Regulations in Pharmaceutical Laboratories

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Ludwig Huber
Compliance Fellow for
Life Sciences and Chemical Analysis

Chairperson: Rob Sample

Agilent Technologies

Regulations and Quality Standards

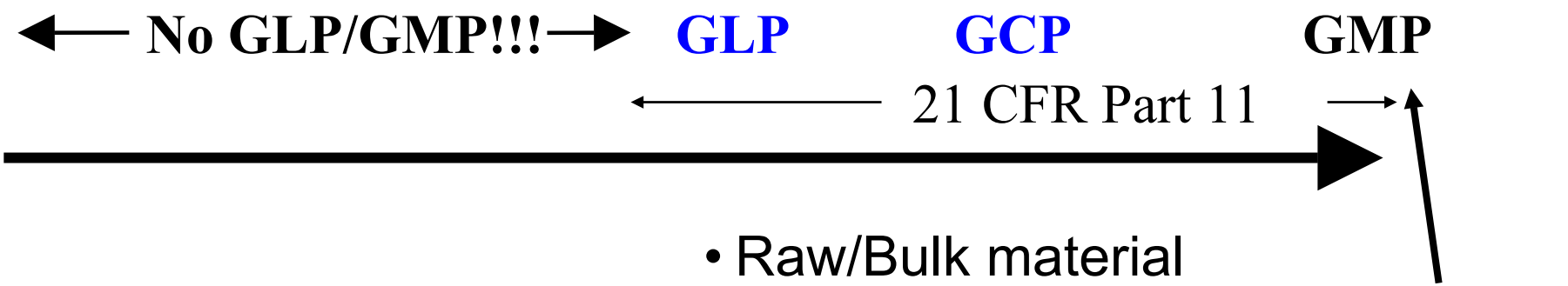
	Developed by	Industries	Applied to
cGMP	US FDA/EU	Pharmaceutical	Manufacturing of drugs raw material and API's
GLP	US FDA OECD & EU	Pharmaceutical Chemical Environmental	Development of drugs (synthetic and natural)
ISO9000 Series	ISO	All industries	All departments
ISO 17025	ISO/ILAC	Testing laboratories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



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

GLP: Study based

GMP: Process based

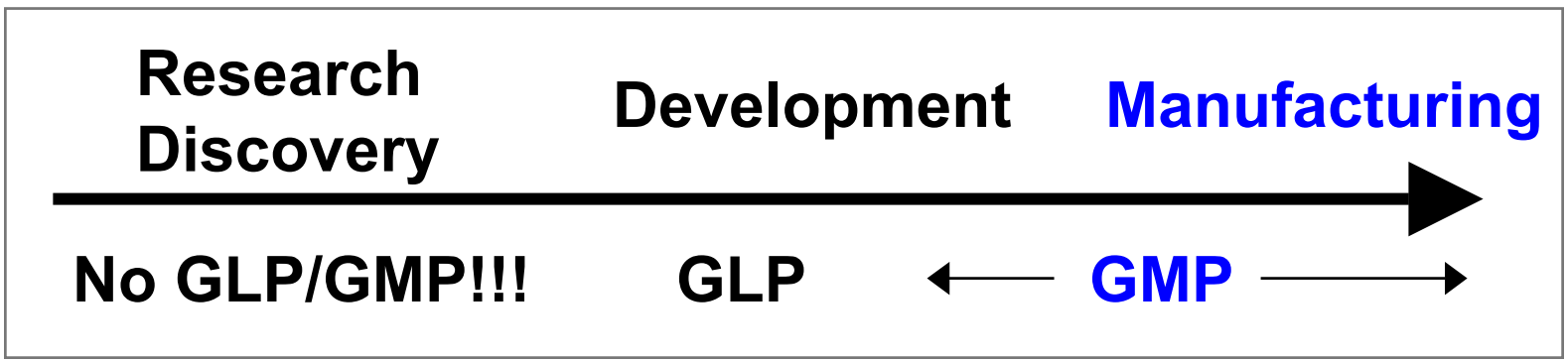
Key Provisions for a GLP Study

- 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

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**

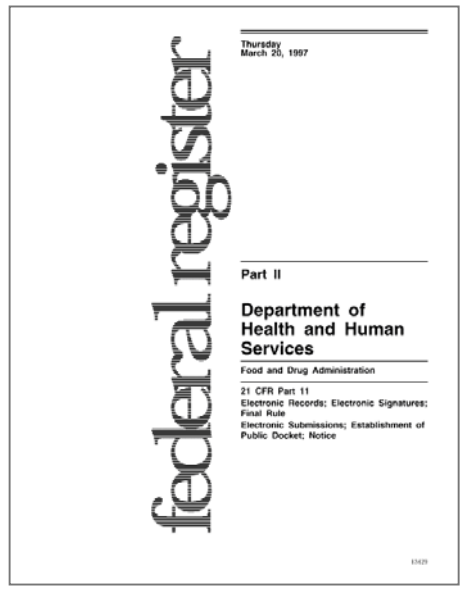
Process based



E-records/signatures - 21 CFR Part 11 Main Requirements

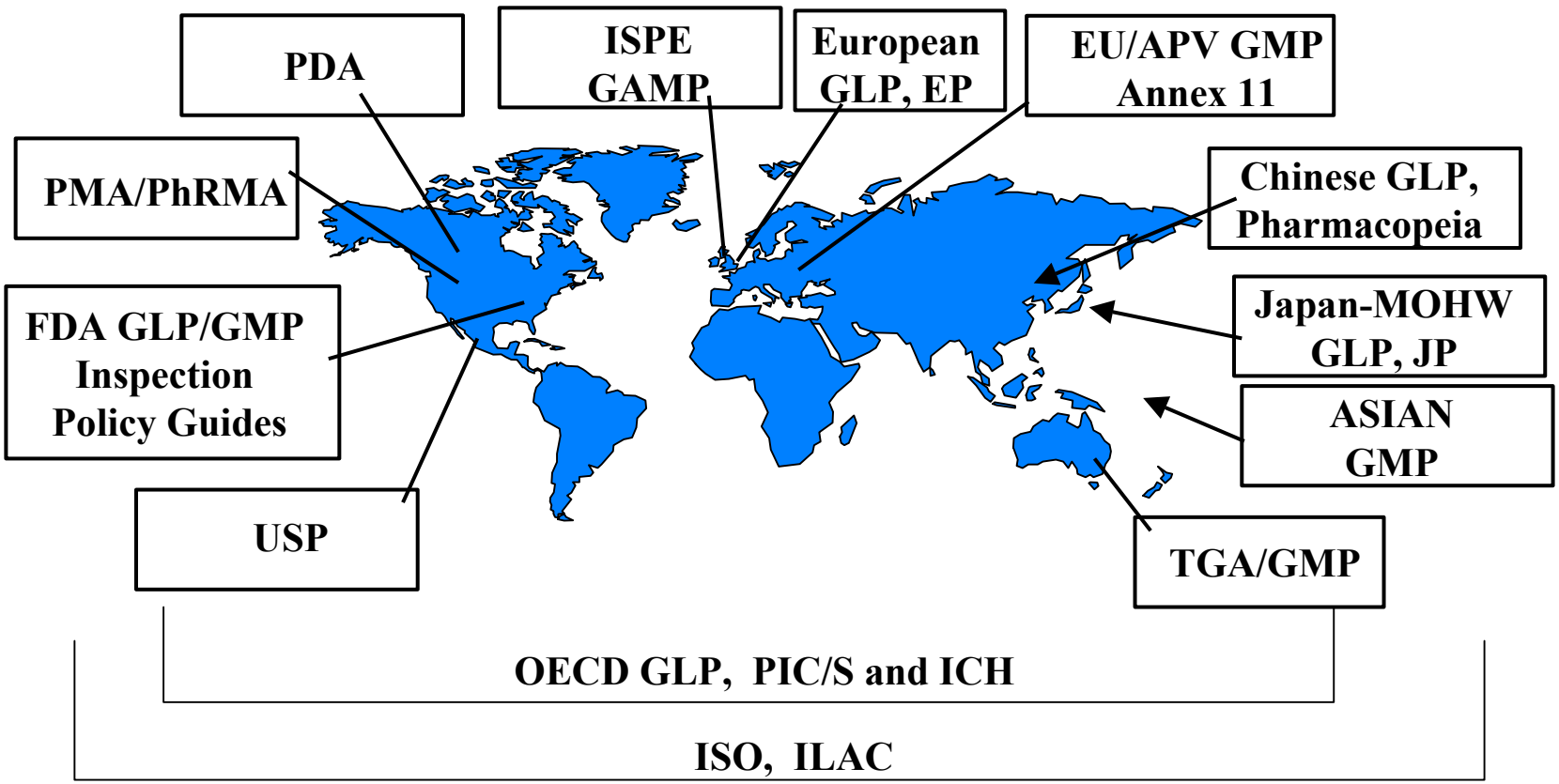
Data integrity

- 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 Manufacturiung 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)

FDA, Investigations Operations Manual
http://www.fda.gov/ora/inspect_ref/iom/iomtc.html

Relation Between Laws, Regulations and Guidelines

Law

Passed Congress
- Federal Food, Drug, and Cosmetic Act

Regulation/Rule

Promulgated by FDA, CFR
- cGMP, GLP, GCP, Food, Clinical
- E-records/signatures

Guidance

Issued by FDA
- Compliance policy
- Inspection, Industry guidance

Inspection report

Issued by FDA
- 483's, EIR's
- Warning letters

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

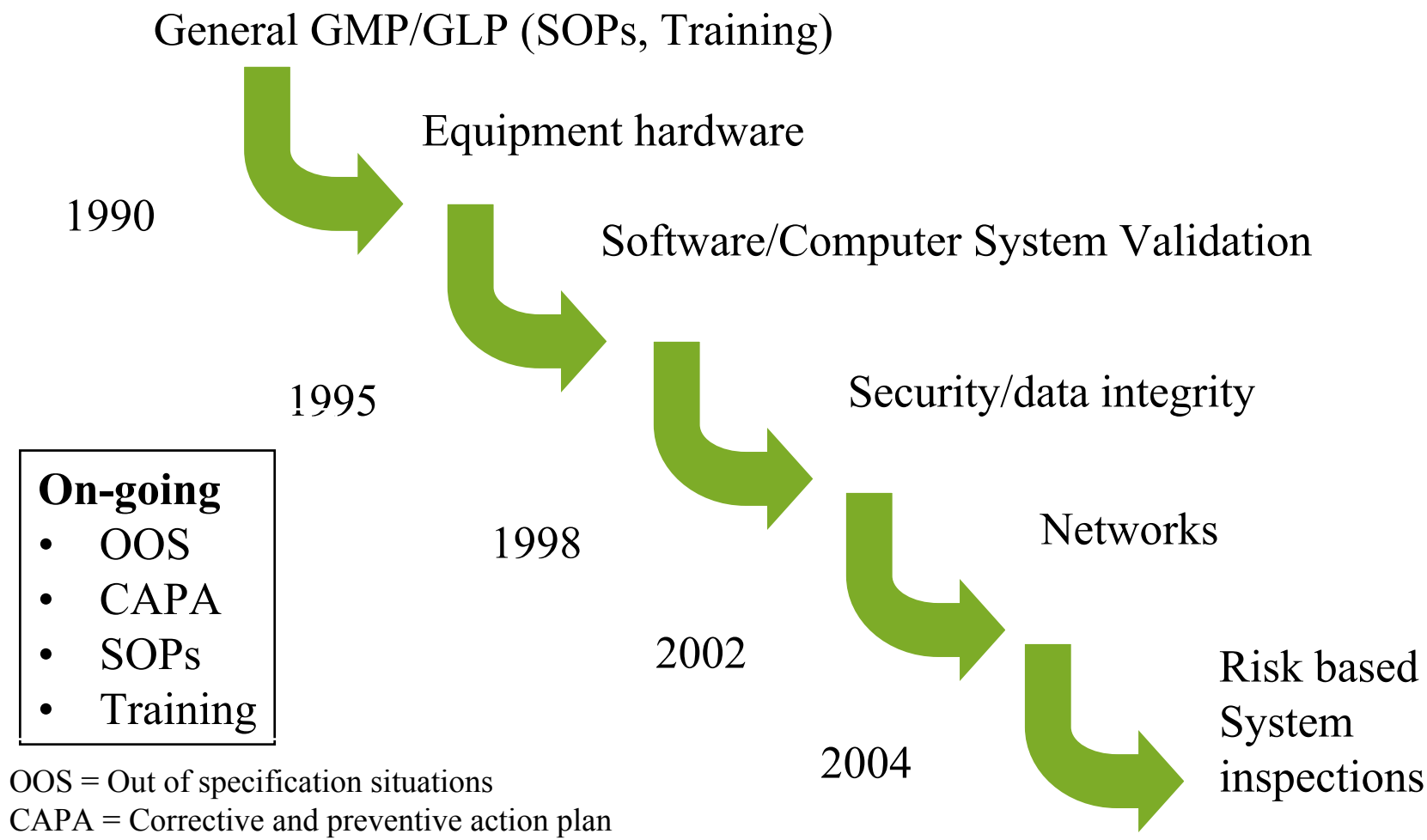
483 Form Inspection Observations

- Written during or after the inspection
- Discussed with and handed out to the user firm in the inspection exit meeting
- May reflects 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



On-going
- OOS
- CAPA
- SOPs
- Training

OOS = Out of specification situations
CAPA = Corrective and preventive action plan
SOPs = Standard operating procedure

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

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

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

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

Ref: 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

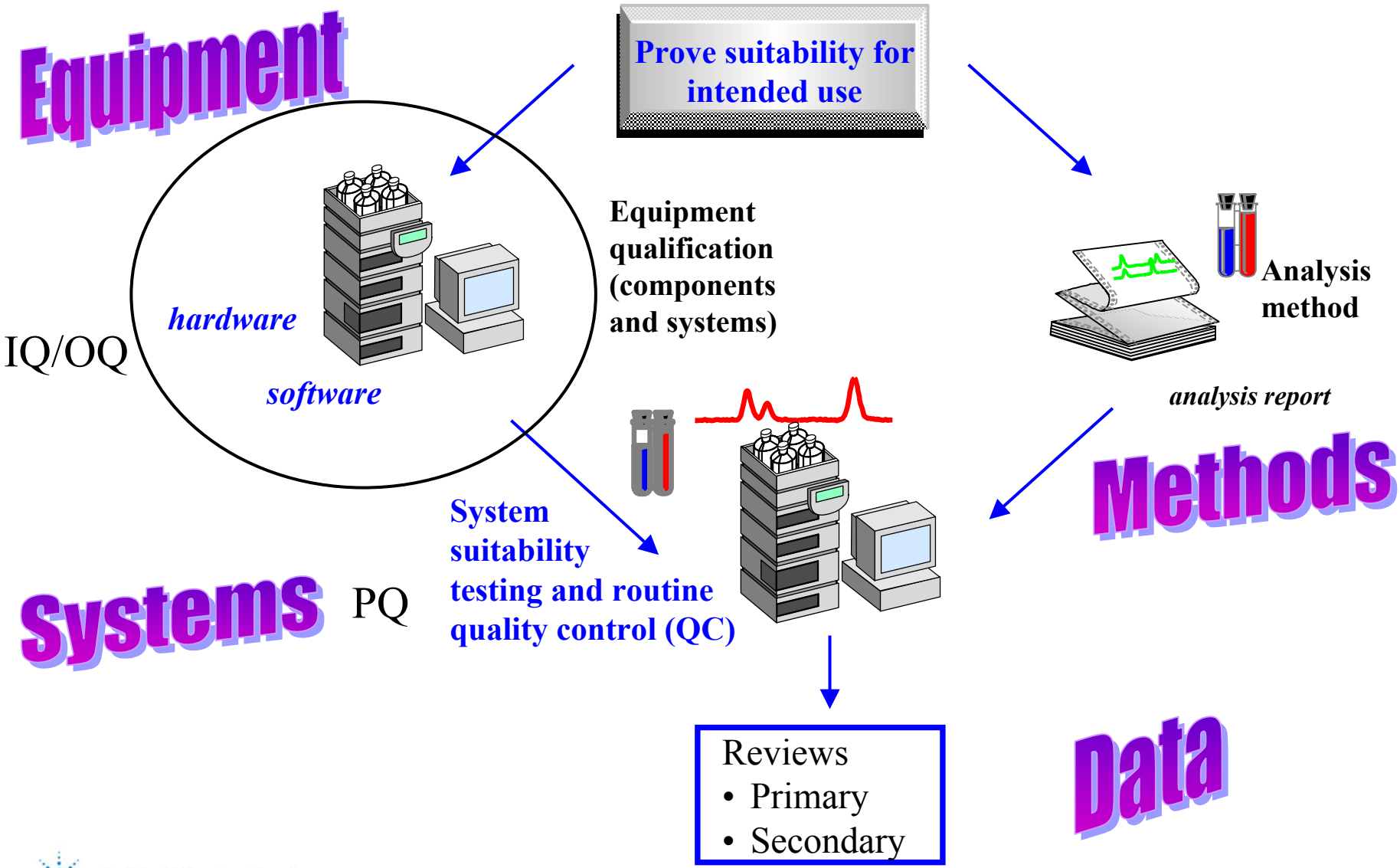
With inspection ready certificates

Laboratory Audits

- 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

Software for method validation

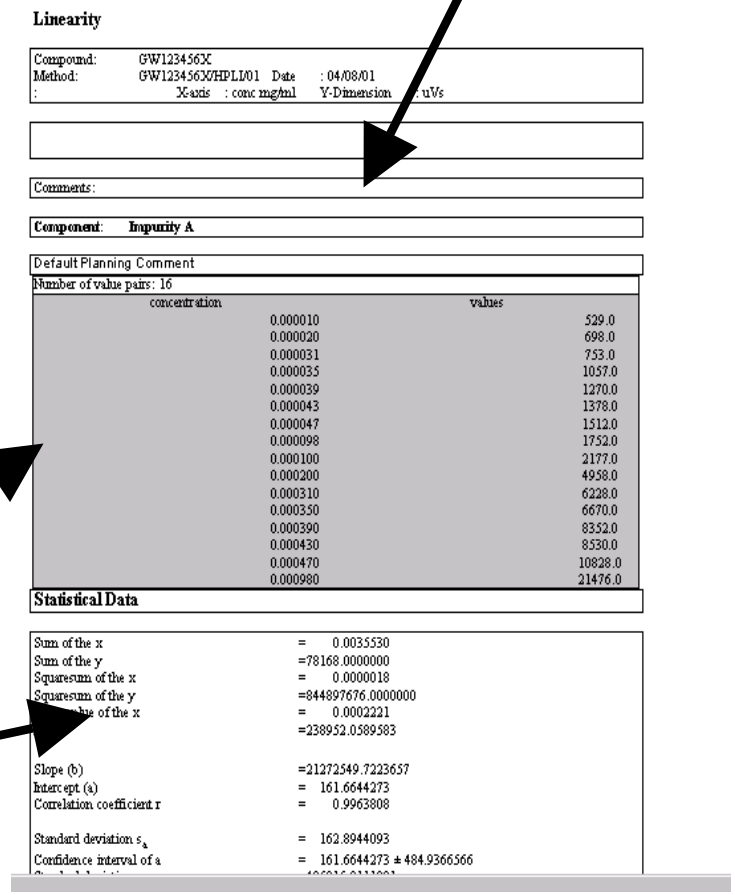
- Calculations and reports according to ICH/USP/EP/JP
- Software validated (development, installation, operation)
- With GMP and 21 CFR Part 11 functionality
  (data security, integrity, audit trail)
- Fully automated system integration
  (1100 series control, data acquisition, evaluation, reporting)

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/HPLL/01 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
ue of the x	= 0.0002221
	=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:

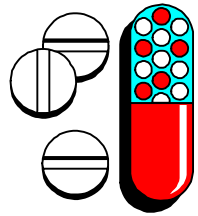
http://www.agilent.com/chem/eseminars-compliance

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

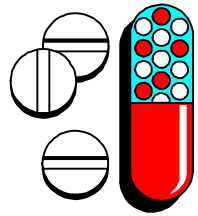
- 21 Series Code of Regulations (CFR), e.g., Good Laboratory Practices, Good Manufacturing Practices for drugs and medical devices , Good Clinical Practices, Food Additives, Electronic records

Website

- www.fda.gov

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

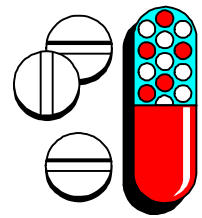
Examples for documents

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

Website

- www.ich.org

Organization for Economic Cooperation and Development (OECD)



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

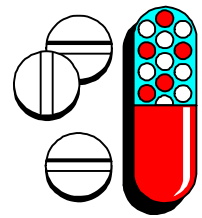
Tasks
- Develops guidelines on selected topics, mainly GLP

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

Good Automated Manufacturing Practice (GAMP) Forum



Members
- Industry from Europe, America

Tasks
- Develops guidelines on using automated systems in regulated industry

Impact
- Industry standard, refered 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

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

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.UPS.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

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

International Organization for Standardization (ISO)

Members
- Industry, organizations in >100 countries

Tasks
- Develops industry standards

Impact
- ISO 9001 prerequisite for equipment suppliers

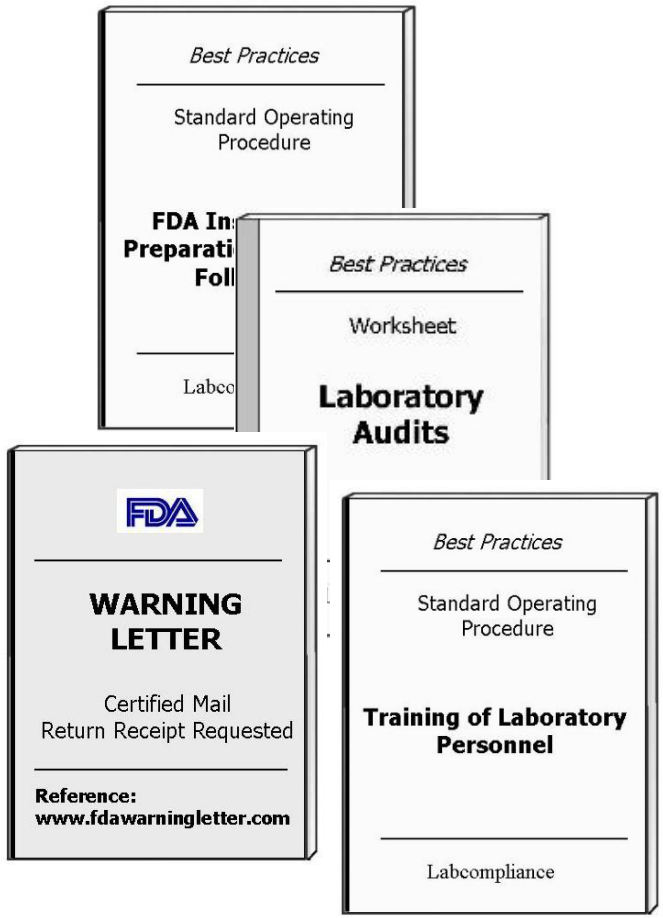
Examples for documents
- ISO 9001 to 9004: Quality systems standards
- ISO 17025 for testing laboratories

Website
- www.iso.org

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