# Regulations and Quality Standards

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

OECD = Organization for Economic Cooperation and Development  
EPA = Environmental Protection Agency  
ILAC = International Laboratory Accreditation Conference

**Specific tasks**
GxP Regulations Along the Drug Life

- Basic Research
- Disease Discovery
- Drug Discovery
- Drug Development
- Clinical Trials I, II, III
- Manufacturing

No GLP/GMP!!! → GLP → GCP → GMP

21 CFR Part 11

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

GLP: Study based
GMP: Process based

Agilent Technologies
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

Research
Discovery

Development

Manufacturing

No GLP/GMP!!!

GLP

GMP

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

• 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

- PDA
- ISPE
- GAMP
- European GLP, EP
- EU/APV GMP Annex 11
- Chinese GLP, Pharmacopeia
- FDA GLP/GMP Inspection Policy Guides
- PMA/PhRMA
- USP
- OECD GLP, PIC/S and ICH
- ISO, ILAC
- TGA/GMP
- Japan-MOHW GLP, JP
- ASIAN GMP
- 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

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

- **Regulation/Rule**
  - Issued by FDA
    - Compliance policy
    - Inspection, Industry guidance

- **Guidance**
  - 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” 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

1990
General GMP/GLP (SOPs, Training)

1995
Equipment hardware

Software/Computer System Validation

1998
Security/data integrity

On-going
- OOS
- CAPA
- SOPs
- Training

1998
1995
1990

2002
Networks

2004
Risk based System inspections

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.

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

Common to all regulations and quality standards

21 CFR Part 11
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

- 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
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

- **Equipment**
  - **IQ/OQ**
  - **PQ**
  - **hardware**
  - **software**
  - Equipment qualification (components and systems)

- **Systems**
  - **PQ**
  - System suitability testing and routine quality control (QC)

- **Methods**
  - Analysis method
  - analysis report

- **Prove suitability for intended use**

- **Reviews**
  - Primary
  - Secondary
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**

<table>
<thead>
<tr>
<th>Compound Method</th>
<th>Planning Info</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>SW123456</td>
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</table>

<table>
<thead>
<tr>
<th>Component</th>
<th>Impurity A</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Numerical values**

<table>
<thead>
<tr>
<th>Concentration</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.000109</td>
<td>529.0</td>
</tr>
<tr>
<td>0.000100</td>
<td>629.0</td>
</tr>
<tr>
<td>0.000101</td>
<td>729.0</td>
</tr>
<tr>
<td>0.000102</td>
<td>829.0</td>
</tr>
<tr>
<td>0.000103</td>
<td>929.0</td>
</tr>
<tr>
<td>0.000104</td>
<td>1029.0</td>
</tr>
</tbody>
</table>

**Statistical values**

<table>
<thead>
<tr>
<th>Data of x</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.000105</td>
<td>0.000106</td>
</tr>
</tbody>
</table>

**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
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, 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
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