Training Course
Computerized System Validation in the Pharmaceutical Industry
Istanbul, 16-17 January 2003

Regulatory Comments

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Agenda

- Regulatory expectations - The inspector`s view
- Which systems are subject to increased regulatory inspectors awareness?
- Presentation of FDA findings during inspections, 483s, Warning Letters
- Discussion

Inspectors expectations

- list of computerised processes / computer-systems
- evaluation for GMP relevance
- GMP risk-assessment
- specifications
- tests
- review / evaluation of results
- documentation
- release
- controls

Two „worlds“ One rule ?

- Automated production systems — product quality
  - Process control systems
  - Influence on the process
- Automated record systems — data integrity
  - Data Acquisition systems
  - Influence on records

Types of documents

production related

manufacturing instruction, - record; Quality Control instruction, - record;

organizational documents

Standard Operating Procedure/SOP; self inspection report; hygiene programme;

other GMP relevant data

distribution records; marketing authorization; complaints; environmental data;

literature

Pharmacopoeia; drug law; EU-GMP-guideline; ...

problems, open questions

- bugfixes. Service-Packs etc.
- customer / supplier responsibilities
- supplier audit / certificates
- hybrid systems
- time documentation (GMT, MEZ, MESZ ...)
- definition of raw data / typewriting
- standard software
- hardware
- complexicity
- blind trusting
- .....

Regulatory Expectation

Organizations are expected to demonstrate control of the processes and systems that affect

- data integrity,
- product quality
- patient safety.

The organization's decision making process, on an organizational and system specific level, should be documented.

Regulatory Impact

Regulatory Impact

includes integrity of regulated data integrity, security, and product quality focus.

Current regulatory expectation for validating such a system:

If the system impacts regulated data, or is used to assist in making regulatory decisions, computer system validation is a regulatory requirement.

Observations of FDA and MCA during Inspections I

Missing system specification

Responsibilities not defined

User training not documented

No systematic data backup

Charts of data flow not existing

No internal audits of the system by QA unit

No documentation of deviations

Source: GMP Trends, The Gold Sheet

Observations of FDA and MCA during Inspections II

Laboratory (very frequent): Application not validated (e.g. Excel, Lotus)

ERP Systems: Method for tracing of batches not validated.

System Security not sufficient (Passwords).

Audit trail does not exist.

Software Change Control System not appropriate.

Source: GMP Trends, The Gold Sheet

FDA Pre-Approval Inspection of a German Manufacturer of finished dosage forms

Excerpt from the 483

ERP System, Raw Materials:

"The XXX computer system for tracking all raw materials, components and products is not validated."

Source: FOI

PIC/S Group - Key Regulatory Messages - 1

- adopt a lifecycle approach
- management and control of all phases
- proprietary systems must be formally risk assessed
- inspectors also consider PQ (beyond GAMP)
- ….

PIC/S Group - Key Regulatory Messages - 2

- …. SOUP (software of unknown pedigree)
- controlled documentation
  - systems description
  - functionality
  - interactions
- IT management
  - quality management policy
  - standards and SOP's
  - controls (BS 7799)
- ….

PIC/S Group - Key Regulatory Messages - 3

- change management and error reporting
- retrospective validation is not acceptable
- BS 7799 and 21CFR Part 11 for audit trails
- EU accepts electronic records and electronic signatures ….

PIC/S Group - Key Regulatory Messages - 4

- ... with rigorous operational controls and audit trail features

  … attached immutable audit trail identifying
  - person
  - time
  - date
  - linking to particular transactions

- ….

PIC/S Group - Key Regulatory Messages - 5

- additional security arrangements for
  - external access
  - inputs
  - outputs

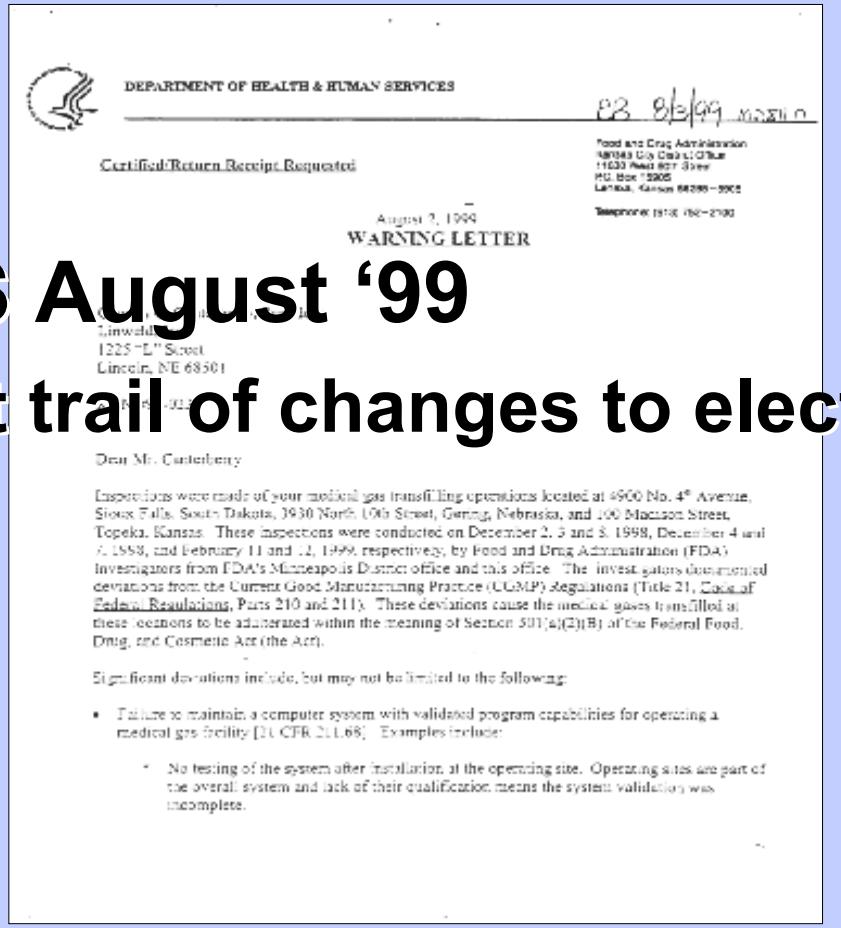
    linking with firms GxP computerised systems
- “open system” security arrangements must be documented
- ….

PIC/S Group - Key Regulatory Messages - 6

- “critical” or “major” deficiencies are no :
  - current, written detailed system description
  - current functional description
  - description of security features
  - description of interactions
  - evidence of QA of s/w development
  - adequate evidence of validation
- depending on the inspectors risk assessment

Excerpt from Recent Warning Letters

Warning Letters (1)



DEPARTMENT OF HEALTH & HUMAN SERVICES

Certified/Return Receipt Requested

August 7, 1999

WARNING LETTER

1225 "L" Street
Lincoln, NE 68501

Dear Mr. Canterbury:

Inspections were made of your medical gas transfilling operations located at 4900 No. 4th Avenue, Sioux Falls, South Dakota, 3930 North 10th Street, Gering, Nebraska, and 100 Madison Street, Topeka, Kansas. These inspections were conducted on December 2, 3 and 8, 1998, December 4 and 7, 1998, and February 11 and 12, 1999, respectively, by Food and Drug Administration (FDA) investigators from FDA's Minneapolis District office and this office. The investigators documented deviations from the Current Good Manufacturing Practice (CGMP) Regulations (Title 21, Code of Federal Regulations, Parts 210 and 211). These deviations cause the medical gases transfilled at these locations to be adulterated within the meaning of Section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (the Act).

Significant deviations include, but may not be limited to the following:

- Failure to maintain a computer system with validated program capabilities for operating a medical gas facility [21 CFR 211.68]. Examples include:
  - No testing of the system after installation, at the operating site. Operating sites are part of the overall system and lack of their qualification means the system validation was incomplete.

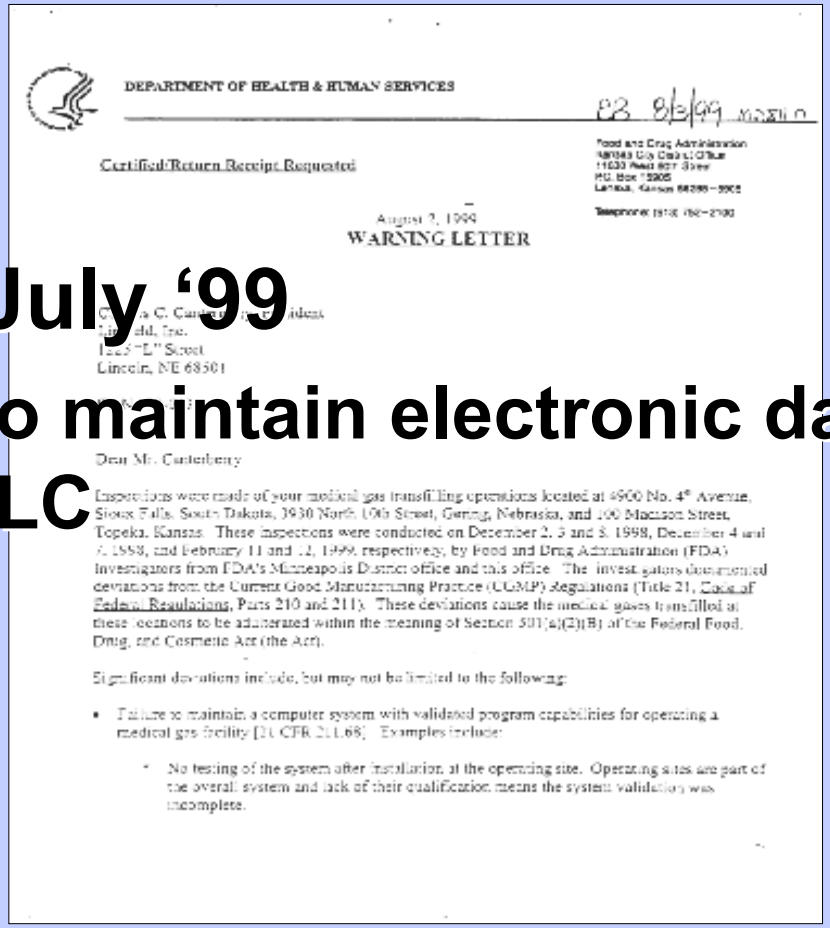
Cypress US August '99

- No audit trail of changes to electronic data

Warning Letters (2)

Gensia US July '99

- Failure to maintain electronic data files from HPLC



DEPARTMENT OF HEALTH & HUMAN SERVICES

Certified/Return Receipt Requested

August 2, 1999

WARNING LETTER

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Warning Letter applicable to CSV
- Medical Devices (Pulsation Counters) -

- http://www.fda.gov/foi/warning_letters/g1121d.pdf

Cardiomedics, Irvine, CA, April 2001

References software design and validation

"...Our inspection disclosed that these devices are adulterated within the meaning of Section 510(h) of the Act, in that the methods used in, or the facilities or controls used for manufacturing, packing and storage are not in conformance with the Good Manufacturing Practice (GMP) requirements for the Quality System Regulation as specified in Title 21, Code of Federal Regulation (CFR),Part 820,as follows..."

Warning Letter applicable for 21 CFR Part 11 - Laboratory, Electronic Record Keeping -

- http://www.fda.gov/foi/warning_letters/m4105n.pdf

  Baxter Healthcare, Deerfield, IL, August 2000

  "...In addition, we further request details regarding steps your firm is taking to bring your electronic cGMP records into conformance with the requirements of 21 CFR Part 11; Electronic Records; Electronic Signatures. ...This inspection disclosed deficient controls in the laboratory electronic record keeping system, which is used for maintaining chromatography and audit trails. In addition to a response to the deficiencies noted earlier in this letter, please outline your firm's global corrective action plan, including timeframes for correction, to address this Part 11 issue..."

Warning Letter applicable for 21 CFR Part 11 - Medical Gases -

- http://www.fda.gov/foi/warning_letters/m2811n.pdf

Lindwell Inc., Lincoln, Kansas, August 1999

"our inspection disclosed numerous and significant deviations from part 11. Examples include: The system does not generate an audit trail, and there is no way to determine if values have been changed on batch production records. This is important because art audit trail can be the only evidence that an electronic record has been altered. We note, for instance, that your system only records the last value entered by an operator and that values, such as Oxygen potency levels that my have been entered earlier and that may indicate potentially serious quality problems, are not recorded. The system prompts an operator when equipment detects that an Oxygen potency value is non-conforming, and permits the operator to record a value that is within specification, but does not record the original out of specification value."

Warning Letter applicable for 21 CFR Part 11 - Laboratory Computer -

- http://www.fda.gov/foi/warning_letters/m3450n.pdf

  Schein Pharmaceutical, Florham Park, N.J., March 2000

  "Failure to maintain the integrity and adequacy of the laboratory's computer systems used by the Quality Control Unit in the analysis and processing of test data. For example a) There was a lack of a secure system to prevent unauthorized entry in restricted data systems. Data edit authorization rights were available to all unauthorized users, not only the system administrator."

Warning Letter applicable for 21 CFR Part 11 - Clinical Trials -

- http://www.fda.gov/foi/warning_letters/m4116n.pdf

  Paradigm Medical, Salt Lake City, Utah, August 2000

  "...It is also noted in the inspection report that you do not have adequate control over the receipt of study data and its subsequent input into the database. There are no records to show when study data is received and when it is entered into the database. There is also no audit trail for changes made to the database. No data queries or clarifications have ever been generated and sent to the sites to verify missing information or to clarify discrepancies...Electronic records, the subject of SOP-100-720, Electronic Database Maintenance, are subject to **21 CFR Part 11**- Electronic Records; Electronic Signatures, as well as to the record keeping regulations found in 21 CFR 812.140. A guidance document regarding this regulation, Computerized Systems Used in Clinical Trials, dated April 1999.

Extract from a 483 1 + 2

“No original or current Functional/Structural Diagrams have been generated through the life of this program…..”

“Quality Assurance critical modules within XXX program to date have not been identified.”

Extract from a 483 - 3

"The following documents lack indication of review or approval : - test scripts
- general test plans
- detailed test plans.

The report generated from these activities lacked a document control number and was not approved by the Quality unit."

Extract from a 483 - 4 + 5

“Software testing had not been conducted simulating worst case conditions.”

“The [in-house] SAP users manual does not indicate which SAP version it refers to.”

Extract from a 483 - 6 + 7

“The firm presented no formally approved documentation specifying the currently approved version number of the SAP system.”

“Training for the use of SAP relied heavily upon the [in-house] SAP users manual which was not an approved document or procedure. ”

Extract from a 483 - 8 + 9

“There are no records to document that IT service provided staff have received training that includes cGMP regulations and related procedures.”

“The firm lacks the controls necessary to ensure of raw data generated by the laboratory computer system. Analysts can overwrite the existing sample information in the …. analytical raw data files and change results by over-writing the sample result raw data files.”

Extract from a 483 - 10 + 11

“The firm does not electronically store all integration parameters and chromatograms.”

“Requirements & design documentation were either not maintained or not updated for all version releases after version 1.0 until version 3.0 (implemented in February 1998).”

Extract from a 483 - 12 + 13

"Functional descriptions maintained after version 3.0 do not define full program module functionality in that these descriptions identify functionality for high level modules only."

"Revision control documentation for XXX revisions does not identify approved modules/module revision numbers. This is applicable to all XXX version releases since XXX version 1.0 to the present version release 3.1.2……."

Extract from a 483 - 14 + 15

“Revision control documentation does not identify what modules are being modified (or created) for the new revision. This is applicable to all XXX version releases since XXX version 1.0 to the present version release 3.1.2.”

“Revision control documentation does not identify specific changes made to modules which are being modified for the new revision. This is applicable to all XXX version releases since XXX version 1.0 to the present version release 3.1.2 .”

Extract from a 483 - 16 + 17

“Original programme code has not been maintained either digitally or in hard copy. Similarly, no historic programme code has been maintained to document when modifications have been made.”

“There were no approved WAN [and LAN] diagrams.”

Extract from a 483 - 18 + 19

“The Quality unit failed to ensure that procedures were in place to all system definition documentation that must be maintained for the WAN [and LAN].”

“The Quality unit failed to ensure that complete WAN system definition documentation is included in WAN documentation.”

Extract from a 483 - 20

“WAN [and LAN] diagrams with appropriate definition documentation identifying corporate sites on the network that use XXXX have not been included in the validation documents.”

Conclusion

Common themes:

- High proportion of CSV related issues
- 21 CFR Part 11 related issues are becoming more prominent
- “Holes” found in earlier visits will be targeted
- Inspections can target any part of validation lifecycle
- Inspections can target any process