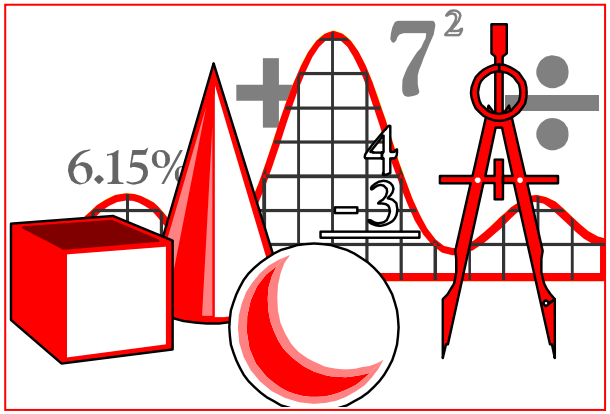
Validation of Sympatec Instruments

Introduction

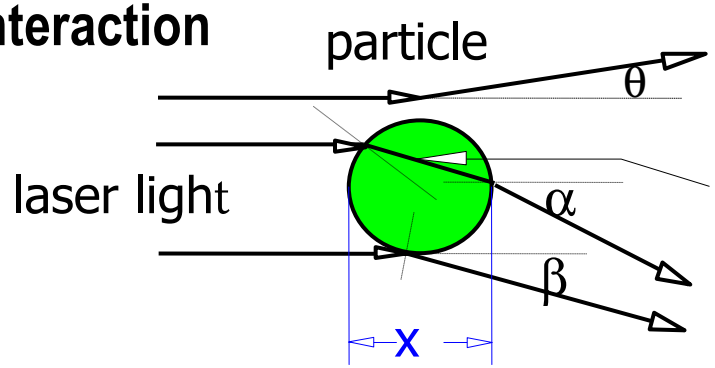
- ★ Principle of Laser Diffraction, e.g.
  - ☆ Fraunhofer vs. Mie
- ★ Verification
  - ☆ Reference materials vs. reticles
  - ☆ Reference material sets
  - ☆ Specifications
- ★ Sympatec's Quality Securing System (SQS)
  - ☆ Staff
  - ☆ Development
  - ☆ Production
    - ✳ Flow
    - ✳ Final control
    - ✳ Certification
  - ☆ Re-certification
  - ☆ Validation binder
  - ☆ Audits



Principle of Laser Diffraction, e.g.

Fraunhofer- vs. Mie-Theory

Physics of interaction

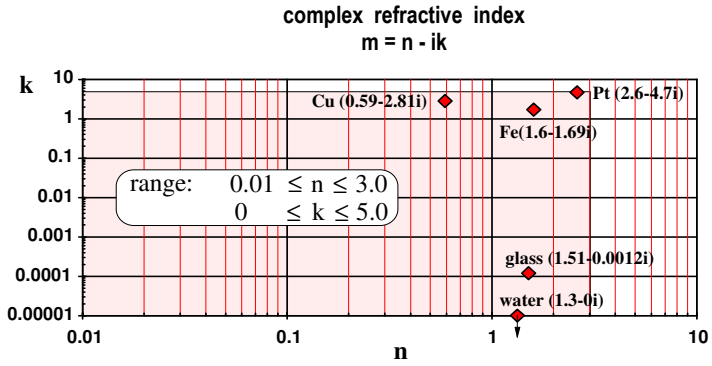


diffraction	Fraunhofer *(no parameters)*
absorption refraction reflection	Mie theory *(n-ik necessary)*

Mie: *Subject to parameters*

Fraunhofer: ✔ *Parameter free*

↳ Can be standardised



Validation of LD systems ➠ Fraunhofer

Verification

Reference Material

★ *Since 1984* Sympatec applies reference materials for HELOS

★ *Verification* of quality of Sympatec instruments

★ Market introduction in January 1995

★ Backbone of *validation*

Definitions

★ Reference material = stable material of *arbitrary particle shape*, it is certified values are referenced to a *reference method*

★ Standard material = *spherical material*, certified values are directly traced to the *standard metre* (via microscopy)

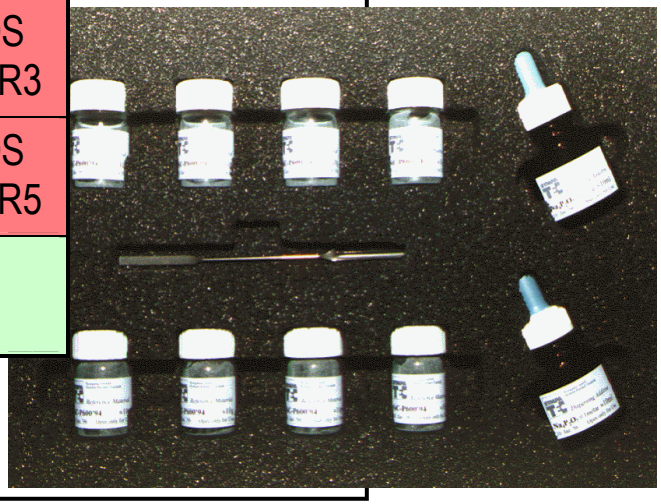
Application Area

★ Check of measuring system by comparison with average values of all *Sympatec instruments* of equal configuration

★ *Dispersing system* is included in the check

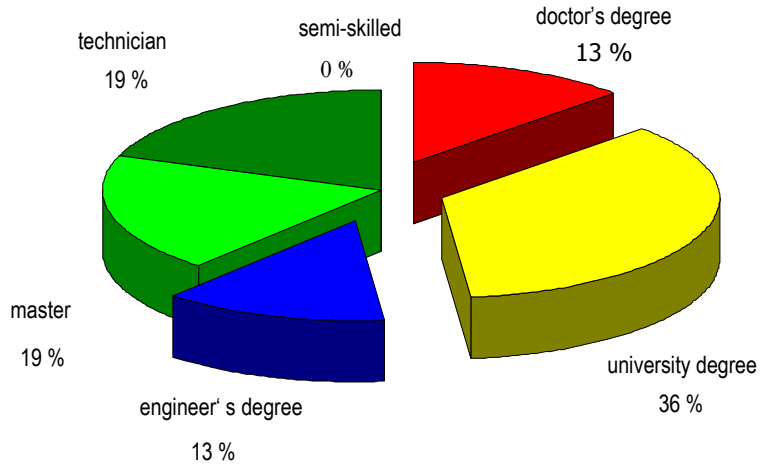
Reference Material Sets

Set	Material	Content	Range
Set 1 HZ0010	SiC-F1200 $x_{50} \approx 4.1$ µm	8 sample bottles of 5 g each 2 bottles of dispersing agent, 10 ml spatula, specifications TKSI-...	R1, R2, R3
Set 2 HZ0020	SiC-P600 $x_{50} \approx 28$ µm	8 sample bottles of 10 g each 2 bottles of dispersing agent, 10 ml spatula, specifications TKSI-...	R3, R4, R5
Set 3 HZ0030	SiC-P50 $x_{50} \approx 420$ µm	8 sample bottles of 20 g each specifications TKSI-...	R6, R7, R8 M7, M8
Set 5 HZ0050	SiC-P80 $x_{50} \approx 250$ µm	8 sample bottles of 20 g each specifications TKSI-...	R5, R6, R7 M6, M7
Set 6 HZ0060	SiC-F1200 $x_{50} \approx 4.1$ µm	64 sample tubes of 1,2 g each, incl. Barcode, specifications TKSI…	ASPIROS R1, R2, R3
Set 7 HZ0070	SiC-P600 $x_{50} \approx 28$ µm	64 sample tubes of 150 mg each, incl. Barcode, specifications TKSI…	ASPIROS R3, R4, R5
Set 8 HZ0080	SiC-P16 $x_{50} \approx 1600$ µm	8 sample bottles of 20 g each specifications TKSI-...	R8 M8



Sympatec's Quality Securing System (SQS)

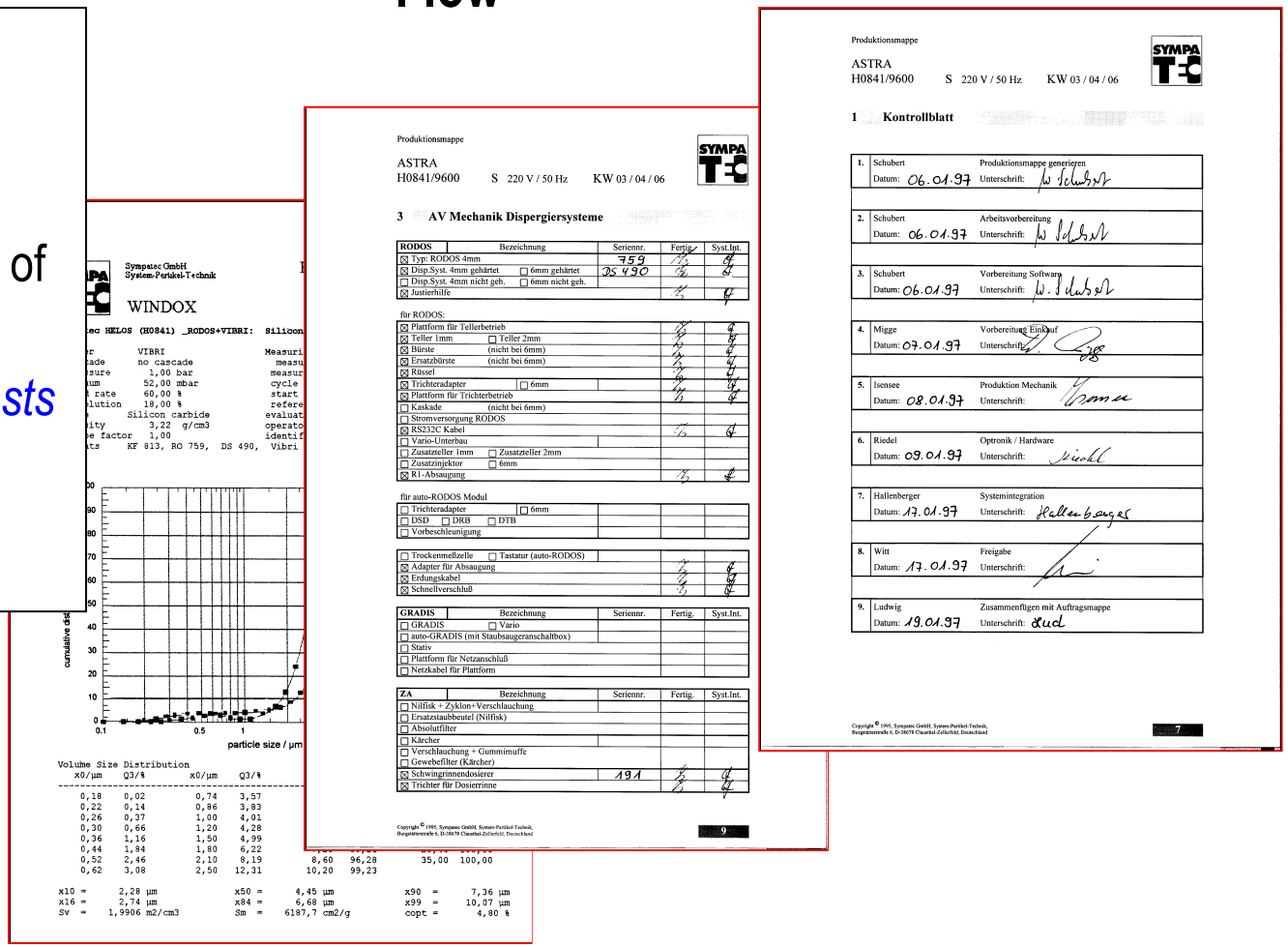
- ★ Development
  - ☆ Mechanics
  - ☆ Hardware
  - ☆ Software
  - ☆ Firmware
  - ☆ Laser diffraction
  - ☆ Ultrasonic extinction
- ★ Audits
- ★ Staff
- ★ Production
  - ☆ Goods inward
  - ☆ Assembling
  - ☆ Final control
  - ☆ Certification
- ★ Re-certification
- ★ Validation binder



Production

Flow

- ✔ *Production file*
- ✔ Definition of *components*
- ✔ Documentation of *serial numbers*
- ✔ Documented *tests*
- ✔ Documented *responsibility*



Sympatec GmbH
System-Partikel-Technik

WINDOX

Volume Size Distribution

x0/µm	Q3/%	x0/µm	Q3/%	x0/µm	Q3/%
0,18	0,02	0,74	3,57		
0,22	0,14	0,86	3,83		
0,26	0,37	1,00	4,01		
0,30	0,66	1,20	4,28		
0,36	1,16	1,50	4,99		
0,44	1,84	1,80	6,22		
0,52	2,46	2,10	8,19	8,60	96,28
0,62	3,08	2,50	12,31	10,20	99,23

x10 = 2,28 µm x50 = 4,45 µm x90 = 7,36 µm
x16 = 2,74 µm x84 = 6,68 µm x99 = 10,07 µm
Sv = 1,9906 m2/cm3 Sm = 6187,7 cm2/g copt = 4,80 %

Produktionsmappe

ASTRA
H0841/9600 S 220 V / 50 Hz KW 03 / 04 / 06

3 AV Mechanik Dispergiersysteme

RODOS	Bezeichnung	Seriennr.	Fertig.	Syst.Int.
☒	Typ: RODOS 4mm	359		
☒	Disp.Syst. 4mm gehärtet ☐ 6mm gehärtet	DS 490		
☐	Disp.Syst. 4mm nicht geh. ☐ 6mm nicht geh.			
☒	Justierhilfe			

für RODOS:

☒	Plattform für Tellerbetrieb			
☒	Teller 1mm ☐ Teller 2mm			
☒	Bürste (nicht bei 6mm)			
☒	Ersatzbürste (nicht bei 6mm)			
☒	Rüssel			
☒	Trichteradapter ☐ 6mm			
☒	Plattform für Trichterbetrieb			
☐	Kaskade (nicht bei 6mm)			
☐	Stromversorgung RODOS			
☒	RS232C Kabel			
☐	Vario-Unterbau			
☐	Zusatzteller 1mm ☐ Zusatzteller 2mm			
☐	Zusatzinjektor ☐ 6mm			
☒	R1-Absaugung			

für auto-RODOS Modul

☐	Trichteradapter ☐ 6mm			
☐	DSD ☐ DRB ☐ DTB			
☐	Vorbeschleunigung			
☐	Trockenmeßzelle ☐ Tastatur (auto-RODOS)			
☒	Adapter für Absaugung			
☒	Erdungskabel			
☒	Schnellverschluß			

GRADIS	Bezeichnung	Seriennr.	Fertig.	Syst.Int.
☐	GRADIS ☐ Vario			
☐	auto-GRADIS (mit Staubsaugeranschaltbox)			
☐	Stativ			
☐	Plattform für Netzanschluß			
☐	Netzkabel für Plattform			

ZA	Bezeichnung	Seriennr.	Fertig.	Syst.Int.
☐	Nilfisk + Zyklon+Verschlauchung			
☐	Ersatzstaubbeutel (Nilfisk)			
☐	Absolutfilter			
☐	Kärcher			
☐	Verschlauchung + Gummimuffe			
☐	Gewebefilter (Kärcher)			
☒	Schwingrinnendosierer	191		
☒	Trichter für Dosierrinne			

Produktionsmappe

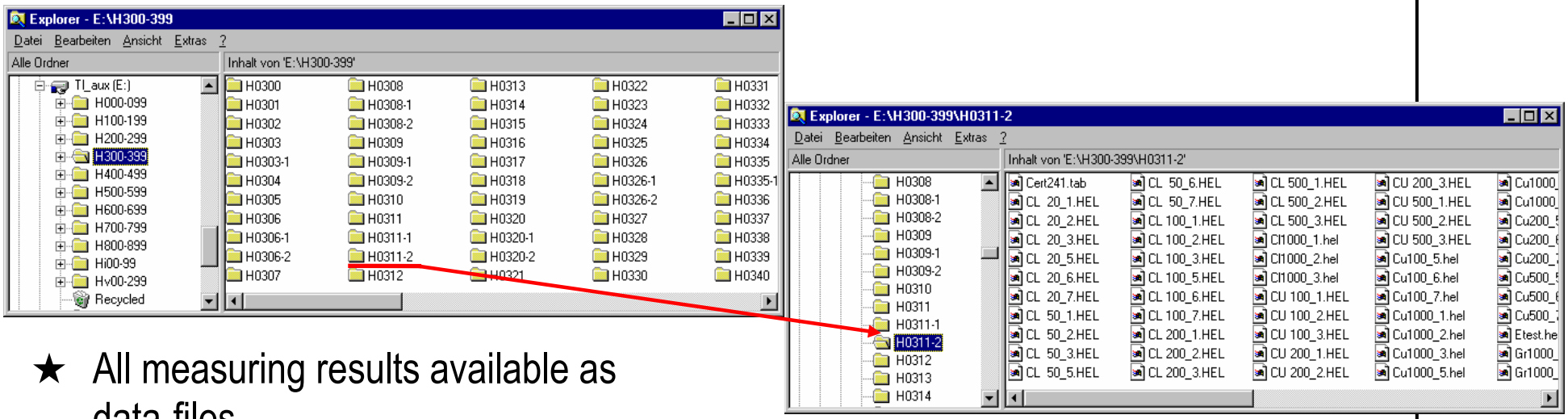
ASTRA
H0841/9600 S 220 V / 50 Hz KW 03 / 04 / 06

1 Kontrollblatt

1.	Schubert	Produktionsmappe generieren	
	Datum: 06.01.97	Unterschrift:	
2.	Schubert	Arbeitsvorbereitung	
	Datum: 06.01.97	Unterschrift:	
3.	Schubert	Vorbereitung Software	
	Datum: 06.01.97	Unterschrift:	
4.	Migge	Vorbereitung Einkauf	
	Datum: 07.01.97	Unterschrift:	
5.	Isensee	Produktion Mechanik	
	Datum: 08.01.97	Unterschrift:	
6.	Riedel	Optronik / Hardware	
	Datum: 09.01.97	Unterschrift:	
7.	Hallenberger	Systemintegration	
	Datum: 17.01.97	Unterschrift:	
8.	Witt	Freigabe	
	Datum: 17.01.97	Unterschrift:	
9.	Ludwig	Zusammenfügen mit Auftragsmappe	
	Datum: 19.01.97	Unterschrift:	

Final Control

- ★ Three stages
  - ✔ Test on reception (laser, detector, optics, etc.)
  - ✔ „Cold“ check (mechanical, electrical, optical)
  - ✔ „Hot“ check (measurements with particles)
- ★ Completely documented with production file



- ★ All measuring results available as data-files
- ★ Extent: Currently >> 150.000 files

Certification

Every Sympatec Instrument has to perform a four-step certification procedure during the system integration process:

1. Electric and optical properties are measured, documented and compared with pre-defined limits
2. Every possible combination of measuring range and dispersing unit is tested with *reference material*:
   - ✔ In general two materials are measured at least three times
   - ✔ x_{10}, x_{16}, x_{50}, x_{84}, x_{90} (and x_{99}) are listed in the specification sheet
   - ✔ The average values are calculated and compared with the established absolute limits
   - ✔ All serial numbers are taken to be listed in the certification sheet
   - ✔ The production file is completed with all the manufacturing notes, signatures, serial numbers and measured results
3. The certificate is *signed off* only, if *all results* are within the limits and the documentation is complete
4. The system is shipped together with the certificate

CERTIFICATE

HELOS system no. H1234

comprising:

Component	Serial Number	Component	Serial Number
HELOS/BF	1331	**MEGAGRADIS**	247
Measuring ranges	R1-R7T	**VIBRI**	
PCI-FOL	279A	**ASPIROS**	111
WINDOX 4	Vers. 2 Rel.1.0	**SUCELL**	133
MIE	050A	Cuvette 2mm	02025
Add-ons		Cuvette 4mm	02024
USB key 1	2012U	**QUIXEL**	258
USB key 2		**CUV-CHASSIS**	
QX		**CUV-50ML/US**	
HP-Vectra	YBQN140632	Glass 50ml	
		Spare glass 50ml	
WINDOWS 2000		**CUV-6ML/SM**	
Monitor	YEUN088617	Glass 6ml	
Keyboard	YBKB020617279786	Spare glass 6ml	
		SAFIR	
Mouse	HCA20570877	**INCELL**	
		SPRAYER	152
Printer		**ROTOR/M**	
RODOS	1259	**INHALER**	
Dispersing line 4mm	DS1213	Vacuum pump	
Dispersing line 6mm			
Nilfisk			
Compressor			

The system listed above was carefully manufactured and extensively tested by Sympatec's System Integration Group.

We certify, that the testing results for the preceding configuration meet the Sympatec specifications listed as TKSI02-4DR without any restriction.

Goslar,
SYMPATEC GmbH
System-Partikel-Technik

Head of Quality Assurance

Goslar,
SYMPATEC GmbH
System-Partikel-Technik

Head of System Integration Group

Production Certificate

CERTIFICATE

HELOS system no. H1234

comprising:

Component	Serial Number/Chk		Component	Serial Number/Chk	
HELOS/BF	1331	☐	**MEGAGRADIS**	247	☐
Measuring ranges	R1-R7T	☐	**VIBRI**		☐
PCI-FOL	279A	☐	**ASPIROS**	111	☐
WINDOX 4	Vers. 2 Rel.1.0	☐	**SUCELL**	133	☐
MIE	050A	☐	Cuvette 2mm	02025	☐
Add-ons		☐	Cuvette 4mm	02024	☐
USB key 1	2012U	☐	**QUIXEL**	258	☐
USB key 2		☐	**CUV-CHASSIS**		☐
QX		☐	**CUV-50ML/US**		☐
HP-Vectra	YBQN140632	☐	Glass 50ml		☐
			Spare glass 50ml		☐
WINDOWS 2000		☐	**CUV-6ML/SM**		☐
Monitor	YEUN088617	☐	Glass 6ml		☐
Keyboard	YBKB020617279786	☐	Spare glass 6ml		☐
			SAFIR		☐
Mouse	HCA20570877	☐	**INCELL**		☐
		☐	**SPRAYER**	152	☐
Printer		☐	**ROTOR/M**		☐
RODOS	1259	☐	**INHALER**		☐
Dispersing line 4mm	DS1213	☐	Vacuum pump		☐
Dispersing line 6mm		☐			☐
Nilfisk		☐			☐
Compressor		☐			☐
		☐			☐
		☐			☐

We certify, that the testing results for the preceding configuration meet the Sympatec specifications listed as TKSI02-4DR without any restriction

Goslar,
SYMPATEC GmbH
System-Partikel-Technik

Head of Quality Assurance

The system listed above was inspected and tested *after installation* by the signer

Place, date .....

Company .....

Signature .....

Name .....

Inspector

Installation Certificate

Re-certification

Required Number of Reference Material Sets:

Dispersing Unit	Measuring Range	HZ0010 SiC-F1200 8 x 10 g	HZ0020 SiC-P600 8 x 10 g	HZ0030 SiC-P50 8 x 20 g	HZ0050 SiC-P80 8 x 20 g
RODOS,	R1 (f = 20 mm)	4			
RODOS/M	R2 (f = 50 mm)	4			
4 mm	R3 (f = 100 mm)	4	4		
Disp.strecke	R4 (f = 200 mm)		4		
	R5 (f = 500 mm)		4		4
	R6 (f = 1000 mm)				4
	R7 (f = 2000 mm)				4
6 mm Dispersing	R6 (f = 1000 mm)			4	
Line only	R7 (f = 2000 mm)			4	
GRADIS,	R5 (f = 500 mm)				4
MEGAGRADIS	R6 (f = 1000 mm)			4	4
	R7 (f = 2000 mm)			4	4
	R8 (f = 5000 mm)			8	
SUCELL,	R1 (f = 20 mm)	0.1			
SUCELL/M,	R2 (f = 50 mm)	0.1			
QUIXEL	R3 (f = 100 mm)	0.1	0.1		
	R4 (f = 200 mm)		0.1		
	R5 (f = 500 mm)		0.1		
	R6 (f = 1000 mm)		0.1		
CUVETTE	R2 (f = 50 mm)	0.1			
50 ml	R3 (f = 100 mm)	0.1	0.1		
	R4 (f = 200 mm)		0.1		
	R5 (f = 500 mm)		0.1		
	R6 (f = 1000mm)		0.1		

Any Sympatec Instrument can be re-certified at customer's location at any time using reference material sets.

Conditions for approval of re-certification:

- ☆ Serial numbers / results in accordance with all limits
- ☆ Testing person approves validity of procedure with his signature

Validation Binder

Contents

- ★ General:
  - ☆ Sympatec's validation procedure
  - ☆ Sympatec's SQS strategy
  - ☆ Sample quotation for a validation procedure
  - ☆ Example of an audit procedure
  - ☆ Organisation chart and status of education
  - ☆ Software validation
  - ☆ Back-up strategy
- ★ System specific documents:
  - ☆ Verification of system specifications
  - ☆ Certificate
  - ☆ Copy of production file (in parts)
  - ☆ Specifications of reference materials
- ★ system specific test procedures (IQ, OQ, PQ) for:
  - ☆ Installation
  - ☆ Documentation
  - ☆ Software files
  - ☆ Ambient conditions
  - ☆ Re-certification (prepared)

Conclusion

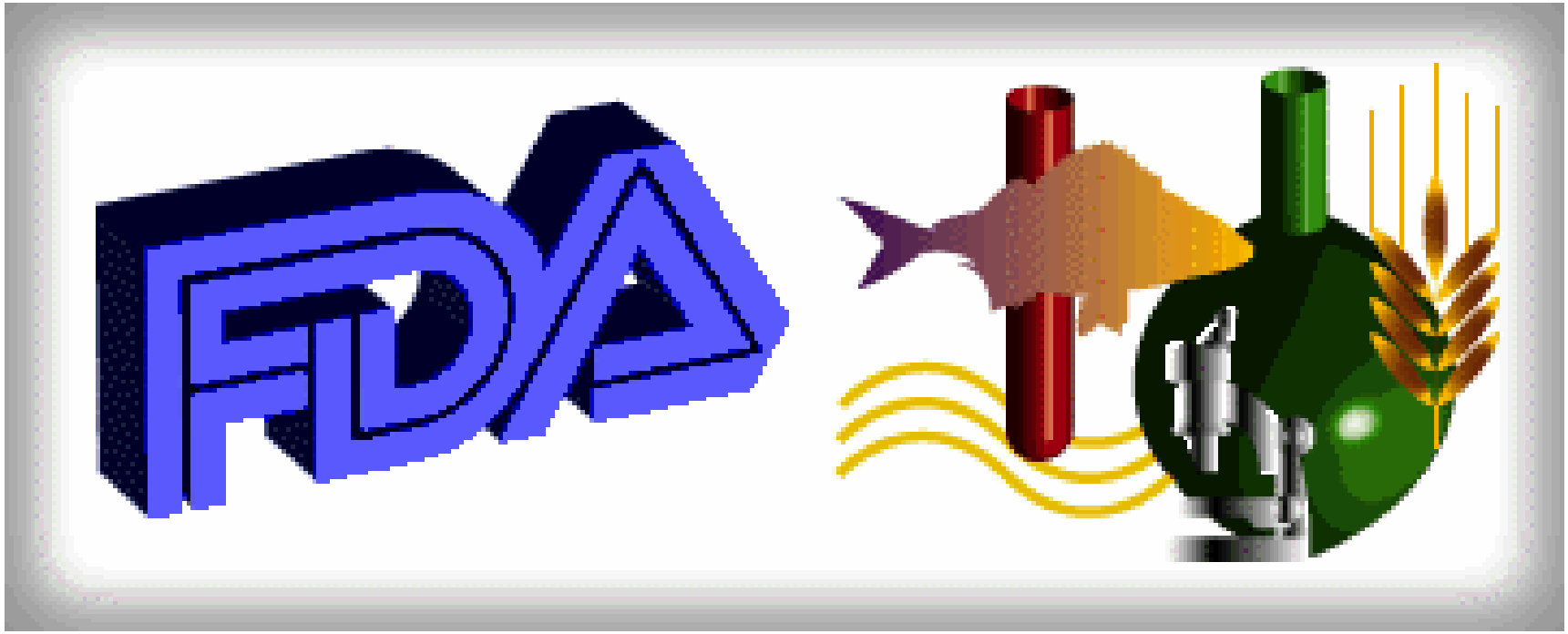
- ★ Sympatec's validation procedure of instruments for particle size analysis has been established as *standard procedure*
- ★ All systems are produced in accordance to the requests of an *optional subsequent validation*
- ★ The validation procedure is supported with
  - ☆ Sympatec's Validation Binder
  - ☆ Sympatec's Reference Materials
  - ☆ Optional audits of Sympatec's production
  - ☆ Certified service engineers
  - ☆ Adapted service contracts
- ★ Currently validation is available for
  - ☆ HELOS*
  - ☆ MYTOS*
  - ☆ OPUS
  - ☆ QICPIC

Sympatec's *validation procedure* is the standard procedure for installations in pharmaceutical industry

✔ * both are compliant with *DIN/ISO 13320-1*

CFR 21 Part 11

Sympatec's Contribution to Compliance



History

- ★ In 1997, the American Commissioner of Food and Drugs published an amendment to the Code of Federal Regulations, Title 21, Chapter 1, which was entitled “part 11 - Electronic Records; Electronic Signatures”.
- ★ The main objective of what was then called “Rule 11” is to set up regulations for *electronic records* that correspond to the existing regulations for *records on paper*, and thus provide rules for the *paperless laboratory*.
- ★ Since none of the computerised systems available at that time was compliant with this new regulation and all manufacturers claimed time to adapt to the rules, execution of the so called “Rule 11” was suspended for some time.
- ★ Since 2001, the FDA has been urging the pharmaceutical industry to achieve compliance with Rule 11.
  - ↳ Consequently, our pharmaceutical customers urged us for support

What Is This Rule 11 About?

Rule 11 contains regulations for the paperless lab. It takes respect to the trend that more and more information is stored electronically instead of on paper.

It contains

- ★ Rules for the storage, archiving, and restoration of *electronic records*
- ★ Rules to identify the *authorship* and maintain the *integrity* of the information (write-protection of data and/or *audit trail* of modifications)
- ★ Rules how *electronic signatures* can be applied to electronic records and under which circumstances they are considered *equivalent* to a signature on paper

Rule 11 is Optional !

Preamble chapter XVI. *Analysis of Impacts*, Section C reads as follows:

1.1 C. Description of the Impact

For any paper record that an entity is required to keep under existing statutes or FDA regulations, FDA will now accept an electronic record instead of a paper one, as long as the electronic record conforms to the requirements of this rule. FDA will also consider an electronic signature to be equivalent to a handwritten signature if it meets the requirements of this rule.

……

……

This action is voluntary; paper records and handwritten signatures are still fully acceptable. No entity will be required to change the way it is currently allowed to submit paper records to the agency.

Where can I find more Information ?

It would exceed the scope of this lecture to present more details. The Rule 11 document is available from the FDA's internet page (PDF document, 38 pages consisting of 35 pages preamble + 3 pages "official" rule)

http://www.fda.gov/ora/compliance_ref/part11/FRs/background/pt11finr.pdf

Outline of the Document

PART 11—ELECTRONIC RECORDS; ELECTRONIC SIGNATURES

Subpart A—General Provisions
- 11.1 Scope
- 11.2 Implementation
- 11.3 Definitions

Subpart B—Electronic Records
- 11.10 Controls for closed systems
- 11.30 Controls for open systems
- 11.50 Signature manifestations
- 11.70 Signature/record linking

Subpart C—Electronic Signatures
- 11.100 General requirements
- 11.200 Electronic signature components and controls
- 11.300 Controls for identification codes/passwords

How can Compliance be achieved ?

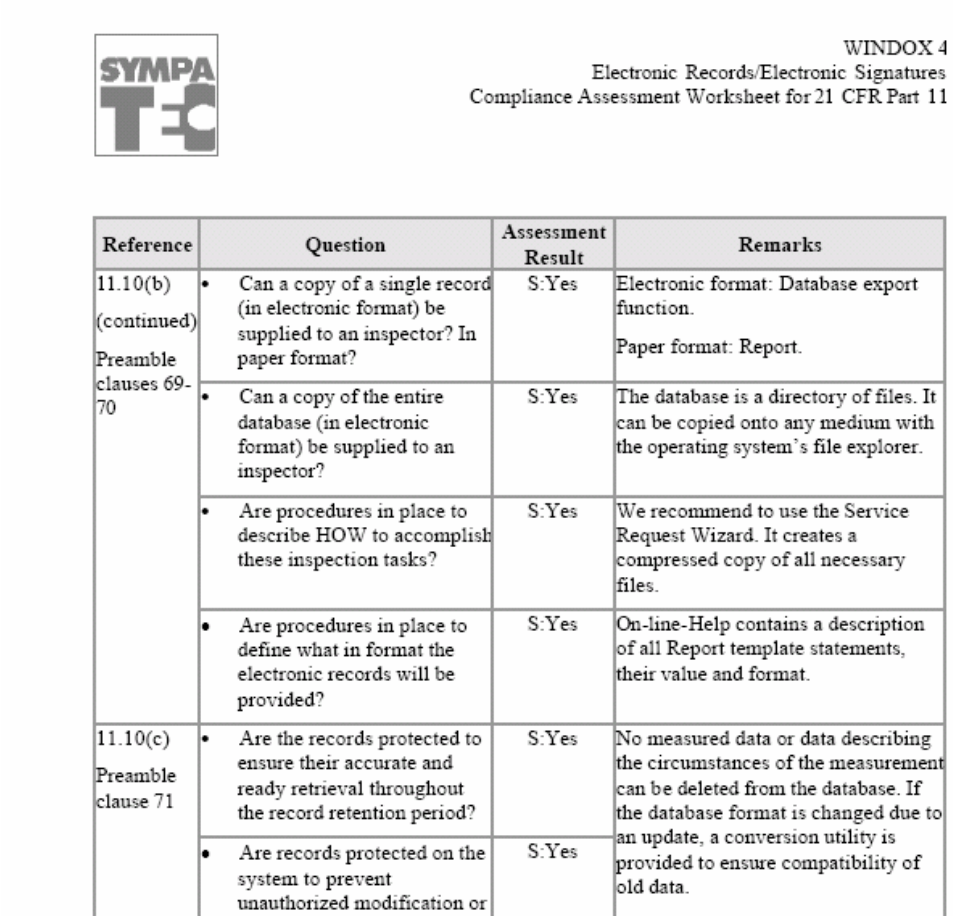
★ A common question is *"The xyz software, is it compliant ?"*
This is a wrong question. It should be:
"How much support for compliance does the computerised system provide?"
What is the difference between both questions?

- ☆ Compliance is not a matter of *Yes or No* but of *better or worse*.
  So there is room for competition among suppliers.
- ☆ It is not only the application software (WINDOX in our case) but the *whole computerised system* that must be considered.
- ☆ Not only the *supplier* but also the *pharmaceutical company* (by SOPs and other administrational measures) must contribute to achieve compliance.

↳ **Compliance requests *cooperation* of the *supplier* and the *pharmaceutical company*.**

What is Sympatec's Contribution to Compliance?

- ★ Sympatec prepared a Rule 11 checklist with:
  - ☆ *Answers* to a potential auditor's questions about our systems with respect to compliance
  - ☆ *Instructions* how to use the WINDOX Rule 11 features properly
  - ☆ *Proposals* of additional measures that the Pharma-ceutical company should take
  - ☆ About 85 of the points have to be fulfilled by the *supplier*, Sympatec
  - ☆ About 115 by the *pharma-ceutical company*



WINDOX 4
Electronic Records/Electronic Signatures
Compliance Assessment Worksheet for 21 CFR Part 11

Reference	Question	Assessment Result	Remarks
11.10(b) (continued) Preamble clauses 69-70	• Can a copy of a single record (in electronic format) be supplied to an inspector? In paper format?	S:Yes	Electronic format: Database export function. Paper format: Report.
	• Can a copy of the entire database (in electronic format) be supplied to an inspector?	S:Yes	The database is a directory of files. It can be copied onto any medium with the operating system's file explorer.
	• Are procedures in place to describe HOW to accomplish these inspection tasks?	S:Yes	We recommend to use the Service Request Wizard. It creates a compressed copy of all necessary files.
	• Are procedures in place to define what in format the electronic records will be provided?	S:Yes	On-line-Help contains a description of all Report template statements, their value and format.
11.10(c) Preamble clause 71	• Are the records protected to ensure their accurate and ready retrieval throughout the record retention period?	S:Yes	No measured data or data describing the circumstances of the measurement can be deleted from the database. If the database format is changed due to an update, a conversion utility is provided to ensure compatibility of old data.
	• Are records protected on the system to prevent unauthorized modification or	S:Yes	

How does the WINDOX Software support Rule 11 ?

★ System requirements:
To ensure the correctness of the user identification, an *operating system with access control* (Windows NT, 2000, or XP) must be used.

★ Standard features:
These features are supplied with *WINDOX* and are always enabled.

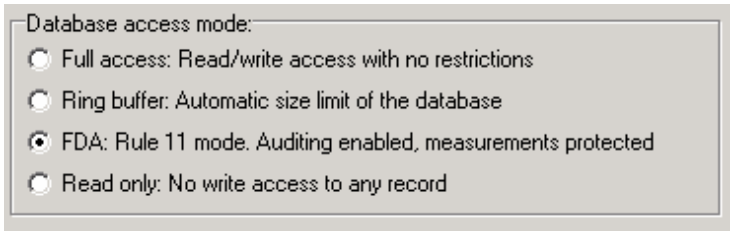
- ☆ WINDOX has been developed under conditions of *Life Cycle Development Quality Control*. This is a must for Rule 11 compliance.
- ☆ WINDOX stores *user logon, date and time* with every data record.
- ☆ WINDOX keeps an *administration log* in which all administrative action (e.g. disabling of “Rule 11 mode”) is written.
- ☆ *Data integrity* is enforced by the WINDOX database.
- ☆ WINDOX is *downward compatible* to the respective predecessor generation of data records. This ensures the restoration of archived data, even if, sometimes, in consecutive steps (HELOS/DOS → WINDOX 3 → WINDOX 4 → WINDOX 5).

How does the WINDOX Software support Rule 11 ?

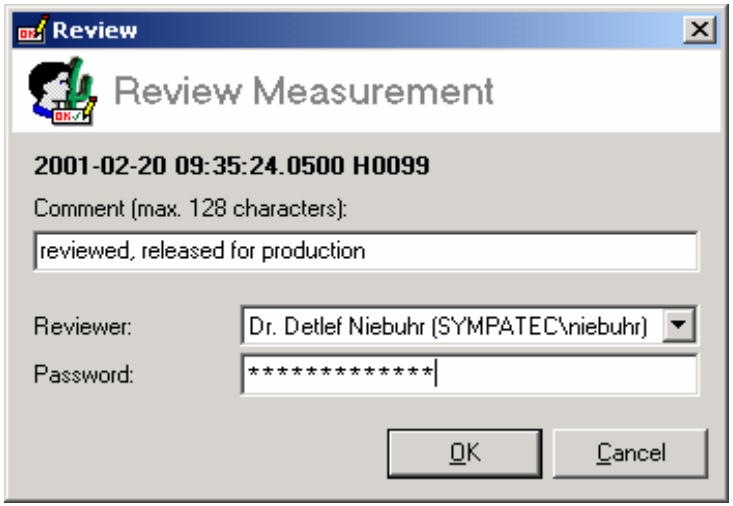
(continued)

★ Additional measures:
These features are supplied but disabled by default, or options to call.

☆ WINDOX has a *"Rule 11 mode"* of database operation and several more switches to enforce data integrity.



☆ WINDOX comes with an optional *digital signature*.
Measurements can be reviewed and signed by someone other than the operator.



Conclusions

Current State

> ***WINDOX fulfils the supplier's part of Rule 11 compliance with respect to digital records, has improved features of data protection and audit trail recording and comes with a digital signature***

Future Steps

- ★ Sympatec will now wait for *feedback* from the Pharmaceutical Industry about the benefits and eventual problems of our Rule 11 support
- ★ A new challenge is the proper *archiving and restoration* of electronic records over a retention period of ten years, as required by the FDA