

# Regulations in Pharmaceutical Laboratories

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**Chairperson: Rob Sample**



**Agilent Technologies**

# Regulations and Quality Standards

	Developed by	Industries	Applied to
<b>cGMP</b>	US FDA/EU	Pharmaceutical	Manufacturing of drugs raw material and API's
<b>GLP</b>	US FDA OECD & EU	Pharmaceutical Chemical Environmental	Development of drugs (synthetic and natural)
<b>ISO9000 Series</b>	ISO	All industries	All departments
<b>ISO 17025</b>	ISO/ILAC	Testing laboratories	Environmental Food, Clinical

OECD = Organization for Economic Cooperation and Development

EPA = Environmental Protection Agency

ILAC = International Laboratory Accreditation Conference

**21 CFR Part 11**  
**ICH**

**Specific tasks**

# GxP Regulations Along the Drug Life



← No GLP/GMP!!! →

GLP

GCP

GMP

← 21 CFR Part 11 →

- Raw/Bulk material
- Active pharmaceutical ingredients (API)

GLP: Study based

GMP: Process based

# Key Provisions for a GLP Study

- Creation of **Quality Assurance** Unit (QAU) to inspect and audit laboratory studies and the accompanying data
- Appointment of a **study director**, ultimate responsibility for the study
- Need for written protocols and **standard operating procedures** (SOPs)
- Analyze **test and control articles** for concentration, uniformity, and stability
- Necessity to utilize **instruments** which are adequately designed, well maintained, calibrated, and standardized

Study based

Focus on traceability

# Key Requirements of cGMP

- Buildings and facilities
- Organization of personnel
- Adequate equipment
- Production and process control
- Packaging and labeling control
- Holding and distribution
- **Laboratory controls**

**Process based**

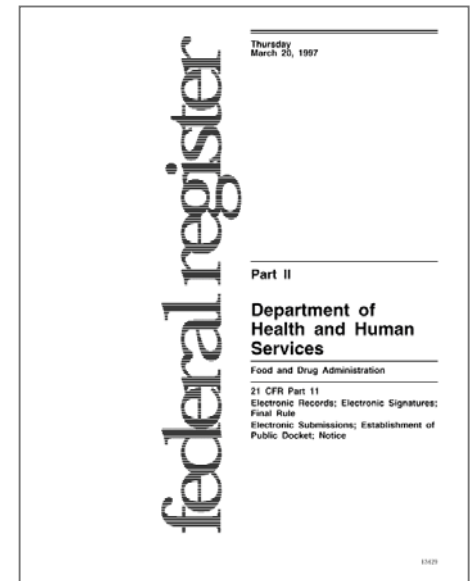


# E-records/signatures - 21 CFR Part 11

## Main Requirements

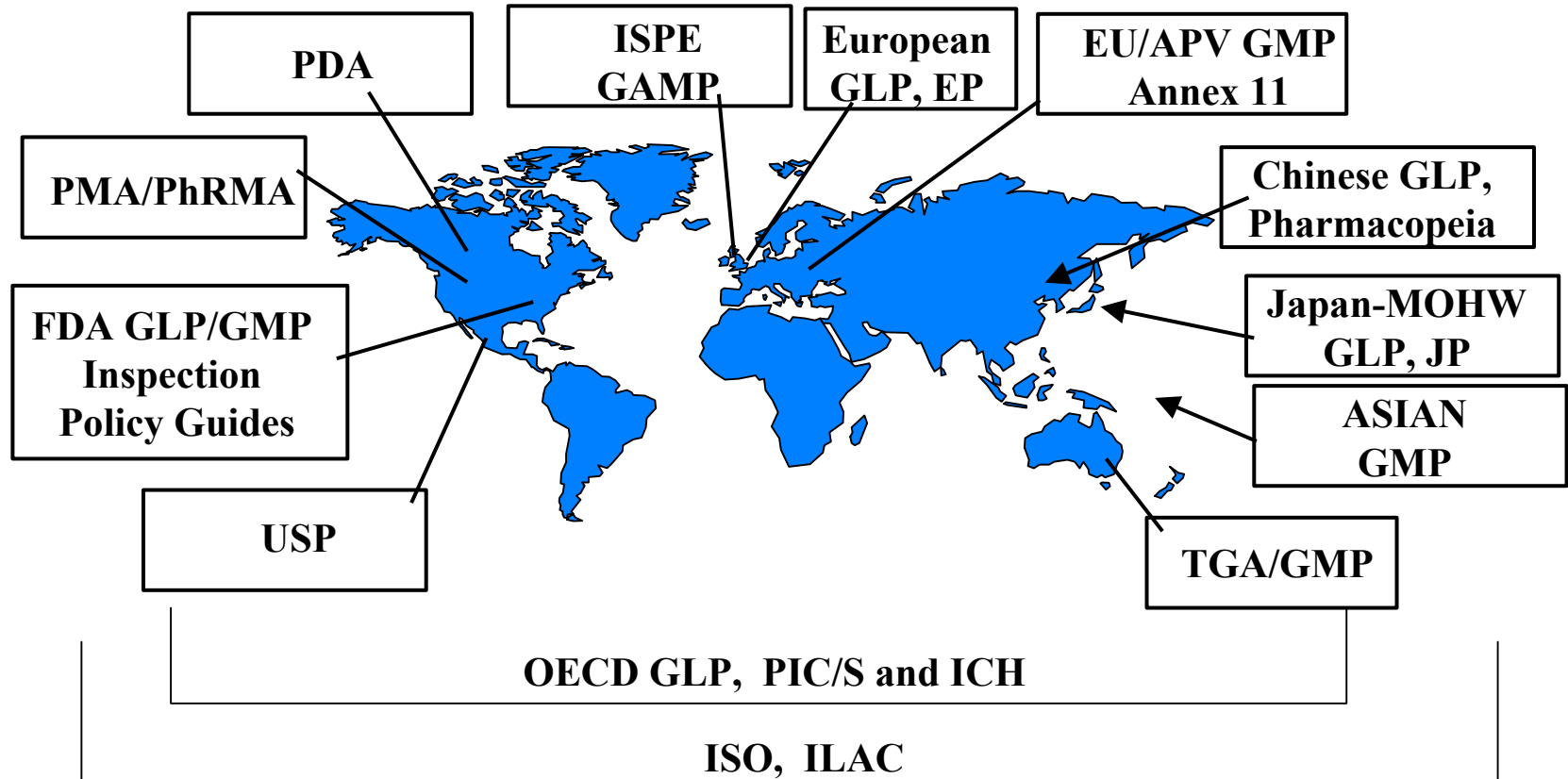
Data integrity

- Validation
- Limited and authorized access to computers and selected tasks
- Computer generated time stamped audit trail
- Binding signatures to records
- Exact copies of data and meta data
- Electronic archiving and ready retrieval



**Scope: When computer are used in GLP/GMP/GCP**

# Organizations and Guidelines



ISPE: International Society for Pharmaceutical Engineering, (Australian) Therapeutic Goods Administration  
APV=(German) Society for Pharmaceutical Engineering, ICH-International Conference for Harmonization  
PDA=Parental Drug Association, OECD=Organization for Economic Cooperation and Development  
GAMP=Good Automated Manufacturing Practice, P=Pharmacopeia

# FDA's Approach to Ensure Public Health

- Develops, promulgates and enforces regulations to implement laws that should protect consumer's health and safety
- Factory inspections  
Pre-approval / post-approval,  
Routine inspections / for cause inspections
- Sampling and analyzing marketed products  
(my result in 'for cause' inspections)

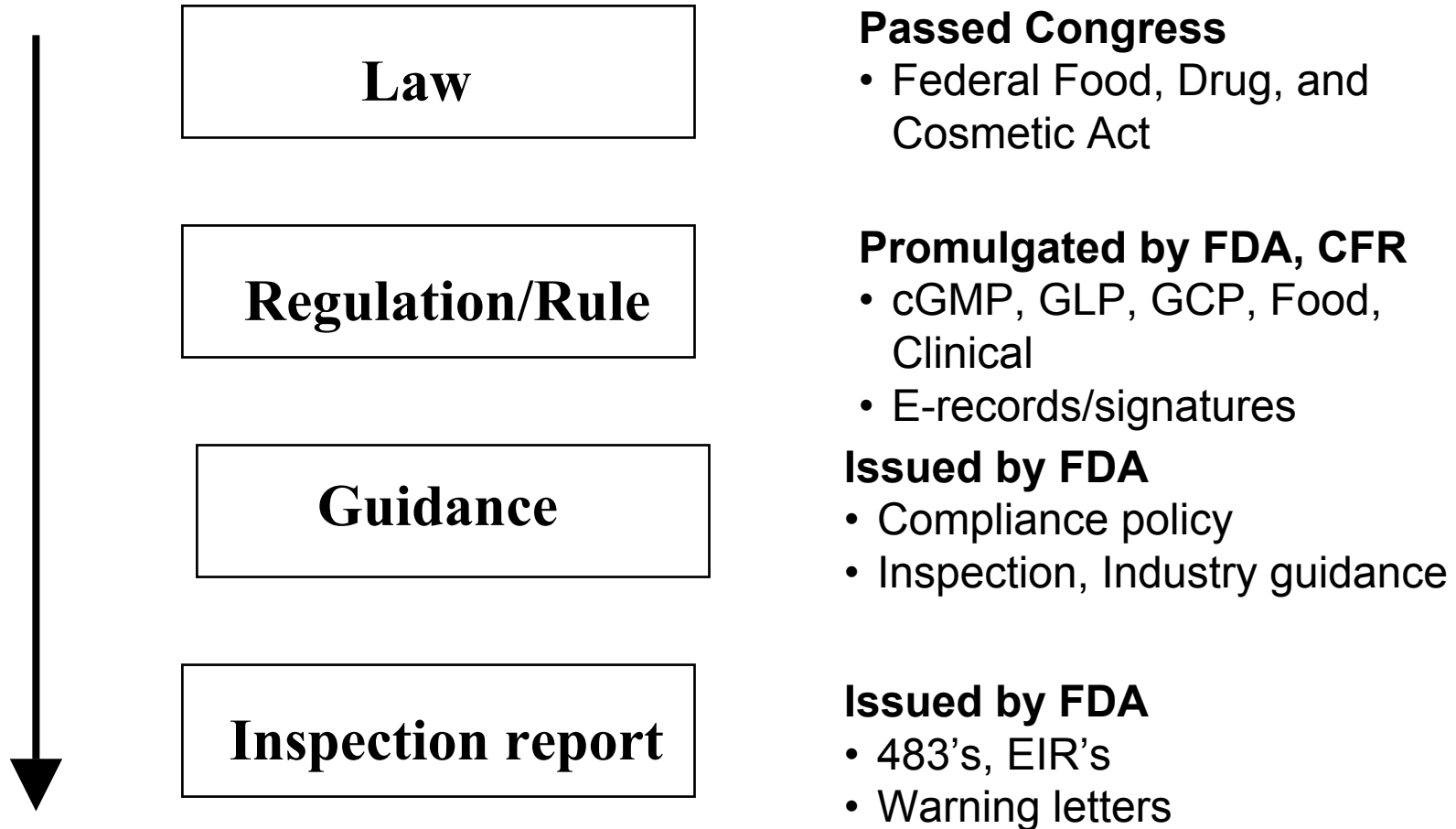
Inspections

FDA, Investigations Operations Manual

[http://www.fda.gov/ora/inspect\\_ref/iom/iomtc.html](http://www.fda.gov/ora/inspect_ref/iom/iomtc.html)



# Relation Between Laws, Regulations and Guidelines



CFR = Code of Federal Regulation

EIR = Establishment Inspection Report

# FDA Inspections

- In the US may or may not be announced, foreign inspections always announced
- Inspectional report right after the inspection ONLY if there are deviations
- Inspectors use special form: 483
- Company can, but does not need to respond
- Depending on severity of deviation FDA issues Warning Letter
- Company must respond within two weeks
- Depending on the response the FDA can take actions
  - ==> Stop manufacturing in USA for US companies
  - ==> Stop import into the USA for foreign companies
  - ==> Companies have to pay fee: up to 500 Mio US\$

# Enforcement

Friday February 16, 6:45 pm Eastern Time

## “Drug Maker” Shares Take Tumble

By J.J. THOMPSON  
Associated Press Writer

TRENTON, N.J. (AP) **“Drug Maker”**

[news](#)] shares dropped 14 percent Friday after the drug maker warned of a sharp fall in first-quarter earnings due to a shutdown of production lines in New Jersey and Puerto Rico.

The company said late Thursday it expected a 15 percent drop in earnings for the quarter ending March 31. “Drug Maker” warned that sales and earnings for all of 2001 also would be lower than expected.

- **M\$ 500 fine**
- **Production of new Block-buster successor delayed**
- **GMP quality problems**



# FDA Inspection Documentation

- 483 Form Inspection Observation
  - only deviations listed
  - discussed during inspection exit meeting
- Establishment Inspection Report (EIR)
  - very much detailed
  - more like an inspection protocol
- Warning letter
  - Since March 1, 2003 reviewed by FDA centers

Examples

[www.fdawarningletter.com](http://www.fdawarningletter.com)

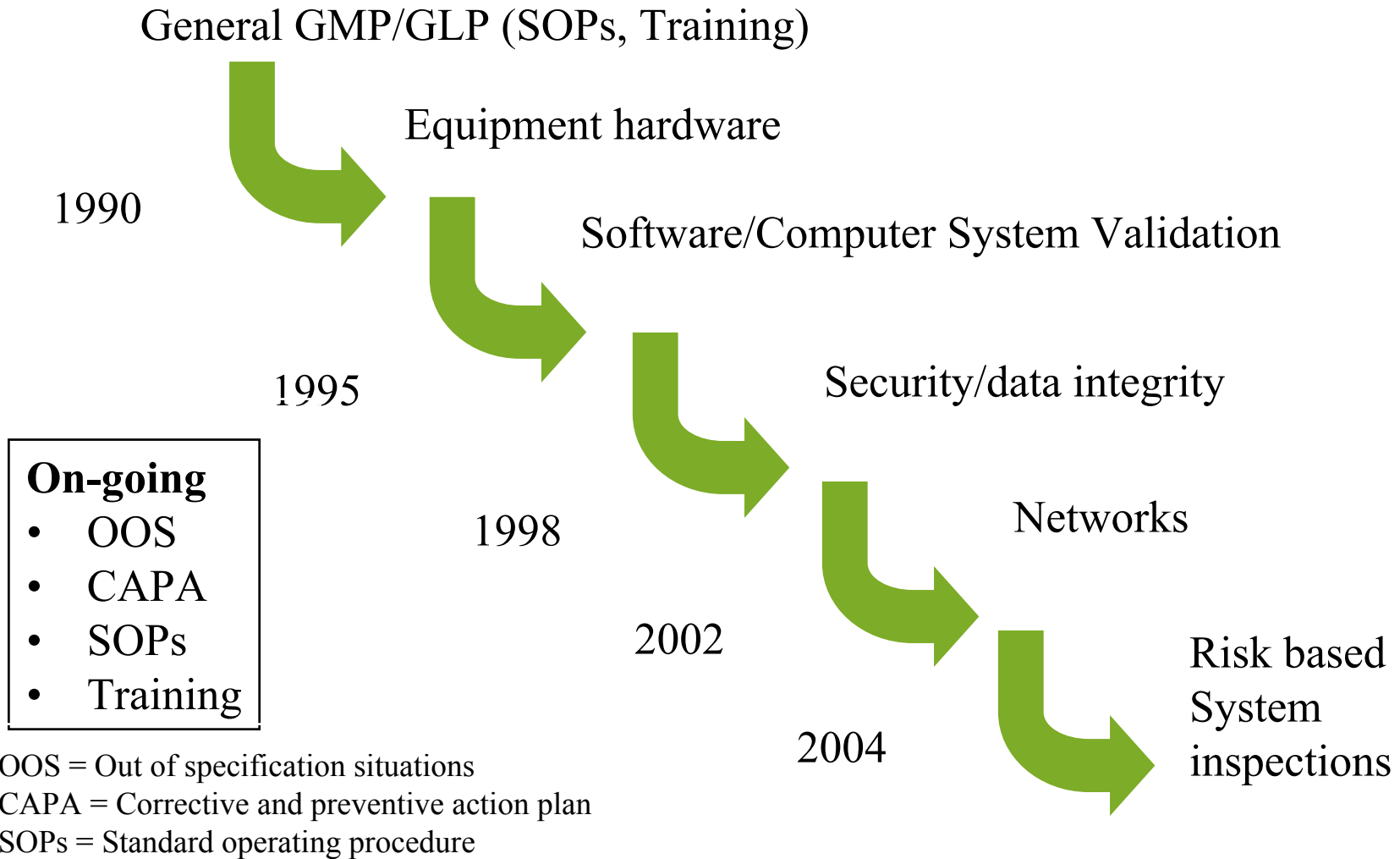
# 483 Form Inspection Observations

- Written during or after the inspection
- Discussed with and handed out to the user firm in the inspection exit meeting
- May reflect the view of single inspector
- Major problem: inconsistency
- Available to the public, including to competition, through FOI (Freedom of Information)
- Can have negative impact on company's reputation
- Can have other consequences: withholding product approvals

# Warning Letters

- Issued in case of severe deviations
- Reviewed by higher level FDA officials and since March 2003 by FDA centers
- Frequently make reference to 483 inspection observations and to company responses
- Companies are advised to respond within 15 days
- Typically follow inspection scheduled
- The FDA publishes warning letters on two websites
  - - <http://www.fda.gov/cder/warn/index.htm>
  - - <http://www.fda.gov/foi/warning.htm>

# Long Term Inspection Trends



# FDA Warning Letter April 2001

## - corrective and preventive actions -

- Failure to establish and maintain **adequate corrective and preventive** action procedures. Not all sources of quality data are analyzed to identify existing and potential causes of nonconforming product and other quality problems.
  - There is no rationale why **other events are not trended** and analyzed

Ref: [www.fdawarningletter.com](http://www.fdawarningletter.com)

**Trend analysis**



# Inspectional Observations

## - methods -

- Failure to establish and document the **accuracy, sensitivity and reproducibility of** test methods employed. For example, the method used to determine the microbiological quality of Water for Injection does not reflect actual sample values

Validation parameters

Ref: [www.fdawarningletter.com](http://www.fdawarningletter.com)

# FDA Inspectional Observations

## - networked systems -

- Complete **diagrams** and **text descriptions** identifying all other network program interfaces with xxxx, and which specify the data being exchanged between the xxxx and other programs **have not been maintained or updated** from original design specifications.
- **Local Area Network diagrams** (LAN) with appropriate definition documentation identifying the locations on site that use XXXX **have not been included** in any XXXX validation documents.

Ref: [www.fdawarningletter.com](http://www.fdawarningletter.com)

**Diagrams, definitions**

# FDA 483 Warning Letter - data security/integrity -

- The firm has not established any security procedures for the laboratory computer systems
- There are no procedures for backing-up data files and no levels of security access established

**back-up**

Ref: [www.fdawarningletter.com](http://www.fdawarningletter.com)

# Key Compliance Requirements for Laboratories

1. Equipment qualification and computer validation
2. Validation of analytical methods and procedures
3. Quality assurance of (certified) reference material
4. People qualification/training
5. Corrective and preventive actions in case of problems
6. Recording, archiving and retrieval of data
7. Laboratory audits

**21 CFR Part 11**

**Common to all regulations and quality standards**

# Ten Step Plan to Build a Quality System

1. Study regulations/quality standards
2. Develop procedures (SOPs)
3. Develop organization infrastructure with roles and responsibilities (E.g., Study director, QA)
4. Train people
5. Validate equipment
6. Validate analytical procedures
7. Develop program to use certified reference material
8. Develop quality control scheme (proficiency testing, system suitability testing, quality control samples)
9. Develop internal audit program
10. Develop procedures for recording and archiving

Use ISO17025 as Guide

# People Qualification/Training

# Agilent Services

- Class room trainings for instrument related techniques (e.g., HPLC, GC, UV)
- Familiarization during installation
- Customized training courses on more details (e.g., Macro programming)
- Free compliance seminars

# With inspection ready certificates

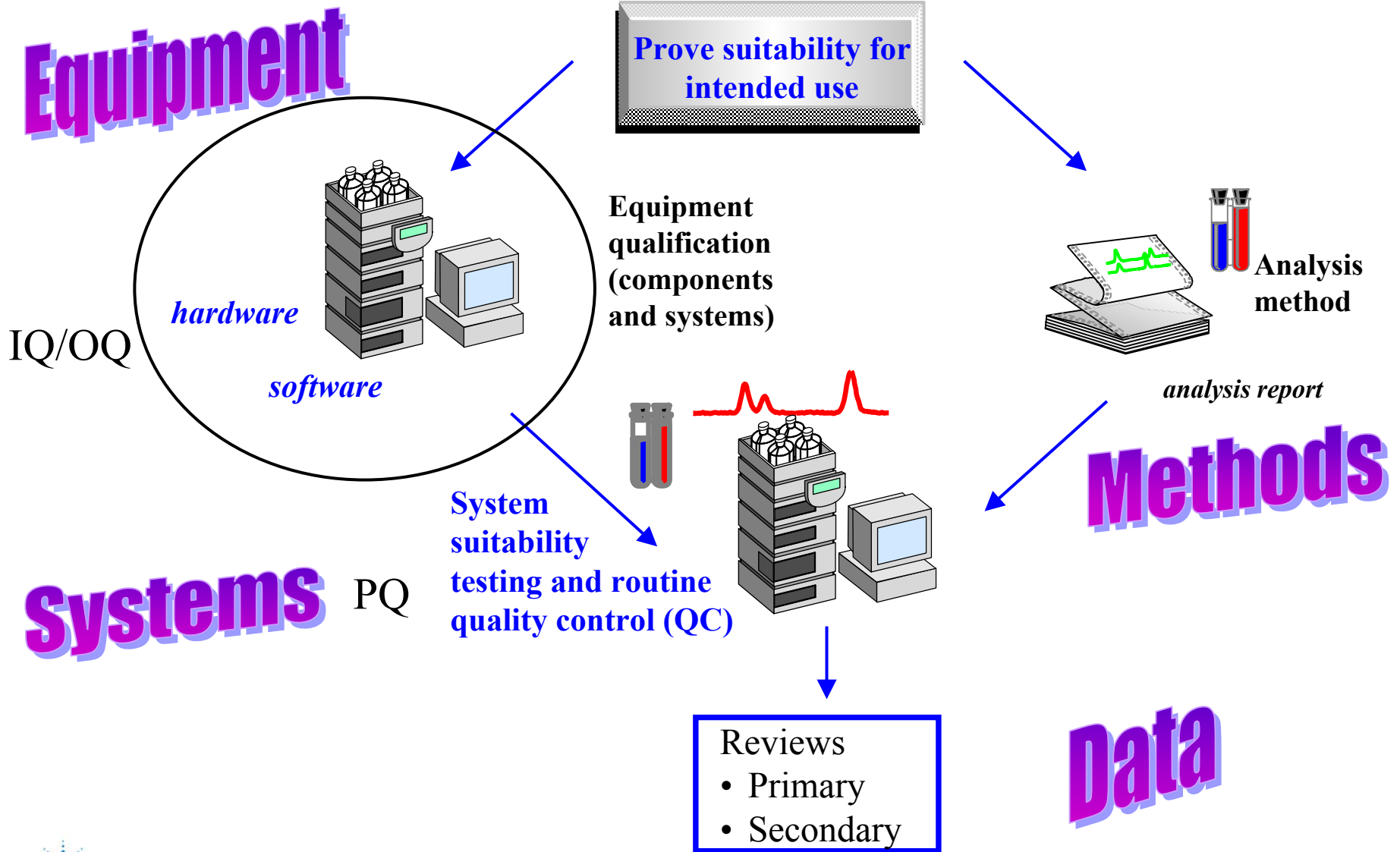
# Laboratory Audits

Audits

- External by accreditation bodies or regulatory authorities
- Internal by laboratory staff (should be independent of the work they are auditing)
- Main audit question:  
are there procedures and are they followed
- Main audit technique  
look at analysis result, as for data, raw data, equipment qualification, method validation, e-record protection

**Quality system --> Test data --> Instrumentation --> Specifications**

# Validation in the Analytical Laboratory





# Validation of Analytical Methods

**Agilent Tools & Services**

## Software for method validation

- Calculations and reports according to ICH/USP/EP/JP
- Software validated (development, installation, operation)
- With GMP and 21 CFR Part 11 functionality  
(data security, integrity, audit trail)
- Fully automated system integration  
(1100 series control, data acquisition, evaluation, reporting)

# Agilent Method Validation - Reports

- Planning info
- Acquisition info
- Numerical results
- Graphical results
- Statistics results
- Residual results
- Comments

## Compound & method info Planning info & comments

### Linearity

Compound: GW123456X  
Method: GW123456X/HPL101 Date : 04/08/01  
X-axis : conc mg/ml Y-Dimension : uVs

Comments:

Component: Impurity A

Default Planning Comment

Number of value pairs: 16

concentration	values
0.000010	529.0
0.000020	698.0
0.000031	753.0
0.000035	1057.0
0.000039	1270.0
0.000043	1378.0
0.000047	1512.0
0.000098	1752.0
0.000100	2177.0
0.000200	4958.0
0.000310	6228.0
0.000350	6670.0
0.000390	8352.0
0.000430	8530.0
0.000470	10828.0
0.000980	21476.0

### Statistical Data

Sum of the x = 0.0035530  
Sum of the y = 78168.0000000  
Squaresum of the x = 0.0000018  
Squaresum of the y = 844897676.0000000  
Square of the sum of the x = 0.0002221  
Square of the sum of the y = 238952.0589583  
Slope (b) = 21272549.7223657  
Intercept (a) = 161.6644273  
Correlation coefficient r = 0.9963808  
Standard deviation  $s_a$  = 162.8944093  
Confidence interval of a = 161.6644273 ± 484.9366566

Numerical values

Statistical values

Provide Inspection Ready Documentation

# Agilent's Recognition and Positioning

- Understands regulatory requirements
  - proven by multiple surveys -
- Work with regulatory agencies AND industry task forces
- Understands customer needs, current AND future
- Products have functionality to comply with all regulations, now AND in the future
- Broadest offering for compliance services
  - worldwide - multi-vendor - from equipment hardware to networks
- Thousand of installations on regulated environment

**References with successful FDA inspections**

GAMP = Good Automated Manufacturing Practices

PDA = Parenteral Drug Association

IVT = Institute of Validation and Technology

# Further Information

**To attend the Agilent e-seminar series, please visit our WEBSITE:**

**<http://www.agilent.com/chem/eseminars-compliance>**

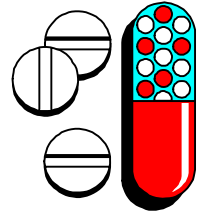
**For further information on our products and services please contact your local Agilent Office.**

# Reference Material



**Agilent Technologies**

# United States Food and Drug Administration (FDA)



## Member

- United States Government

## Tasks

- Promulgates and enforces US regulations

## Impact

- By far the highest impact on pharmaceutical industry through toughest enforcement. Can stop manufacturing in the US or stop import.

## Examples for documents

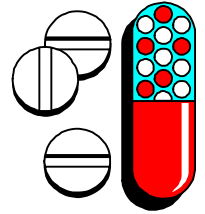
- 21 Series Code of Regulations (CFR), e.g., Good Laboratory Practices, Good Manufacturing Practices for drugs and medical devices , Good Clinical Practices, Food Additives, Electronic records

## Website

- [www.fda.gov](http://www.fda.gov)

Corresponding agencies in other countries

# International Conference for Harmonization (ICH)



## Members

- Industry and government
- Industrial countries (US/Canada/EU/Japan)

## Tasks

- Develops guidelines on selected topics

## Impact

- Guidelines signed into regulations in member countries
- Entered into the federal register in the US, but no in regulation

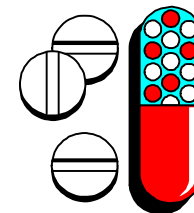
## Examples for documents

- Clinical trials Method validation, active pharmaceutical ingredients (API)

## Website

- [www.ich.org](http://www.ich.org)

# Organization for Economic Cooperation and Development (OECD)



## Members

- Health agencies of industrial countries (US/Canada/EU/Japan)

## Tasks

- Develops guidelines on selected topics, mainly GLP

## Impact

- Guidelines signed into regulations in member countries
- Entered into the federal register in the US, but not CFR

## Examples for documents

- Consensus documents – GLP and Computers

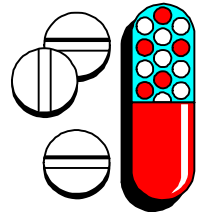
## Website

- [www.oecd.org](http://www.oecd.org)





# Good Automated Manufacturing Practice (GAMP) Forum



## Members

- Industry from Europe, America

## Tasks

- Develops guidelines on using automated systems in regulated industry

## Impact

- Industry standard, referred by Agencies, e.g. FDA, EU

## Examples for documents

- GAMP 4 – Validation of computer systems
- Implementing 21 CFR Part 11
- Network qualification coming

## Website

- [www.gamp.org](http://www.gamp.org)



# International Society for Pharmaceutical Engineering (ISPE)

## Members

- Industry, organizations in EU, America, Japan

## Tasks

- On-line shop for GAMP products, provides trainings around the world, consulting agencies e.g., US FDA

## Impact

- High influence on US FDA

## Examples for documents

- Authored Part 11 white paper and influenced new FDA Part 11 Guide
- ISPE Journal

## Website

- [www.ISPE.org](http://www.ISPE.org)

# United States Pharmacopeia (USP)

## Members

- Organization Located in the United States

## Tasks

- Develops standards for FDA regulated industry; for techniques and methods

## Impact

- Standards for FDA regulated industry

## Examples for documents

- Chromatographic system suitability testing, UV dissolution

## Website

- [www.USP.org](http://www.USP.org)

Corresponding organizations in EU (EP) and Japan (JP)

# Pharmaceutical Inspection Convention Scheme (PIC/S)

## **Members**

- Regulatory Agencies EU, Australia, Canada, Singapore, Malaysia

## **Tasks**

- Develops guidelines for inspectors

## **Impact**

- Guidelines seen as standards by industry in EU

## **Examples for documents**

- Good computer practices, validation master plan

## **Website**

- [www.picscheme.org](http://www.picscheme.org)

# Parenteral Drug Association (PDA)

## Members

- Industry, organizations in NA, EU, Japan, Taiwan

## Tasks

- Develops technical papers on selected topics

## Impact

- Some became industry standards, e.g. Tech paper # 32 on vendors audits

## Examples for documents

- Technical papers  
#31: Data acquisition systems; #32: vendor audits

## Website

- [www.pda.org](http://www.pda.org)

# International Organization for Standardization (ISO)

## Members

- Industry, organizations in >100 countries

## Tasks

- Develops industry standards

## Impact

- ISO 9001 prerequisite for equipment suppliers

## Examples for documents

- ISO 9001 to 9004: Quality systems standards
- ISO 17025 for testing laboratories

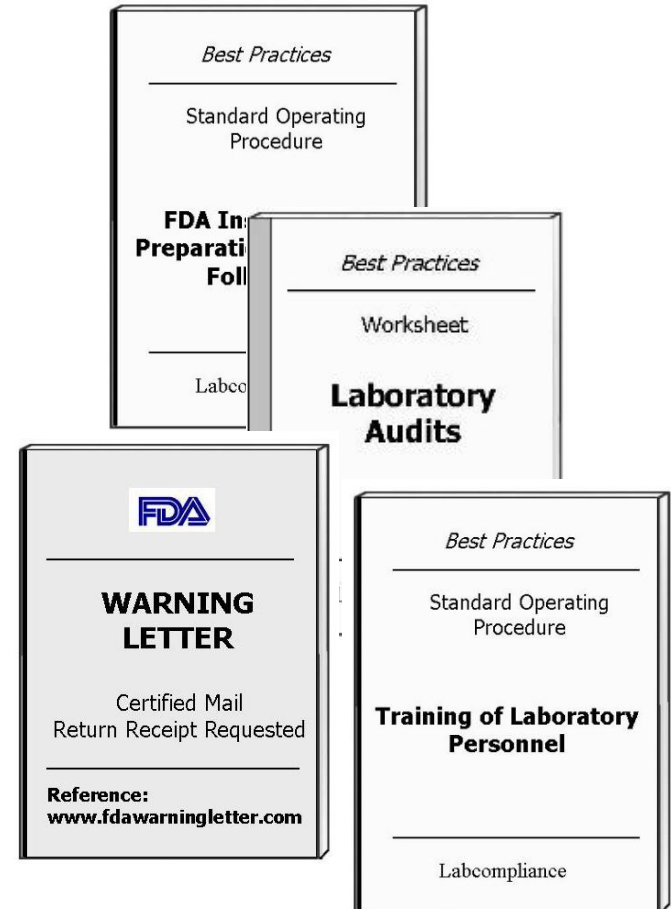
## Website

- [www.iso.org](http://www.iso.org)

Enforcement through private companies, that can be selected by clients

# Reference Material Available on the Internet

- Regulations (EU, FDA)
- Guidance documents
- ICH guidelines/IVT standard
- Laboratory audit worksheet
- Standard operating procedures
- Examples of warning letters and FDA inspectional observations
- Agilent publications on validation and compliance



Ref: [www.labcompliance.com/agilent/regulations](http://www.labcompliance.com/agilent/regulations)