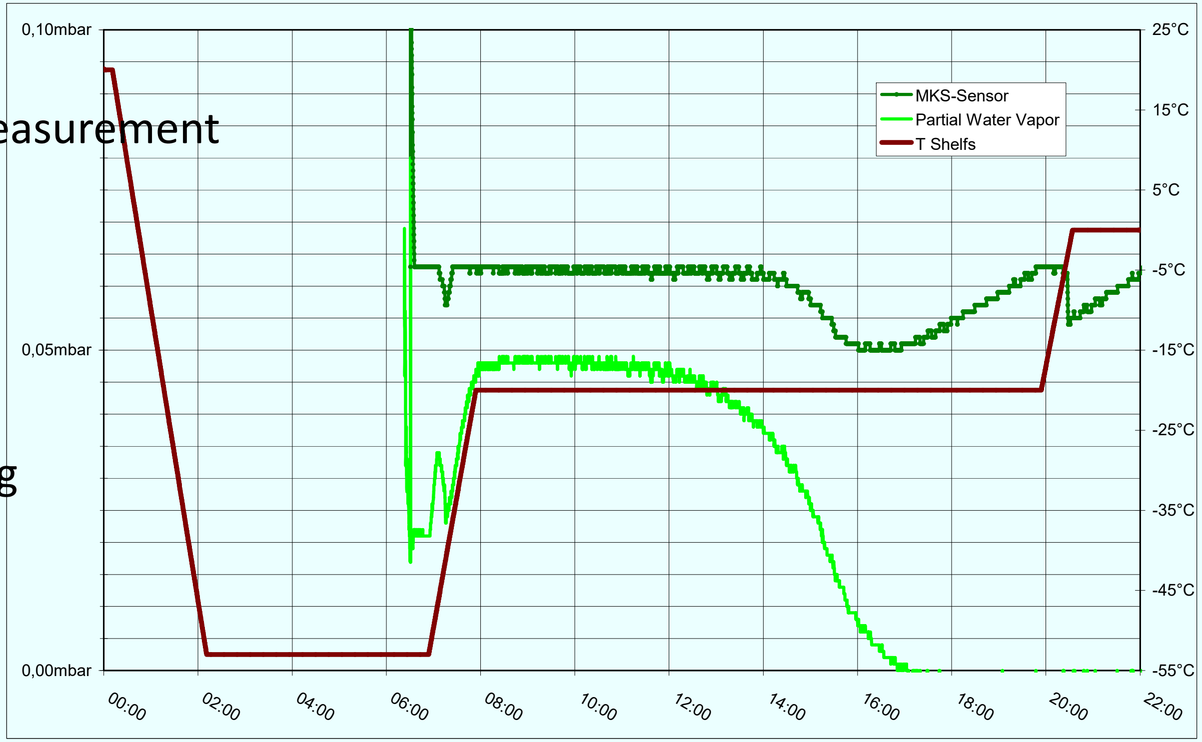
- Vapor Flow into Condensor
  - TDLAS
  - Analysis of Pressure Rise Measurement e.g. the frequent measurement of Sublimation / Evaporation Rate

$$ER = \frac{\Delta p / [\mu bar]}{\Delta t / [s]} \cdot \frac{V_c / [m^3]}{\vartheta_S / [K]} \cdot \frac{1}{m_{Tr} / [kg]} \cdot 0{,}7803 = \left[\frac{1}{h}\right]$$

PAT @ Sublimation:

Further Process Feedback for Sublimation

- Vapor Concentration
  - Comparative Pressure Measurement
  - Cold Plasma
  - NIR Gas Analysis
  - MS Gas Analysis
  - Dew Point Detection
  - Inert Gas Flow Monitoring



PAT @ Sublimation:

Process Feedback for Sublimation

- Ice Loss of Load
  - (Micro) Balance at Product Area
  - Sample Thief with Balance

- Ice Increase at Condenser
  - Weighing Function at the Ice Condenser
  - Thickness indication of Ice Layer

- Structural change of Product (Nucleation Sensors)

Recipe & Transfer Parameters

Investigation of the sublimation process

- A freeze Drying Microscope allows a detailed analysis of the drying process and a proper assessment for the suitability of the porosity of the frozen structure.

- The Correlation of the Evaporation Rate with the Water/Ice content allows a safe prediction of the End of Primary Drying

- The profile of T_{Ice} vs. Progress can be considered as transfer Parameter. As long this profile is likewise at different Lyos, the processes can be considered as comparable.

Principles for Sublimation

Procedure	*Principle*	*Result*
BTM / MTM product parameter	**Indirect calculation of T_{Ice} by Pressure Rise Analysis**	**Direct control of temperature at sublimation front**
Gas Flow process parameter	**Indirect calculation of sublimation rate by detecting vapor velocity**	**Determination of end point of sublimation phase**
Gas Moisture process parameter	**Direct measurement of partial vapor concentration**	**Determination of end point of sublimation phase**

Some Questions of mine :

- ✓ meaning of K_v?
- ✓ Volume per kg Ice (80µbar, -44°C)?
- ✓ Increase of process speed by raise of T_{ice} +1°C?
- ✓ Difference between T_{shelf} & T_{ice}?
- ✓ Difference between T_{shelf} & $T_{silicone\ oil}$?
- ✓ „Comparative Pressure measurement“?
- ✓ Indicators for end point of sublimation?

Hands-on:

Barometric / Manometric Temperature Measurement

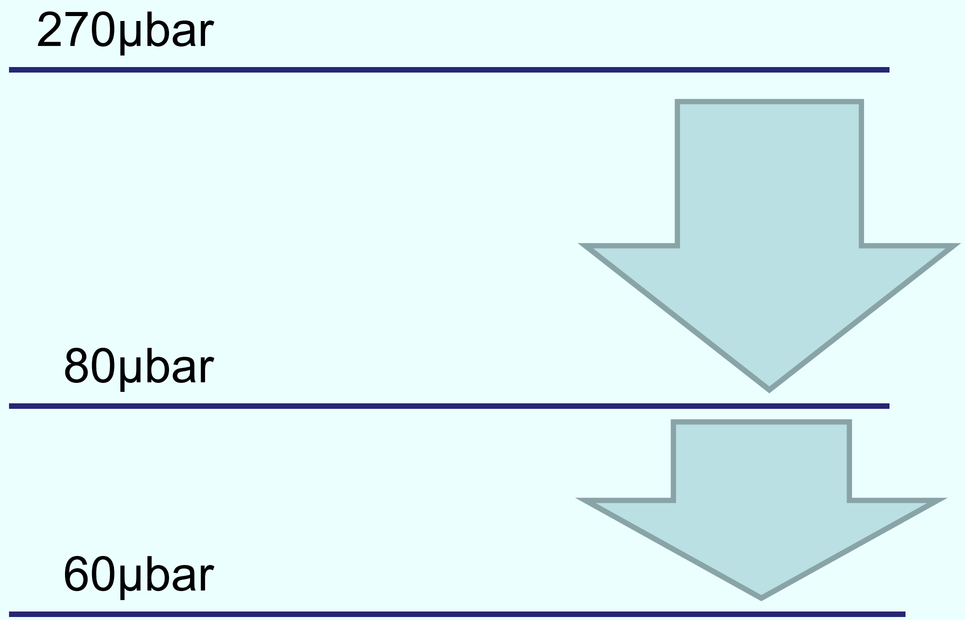
Theory of Barometric Temperature Measurement (BTM)

Pressure profile is driving force of lyophilization

Pressure at sublimation front, not directly measureable

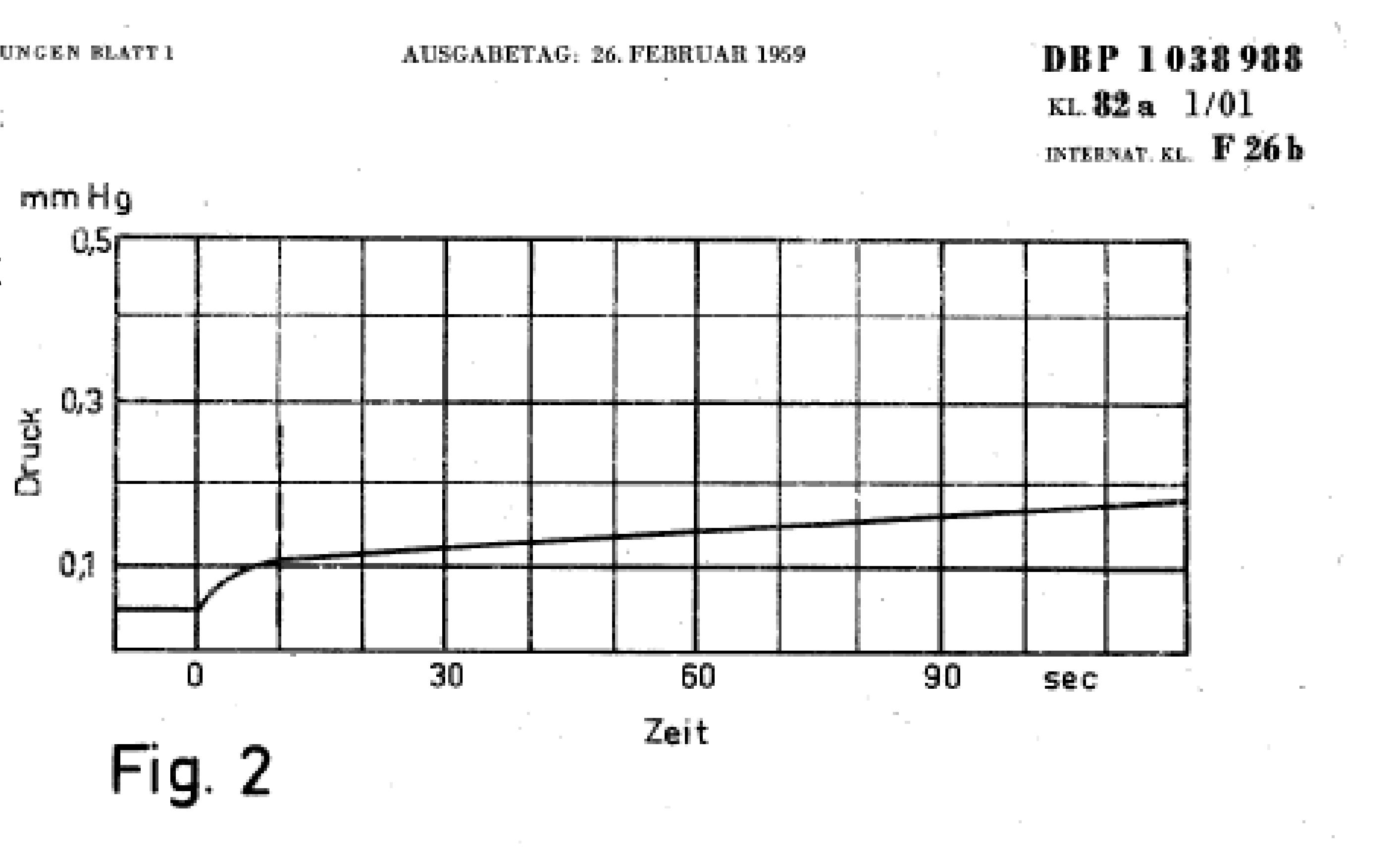
Chamber pressure, directly measureable

Condenser pressure, directly measureable



Theory of Barometric Temperature Measurement (BTM)

- Indirect measurement of pressure at sublimation front by closing the intermediate valve



Theory of Barometric / Manometric Temperature Measurement (BTM / MTM)

- Pressure equalizes at equilibrium point
- Further pressure rise is result of steady warming of the whole batch => Risk of product melt
- Equilibrium point and pressure rise characteristic changes with sublimation progress

Theory of Barometric Temperature Measurement (BTM)

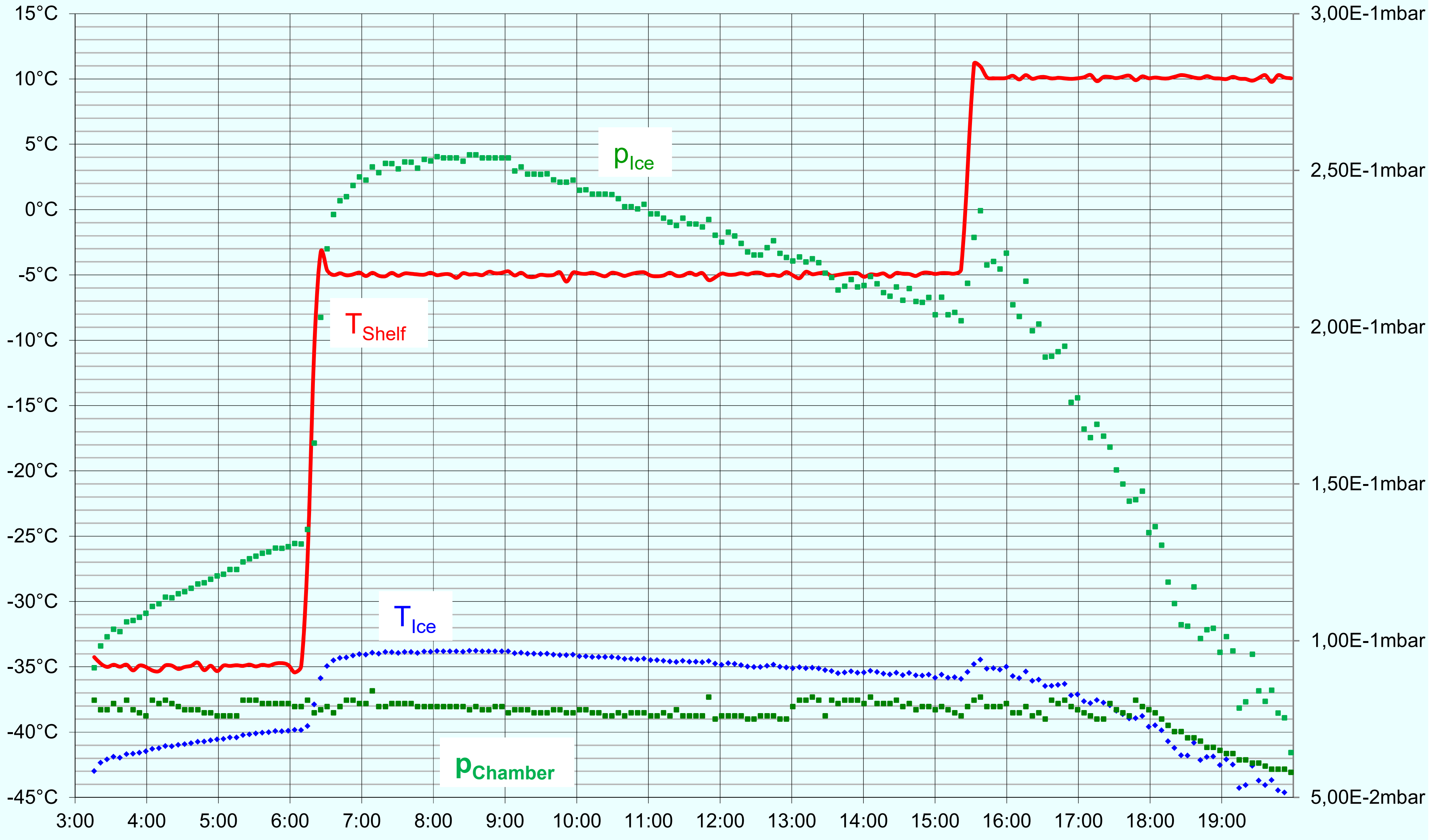
- Procedure is sensitive against low number of remaining vials
- A change of shelf temperature for cycle tuning is not recommendable => process inhomogeneity
- The numeric fit-procedure allows the calculation of the results with MS-Excel

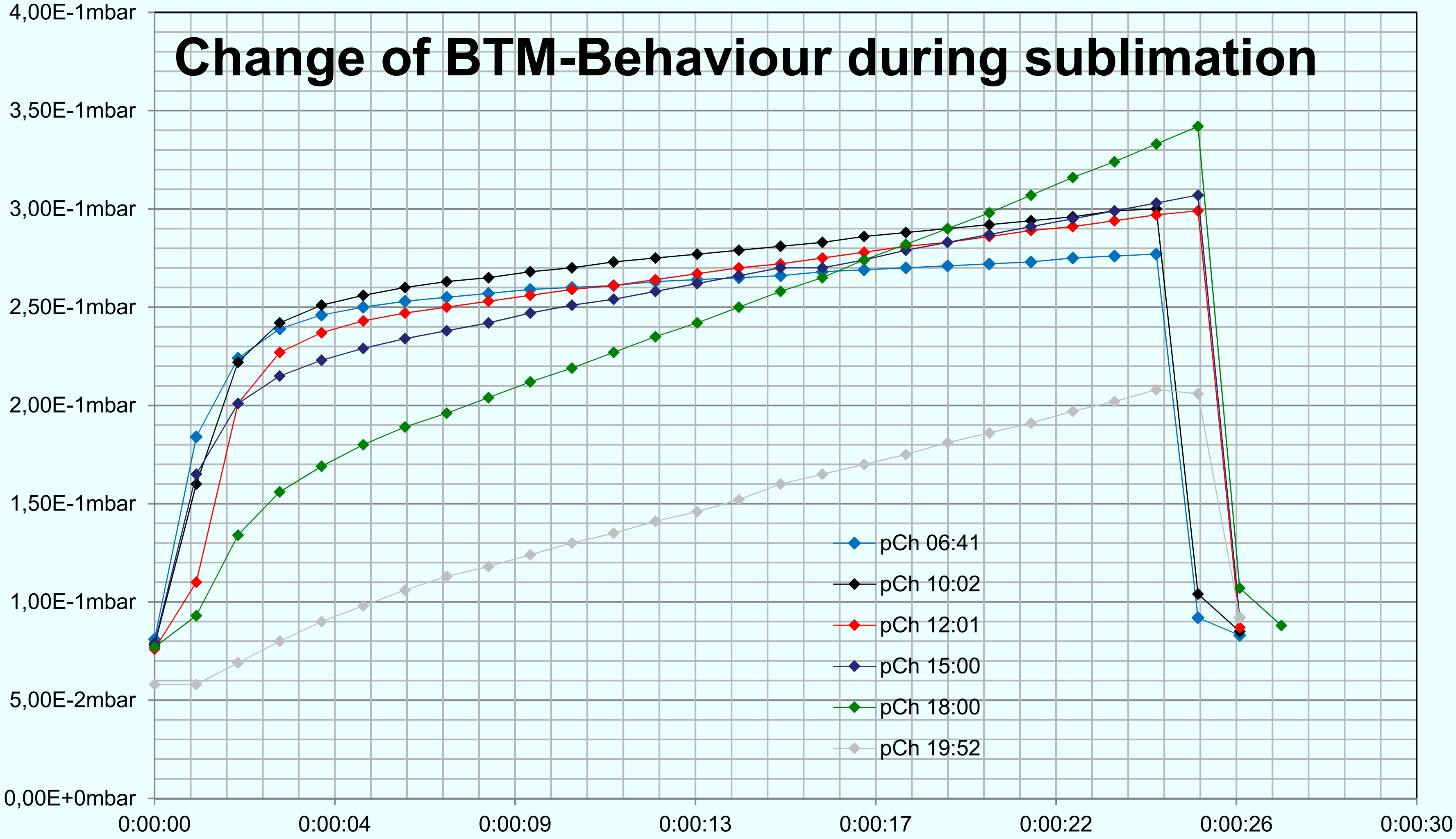
Theory of Barometric Temperature Measurement (BTM)

$$P_{(t)} = P_{Ice} - (P_{Ice} - P_0) \cdot e^{-t \cdot \frac{N \cdot A_p \cdot 62{,}3 \cdot T'}{18 \cdot V \cdot R_p \cdot 3600}} + 0{,}0465 \cdot P_{Ice} \cdot \left(\frac{24{,}7 \cdot L_{Ice} \cdot (P_{Ice} - P_0)}{R_p} - 0{,}0102 \cdot L_{Ice} \cdot \frac{\left(T' - \frac{6144{,}96}{24{,}01849 - \ln(P_{Ice})} \right)}{1 - 0{,}0102 \cdot L_{Ice}} \right) \cdot \left(1 - 0{,}811 \cdot e^{\left(-0{,}114 \cdot \frac{t}{L_{Ice}} \right)} \right) + EX \cdot t$$

Symbol	Unit	Description	
$P_{(t)}$	[Torr]	Chamber pressure	Measured
P_{Ice}	[Torr]	Vapor pressure at sublimation front	To be solved
P_0	[Torr]	Chamber pressure at start of BTM	Measured
N	[ ]	Number of vials	To be known
A_p	[cm²]	Average surface of the vial	To be known
T’	[K]	Shelf temperature	Measured
V	[l]	Effective chamber Volume	To be known
R_p		Flow resistance of dried cake	To be solved
L_{Ice}	[cm]	Filling level, Layer thickness	To be known
EX		Linear part of pressure rise due to leak rate and warming of product	To be solved
t	[s]	Time	Measured

Hands On


15°C
10°C
5°C
0°C
-5°C
-10°C
-15°C
-20°C
-25°C
-30°C
-35°C
-40°C
-45°C
3,00E-1mbar
2,50E-1mbar
2,00E-1mbar
1,50E-1mbar
1,00E-1mbar
5,00E-2mbar
3:00
4:00
5:00
6:00
7:00
8:00
9:00
10:00
11:00
12:00
13:00
14:00
15:00
16:00
17:00
18:00
19:00
pIce
TShelf
TIce
pChamber


Change of BTM-Behaviour during sublimation
4,00E-1mbar
3,50E-1mbar
3,00E-1mbar
2,50E-1mbar
2,00E-1mbar
1,50E-1mbar
1,00E-1mbar
5,00E-2mbar
0,00E+0mbar
0:00:00
0:00:04
0:00:09
0:00:13
0:00:17
0:00:22
0:00:26
0:00:30
pCh 06:41
pCh 10:02
pCh 12:01
pCh 15:00
pCh 18:00
pCh 19:52

The material shown in this presentation does not represent the official oppinion of Bayer Pharma or any linked subsidiary company

Bayer Pharma or any linked subsidiary company are not responsible for any content of this presentation

Thank you for your attention!

<u>Questions?</u>

Table of critical temperatures

Sucrose	**amorphous**	**307,9µbar**	**-32°C**
Mannitol	**crystalline**	**3.685,0µbar**	**-6°C**
Lactose	**amorphous**	**466,9µbar**	**-28°C**
NaCl	**crystalline**	**850,2µbar**	**-22°C**
$CaCl_2$	**crystalline**	**23,8µbar**	**-54°C**

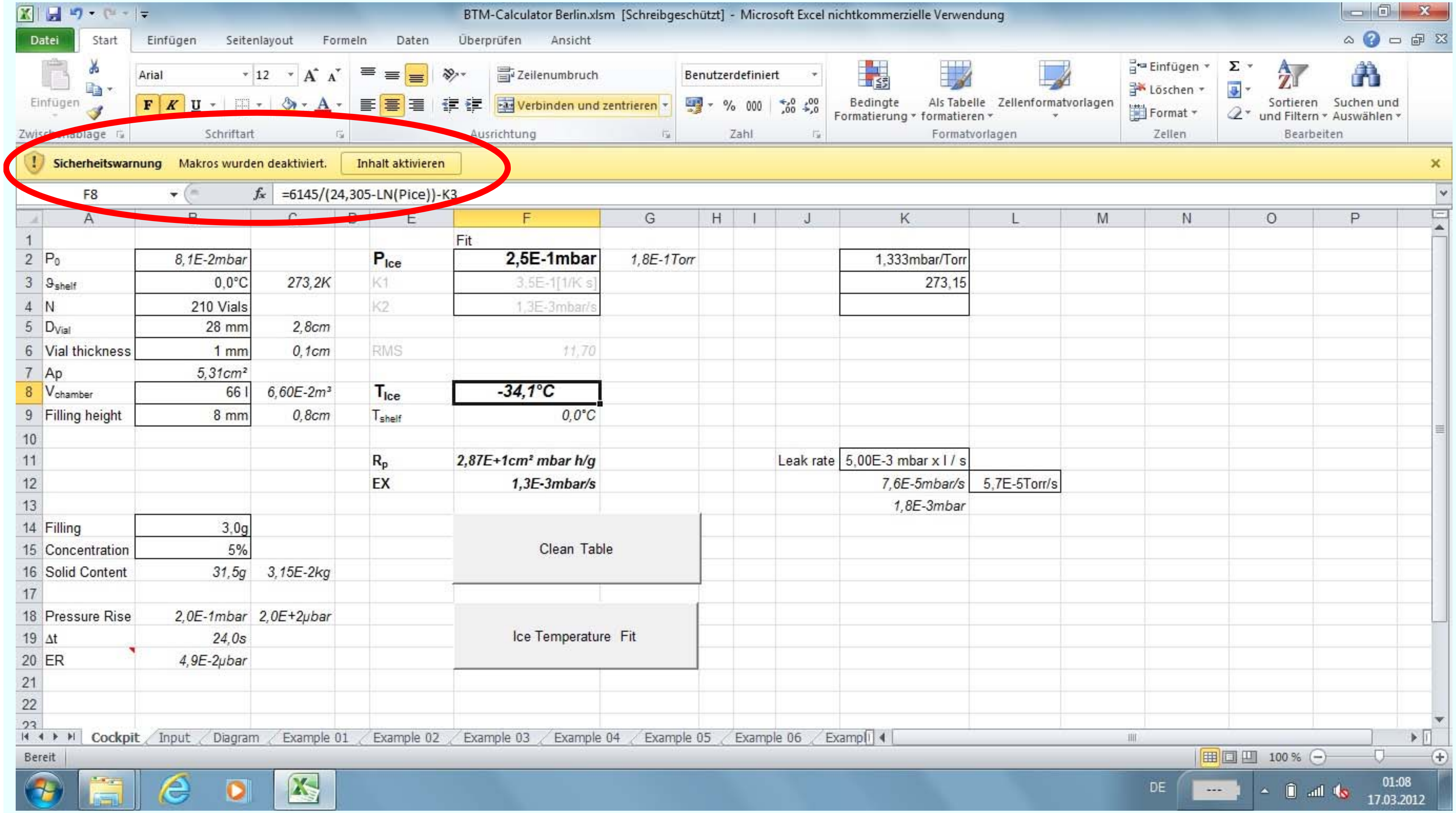
Preparation to use the Excel-Solver

- Activate Macros / Deactivate “protection”
- Register Solver in MS-Excel
- Install Solver as VBA-Reference

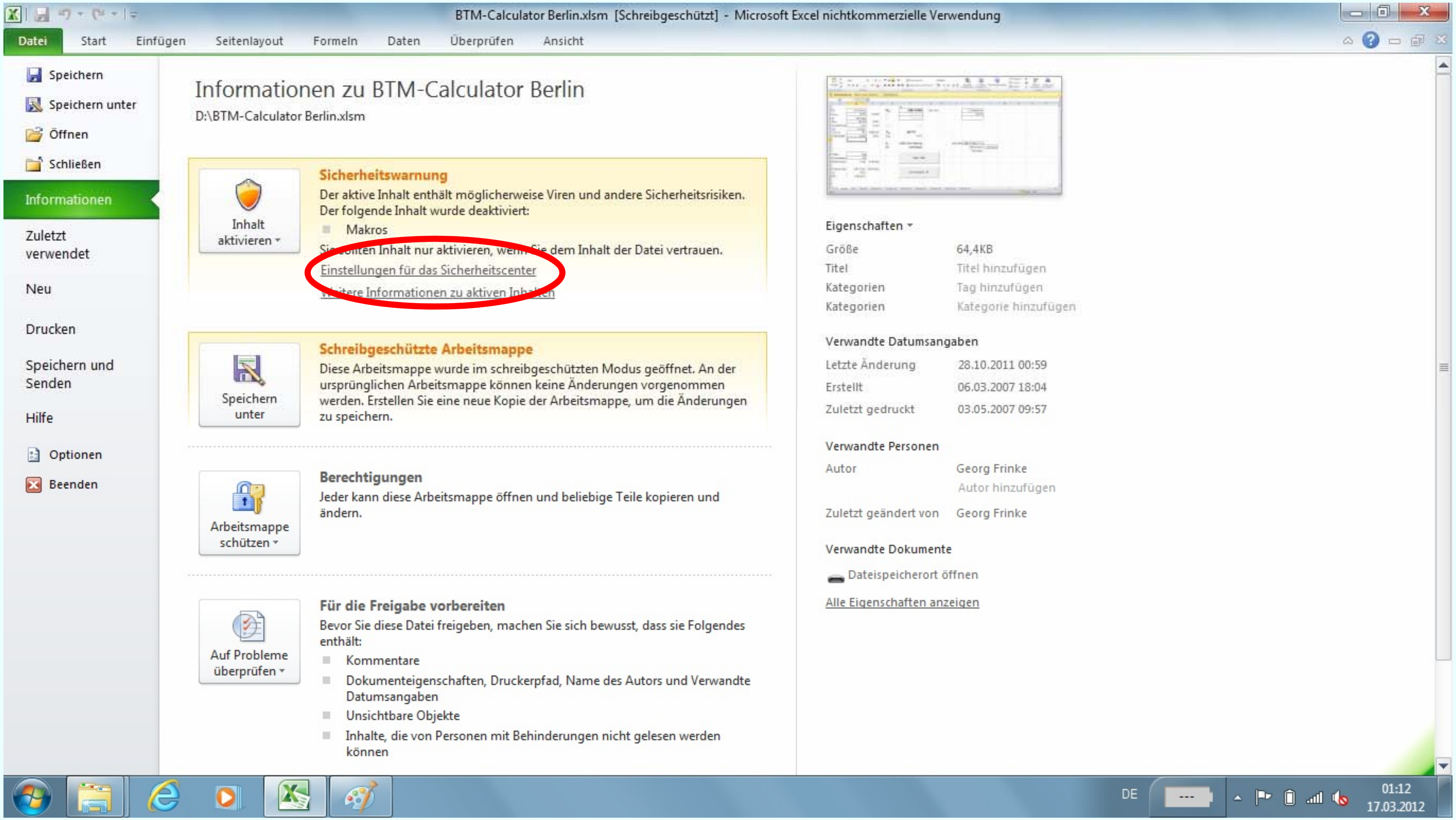
PDA
Parenteral Drug Association

Connecting People, Science and Regulation ®

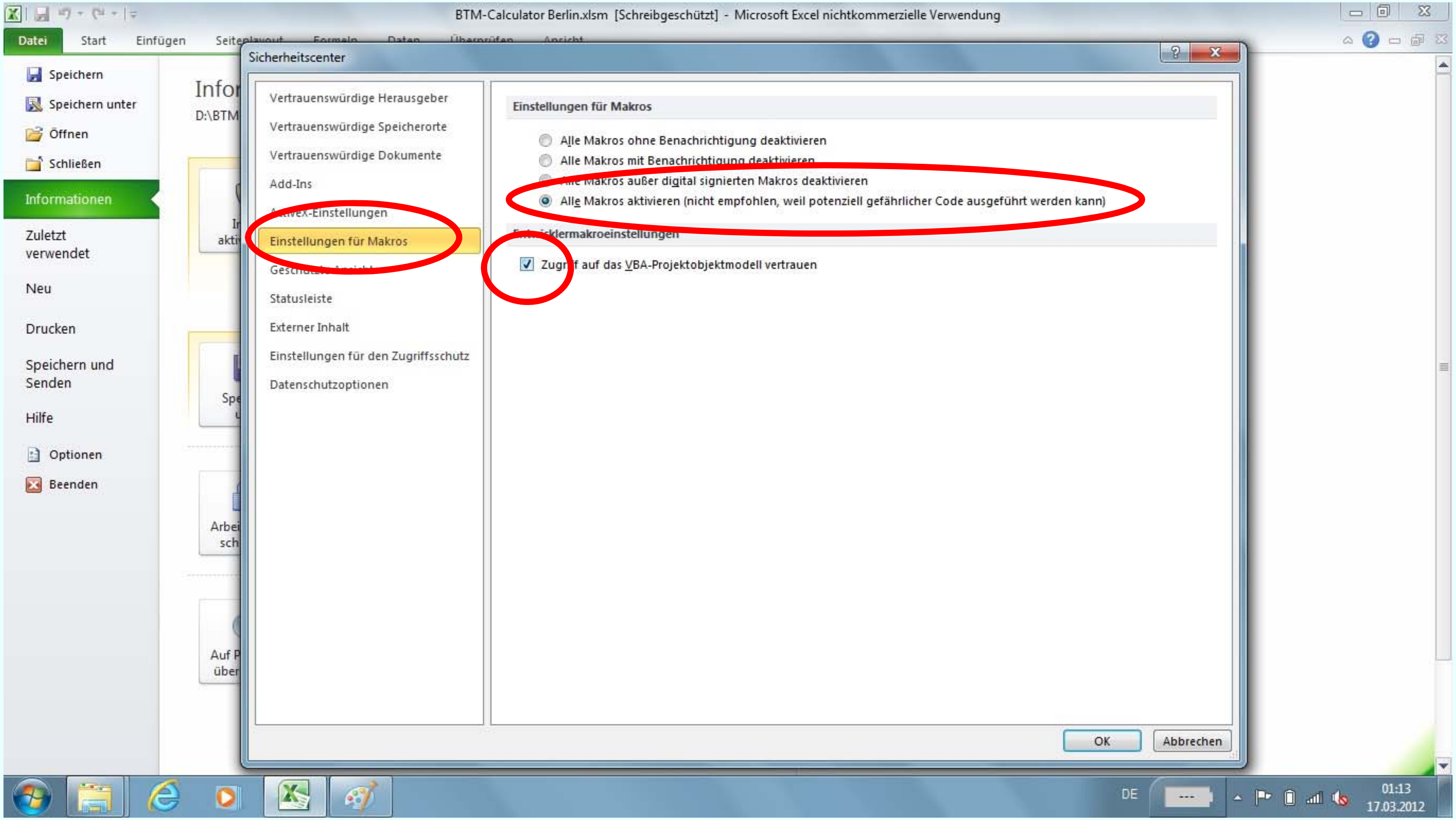
Activate Macros / Deactivate “protection”



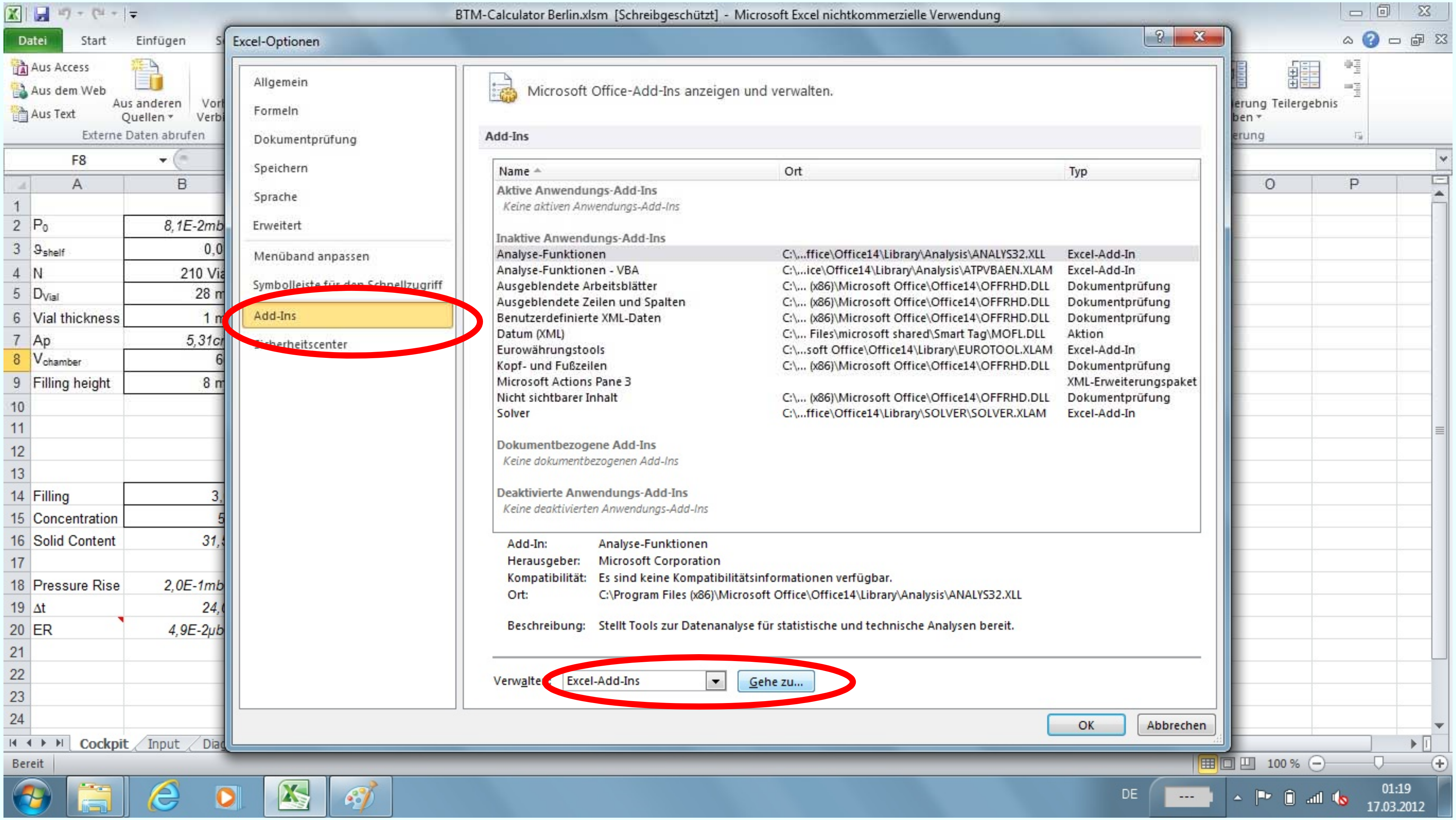
Activate Macros / Deactivate “protection”



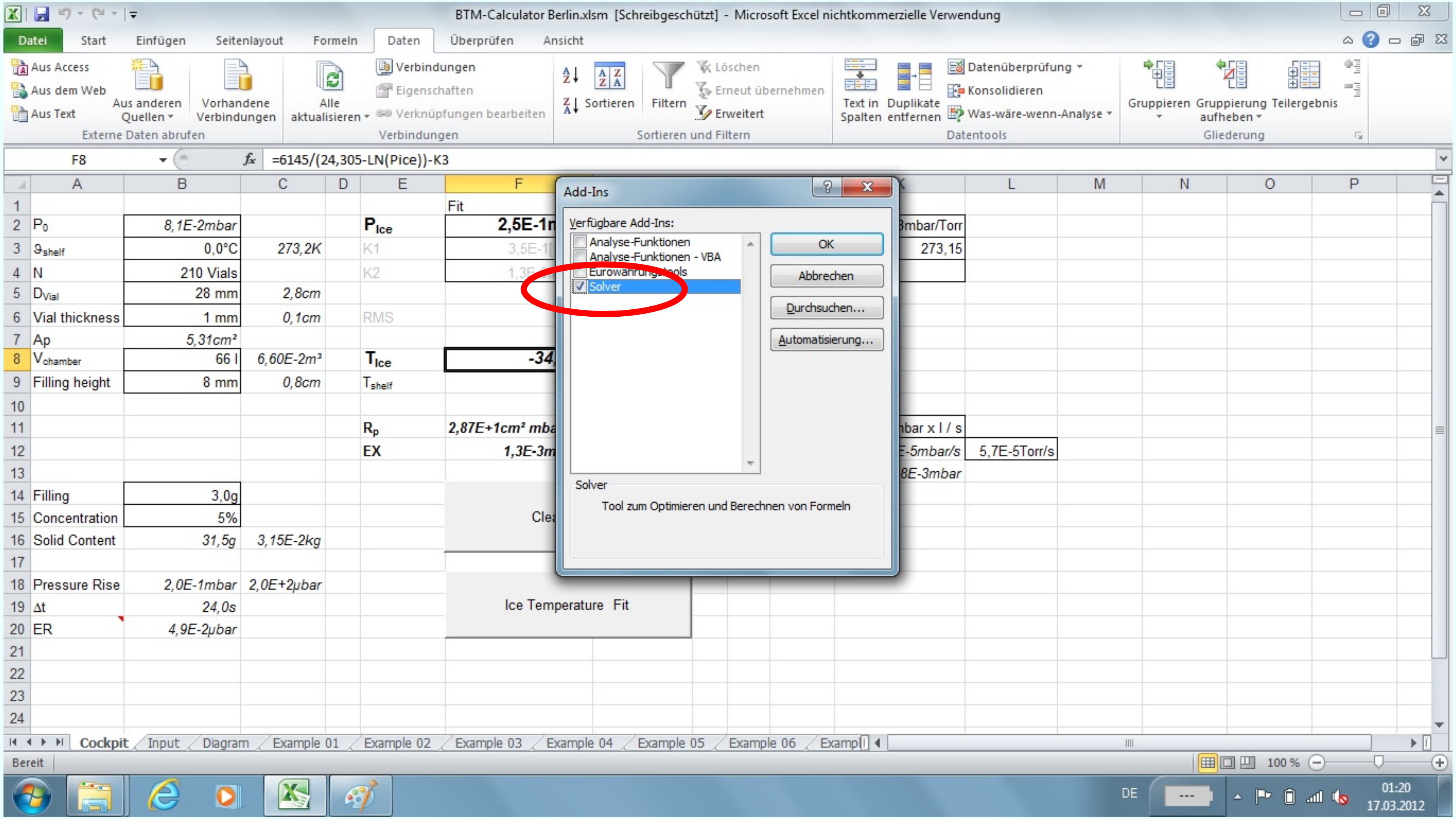
Activate Macros / Deactivate "protection"



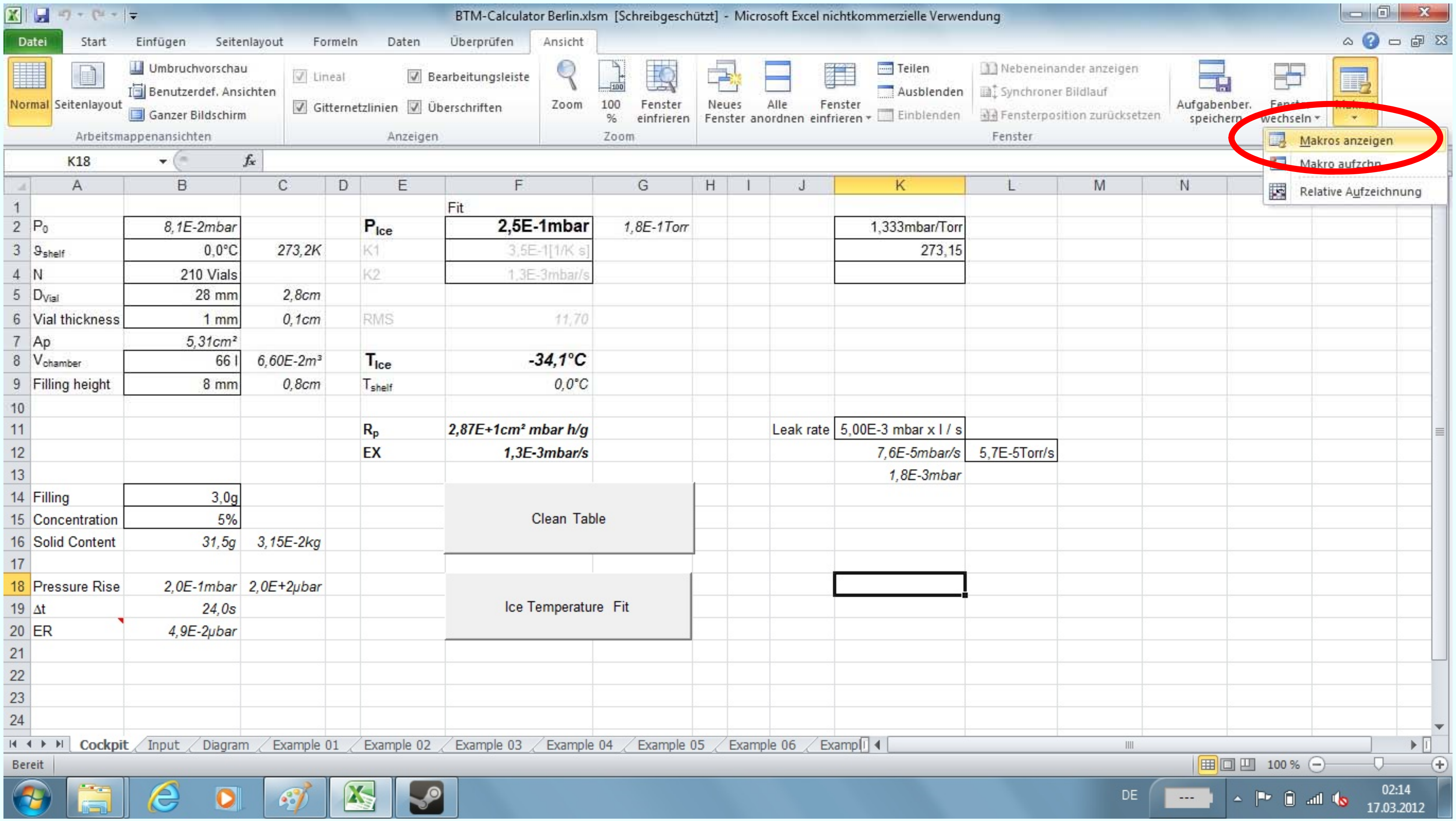
Register Solver in MS-Excel



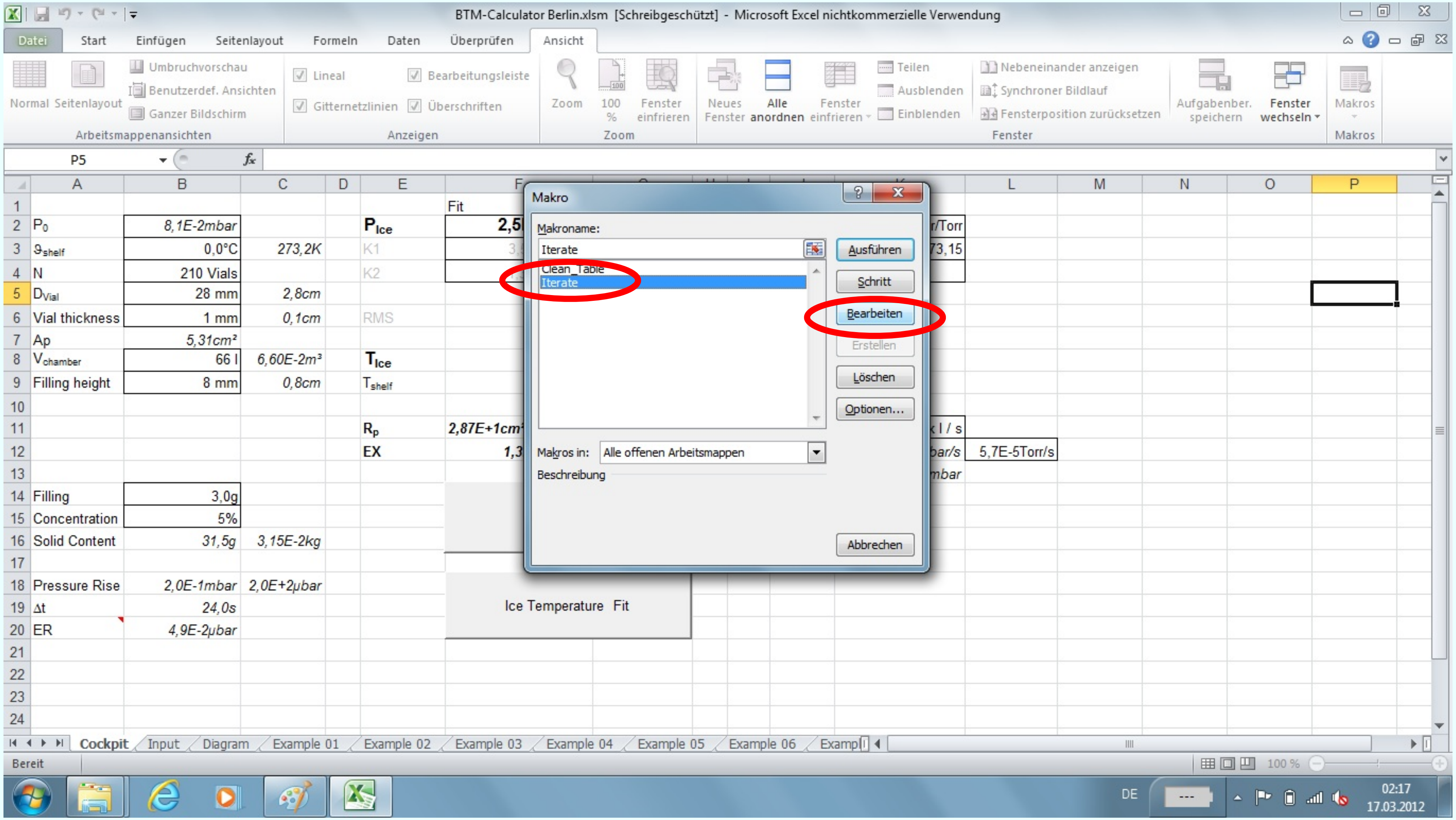
Register Solver in MS-Excel



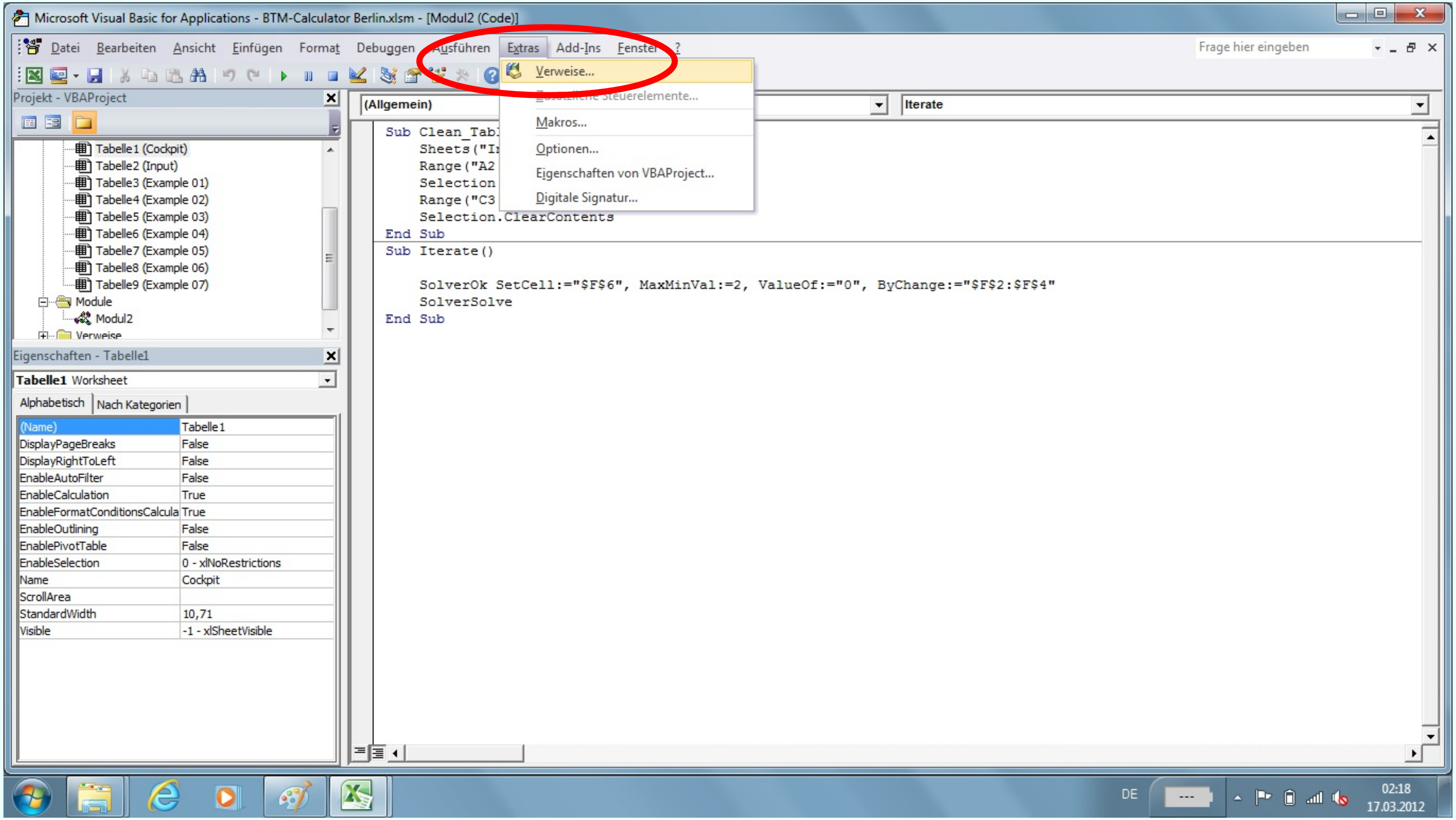
Install Solver as VBA-Reference



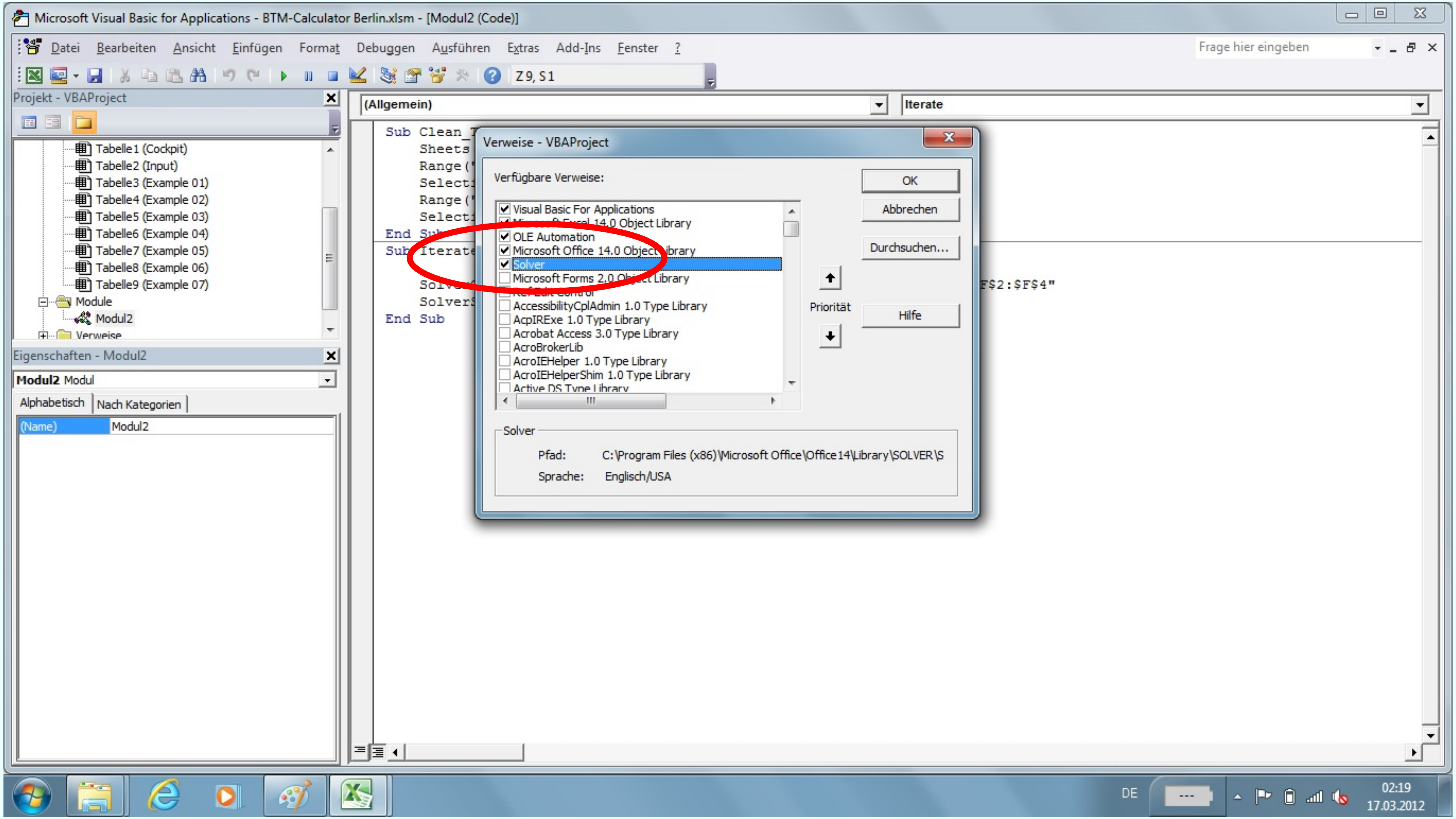
Activate Macros / Deactivate "protection"



Activate Macros / Deactivate “protection”



Activate Macros / Deactivate "protection"



Then close all windows, except Excel table

…Run “solver” once manually…

..and careful listen to the further explanations of the instructor