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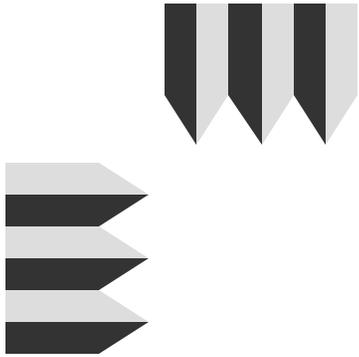
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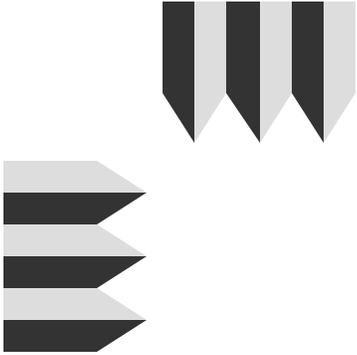
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The Challenge of Long-term Archiving of Electronic Raw Data and Electronic Clinical Data (Part 1)

“A keyboard. How quaint!”

Montgomery Scott, Cmdr., SF, UFP

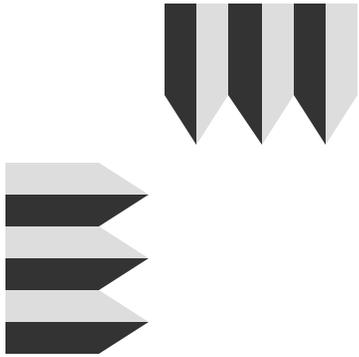


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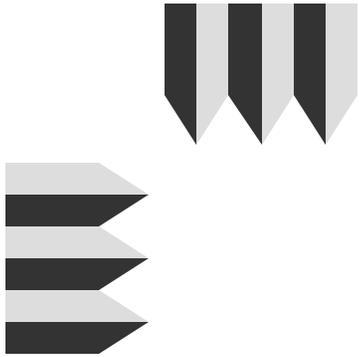
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Today's Goals

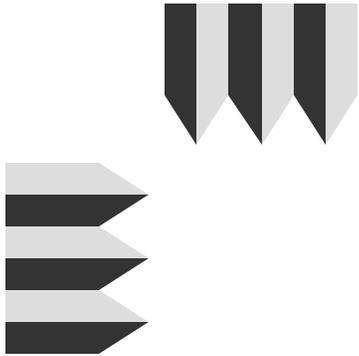
- **Review the “state of the industry” with regard to electronic archiving**
- **Develop an appreciation for the immediacy and scope of the archiving challenge**
- **Get a presentation together for the boss**
- **Review some of the basic hypothesized designs for electronic archiving solutions**

NOTE: To the instructors' knowledge, there is currently no available solution to the electronic archiving challenge



Today's Agenda

- **E-Archiving requirements**
 - State of the industry
 - Regulatory requirements
- **E-Archiving architectural challenges**
 - Data diversity and obsolescence
 - Maintaining a chain of custody
 - All the angles: tech, legal, RA, QA
 - Currently postulated architectures
- **Facilitated discussion**



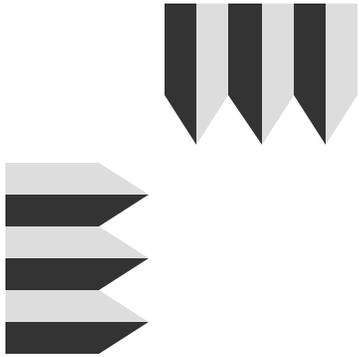
But First, A Word From Our Sponsors

**The Hollis Group, Inc.
Station Square Two, Suite 109
Paoli, PA 19301**

v - 610-889-7350

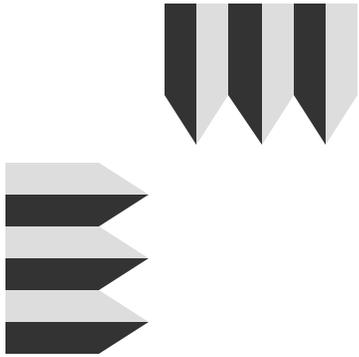
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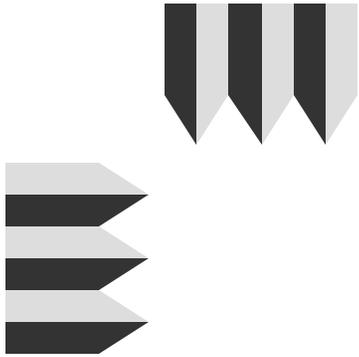
Electronic Archiving – The State of the Industry

- **In the Fall of 2000, The Hollis Group, Inc. conducted a survey to identify needs for long-term retention of electronic records in FDA-regulated industries.**
- **Businesses included in the survey were manufacturers of pharmaceutical drugs, medical equipment, medical & dental instruments, medical & dental supplies, and ophthalmic goods.**



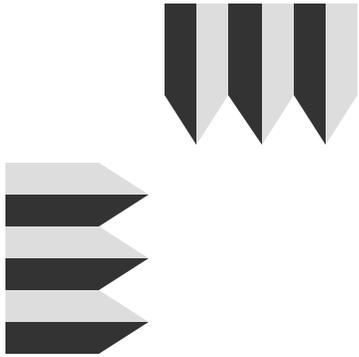
Electronic Archiving – An Industry Survey

- **The Hollis Group wanted to discover how familiar Quality Assurance and Regulatory Affairs personnel were with the details of 21 CFR 11.**
- **We were specifically interested in their knowledge of the regulatory requirements and their companies' plans to retain, retrieve and read electronic records and electronic raw data.**



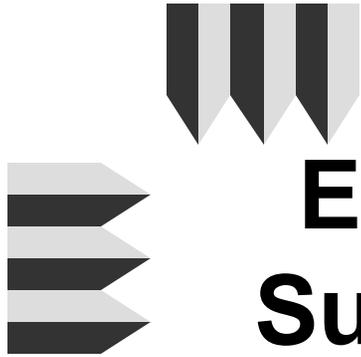
Electronic Archiving – An Industry Survey (cont.)

- **We gathered information to determine the level of awareness of the costs associated with the retention of records, both paper and other media.**
- **The survey also included estimated expertise in computer system validation.**
 - **Validation is a key requirement for the computer systems used to generate the original electronic raw data and records.**



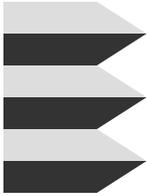
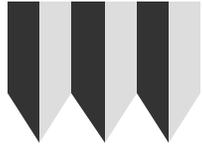
Electronic Archiving – Survey Structure

- **The telephone survey ran from September 30, 2000 to November 3, 2000.**
- **The companies were selected based on data obtained from Dunn & Bradstreet, specifically SIC codes 283, 384, and 385, which cover companies listing their primary business areas as pharmaceuticals, biotech products, medical devices, ophthalmic goods, dental supplies and x-ray equipment.**
- **A total of 82 companies were contacted. Of those 35, or 43%, agreed to participate in the survey.**



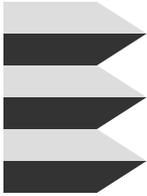
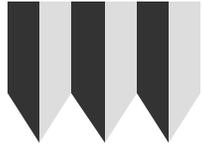
Electronic Archiving Industry Survey – General Observations

- **The majority of those interviewed did not know the costs of retaining records.**
 - This applied to all types of records: paper, microfilm/microfiche, or electronic media.
- **Most of the companies interviewed, 77%, expect to have to increase their budgets to retain, retrieve and read electronic records.**
 - However, of those who expect to increase their budgets, 57% have no idea how much their budgets will need to be increased.



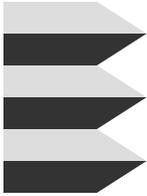
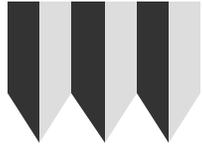
General Observations (cont.)

- **All of the companies surveyed (100 %) retain paper records.**
- **Companies maintaining electronic records most often use magnetic tape (77%) or floppies and CD's (73%), or both.**
- **The majority of the respondents are aware of the need to save electronic raw data.**
 - **Only about 50% of those surveyed are aware of the detailed requirements of 21 CFR 11 regarding the retention of electronic records.**



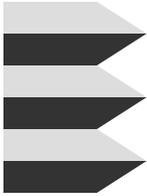
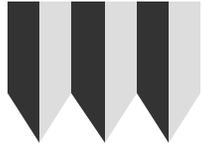
General Observations (cont.)

- **Less than 25% of the companies surveyed have a written plan or policy for the long-term retention of electronic records.**
- **Approximately 50% are actively working on a plan.**
 - **The rest have not or do not intend to create a plan.**
 - **i.e., 25% plan to NOT write an archive plan**
- **Of the persons interviewed, 63% were aware or very aware of the contents of either the plan in place or the in-process plan.**



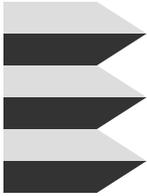
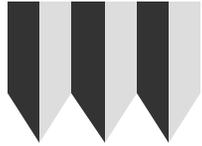
General Observations (cont.)

- **Of the companies that have or are working on a plan, all are wrestling with the technology to read data that has been retained.**
- **Most are struggling to create viable solutions for the short term.**
- **Most say they may be OK today, but are not sure about their status in the future.**



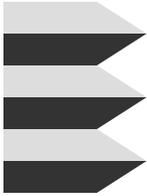
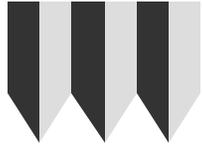
General Observations (cont.)

- **Approximately 20% of those interviewed did think that the ability to retrieve an electronic record was not different than being able to read that electronic record.**
- **The rest believed these two actions were different.**
 - **However, among this group the explanations of ‘retrieve’ and ‘read’ varied greatly.**



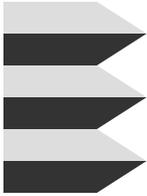
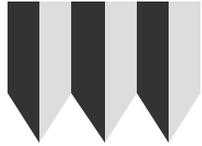
General Observations (cont.)

- **Fewer than five (5) companies have explored the ability of existing technology to retain viable electronic records for up to several decades.**
 - None of them has a solution.
- **Depending upon the industry's mandated record retention times, electronic records may need to be retained anywhere from 5 years to over 30 years.**
 - Some people opine that some records need to be saved in perpetuity.



General Observations (cont.)

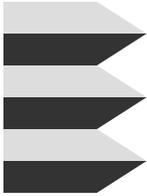
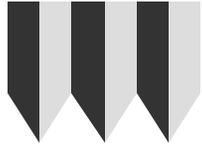
- **A comparison of the Large (>\$300M Annual Sales), Medium (\$10-\$300M) and Small (< \$10M) participants revealed that the major difference lies in their knowledge of and familiarity with the regulation.**
- **Large companies tended to be more knowledgeable than the Medium-sized companies, while Medium-sized companies were more knowledgeable than the Small companies.**



General Observations (cont.)

On the question of outsourcing:

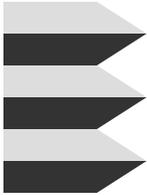
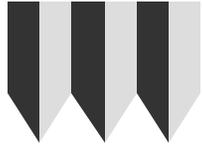
- 66% indicated they would or would consider outsourcing the long-term retention of electronic records.**
- 63% indicated they would or would consider outsourcing the retention of operational configurations if they were required to retain them.**
- 76% indicated they would or would consider outsourcing the conversion of old raw data to their current formats.**



General Observations (cont.)

On the question of consultants:

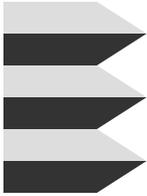
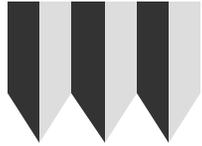
- 83% indicated it would be valuable to very valuable to use a qualified consultant to assist in designing a solution.**
- 90% indicated it would be valuable to very valuable to use a qualified contractor to implement the solution.**



General Observations (cont.)

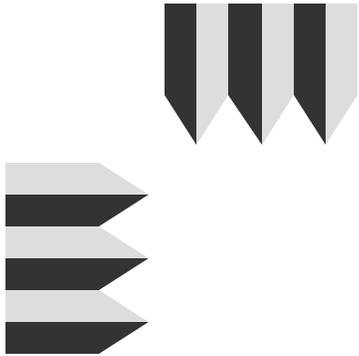
A comparison of the differences between Large (>\$300M Annual Sales), Medium (\$10-\$300M) and Small (< \$10M) companies revealed that there was no significant difference in the probability that they would outsource part or all of the retention of electronic records.

- Interestingly, other than in general knowledge of the rule, there were no statistically significant correlations by company size.**



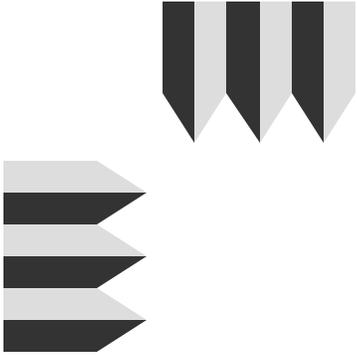
General Observations (cont.)

- **We are all in the same boat.**
- **The boat is sinking, FAST!**
- **Nobody has found any lifeboats.**
- **The water is filled with FD..., er, sharks**



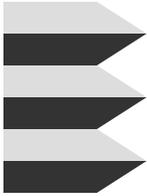
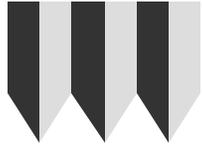
HEY BOSS!

- **First, get her attention**
- **Then, let her know that this is going to cost BIG BUCKS and much staff time**
- **Next, explain that this expense is permanent, ongoing, and ever-increasing**
- **Last, review a few possible solutions and get a project going to select the right one(s)**



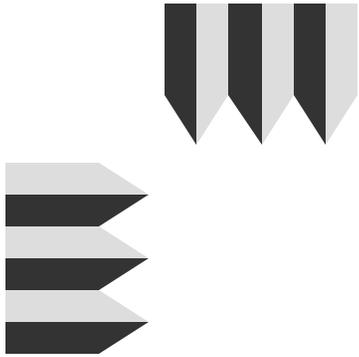
The Project Staff

- **Records management**
- **Information technology**
- **Regulatory affairs**
- **Corporate legal**
- **Corporate audit**
- **Information security**



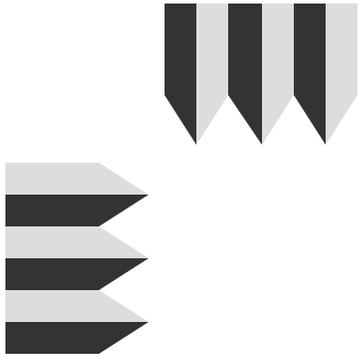
Why RA and Legal?

- **Let's assume we're going to transfer some set of data (T_n) to the archives**
- **There is a high probability that this is a subset of the entire record set**
- **This means that we need to decide what to do with the original set and the residual subset**
 - **Save the 100%?**
 - **Save just the T_n ?**
 - **(Delete the 100% - T_n ?)**
- **RA and Legal will probably need to review this decision on a case-by-case basis**
 - **Unless we have a really, really good policy**



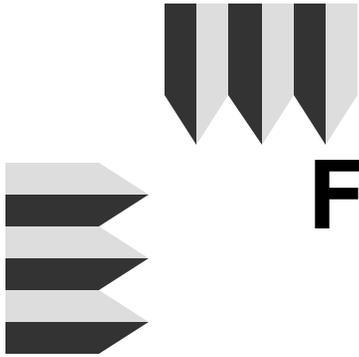
To Switch Topics...





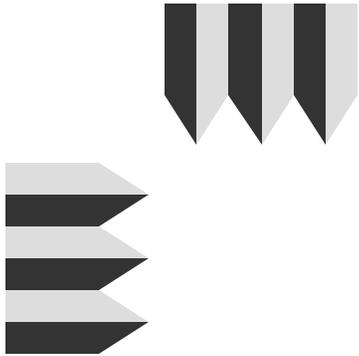
In a Nutshell, The Regulators Require:

- **Qualified records as source documents**
 - **Audit trails, systems controls, etc.**
- **A chain of custody of the records**
 - **Authenticity == attributability + irrefutability**
- **Retention of the raw data, source records, authentication, and execution environment**
 - **For purposes of reconstruction**
- **Inspection-on-demand of all of the above at the sponsor and at the site**



FDA Requirements for Long-Term Archiving

- **21 CFR 11 Electronic Records; Electronic Signatures**
- **Guidance for Industry Computerized Systems Used in Clinical Trials**
- **GCP's, GLP's, and GMP's**
 - **Generically, GXP's**
 - **“The Predicate Rule”**



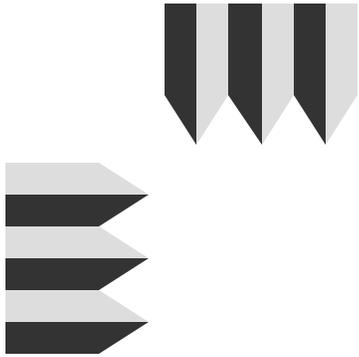
21 CFR 11 Archiving Requirements

§ 11.50 Signature manifestations.

(a) Signed electronic records shall contain information associated with the signing that clearly indicates all of the following:

- (1) The printed name of the signer;**
- (2) The date and time when the signature was executed; and**
- (3) The meaning (such as review, approval, responsibility, or authorship) associated with the signature.**

(b) The items identified in paragraphs (a)(1), (a)(2), and (a)(3) of this section shall be subject to the same controls as for electronic records and shall be included as part of any human readable form of the electronic record (such as electronic display or printout).

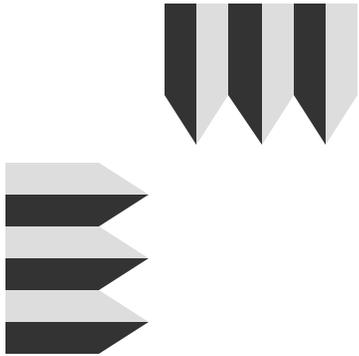


21 CFR 11 Archiving Requirements (cont.)

§ 11.10 Controls for closed systems.

Persons who use closed systems to create, modify, maintain, or transmit electronic records shall employ procedures and controls designed to ensure the authenticity, integrity, and, when appropriate, the confidentiality of electronic records, and to ensure that the signer cannot readily repudiate the signed record as not genuine. Such procedures and controls shall include the following:

(b) The ability to generate accurate and complete copies of records in both human readable and electronic form suitable for inspection, review, and copying by the agency. Persons should contact the agency if there are any questions regarding the ability of the agency to perform such review and copying of the electronic records.

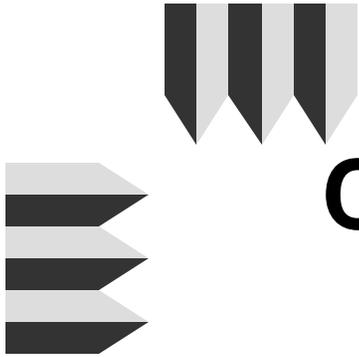


21 CFR 11 Archiving Requirements (cont.)

§ 11.10 Controls for closed systems.

(c) Protection of records to enable their accurate and ready retrieval throughout the records retention period.

(e) Use of secure, computer-generated, time-stamped audit trails to independently record the date and time of operator entries and actions that create, modify, or delete electronic records. Record changes shall not obscure previously recorded information. Such audit trail documentation shall be retained for a period at least as long as that required for the subject electronic records and shall be available for agency review and copying.



Clinical Computer Guidance Archiving Requirements

Certified Copy means a copy of original information that has been verified, as indicated by dated signature, as an exact copy having all of the same attributes and information as the original.



Clinical Computer Guidance Archiving Requirements (cont.)

III. GENERAL PRINCIPLES

A. Each study protocol should identify at which steps a computerized system will be used to create, modify, maintain, archive, retrieve, or transmit data.

B. For each study, documentation should identify what software and, if known, what hardware is to be used in computerized systems that create, modify, maintain, archive, retrieve, or transmit data. This documentation should be retained as part of study records.



Clinical Computer Guidance Archiving Requirements (cont.)

III. GENERAL PRINCIPLES

E. The design of a computerized system should ensure that all applicable regulatory requirements for record keeping and record retention in clinical trials are met with the same degree of confidence as is provided with paper systems.

K. Computerized systems should be designed: (1) So that all requirements assigned to these systems in a study protocol are satisfied (e.g., data are recorded in metric units, requirements that the study be blinded); and, (2) to preclude errors in data creation, modification, maintenance, archiving, retrieval, or transmission.



Clinical Computer Guidance Archiving Requirements (cont.)

V. DATA ENTRY

B. Audit Trails

b. Audit trails must be retained for a period at least as long as that required for the subject electronic records (e.g., the study data and records to which they pertain) and must be available for agency review and copying.



Clinical Computer Guidance Archiving Requirements (cont.)

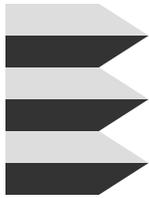
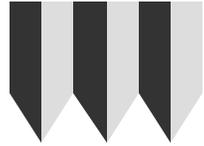
C. Retrieval of Data

1. Recognizing that computer products may be discontinued or supplanted by newer (possibly incompatible) systems, it is nonetheless vital that sponsors retain the ability to retrieve and review the data recorded by the older systems. This may be achieved by maintaining support for the older systems or transcribing data to the newer systems.



Clinical Computer Guidance Archiving Requirements (cont.)

2. When migrating to newer systems, it is important to generate accurate and complete copies of study data and collateral information relevant to data integrity. This information would include, for example, audit trails and computational methods used to derive the data. Any data retrieval software, script, or query logic used for the purpose of manipulating, querying, or extracting data for report generating purposes should be documented and maintained for the life of the report. The transcription process needs to be validated.



Clinical Computer Guidance Archiving Requirements (cont.)

D. Reconstruction of Study

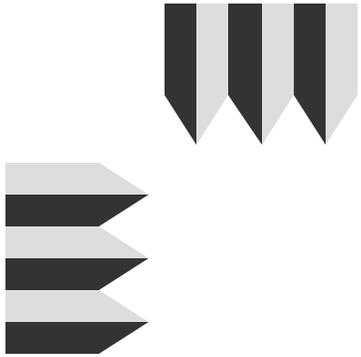
FDA expects to be able to reconstruct a study. This applies not only to the data, but also how the data were obtained or managed. Therefore, all versions of application software, operating systems, and software development tools involved in processing of data or records should be available as long as data or records associated with these versions are required to be retained. Sponsors may retain these themselves or may contract for the vendors to retain the ability to run (but not necessarily support) the software. Although FDA expects sponsors or vendors to retain the ability to run older versions of software, the agency acknowledges that, in some cases, it will be difficult for sponsors and vendors to run older computerized systems.



Clinical Computer Guidance Archiving Requirements (cont.)

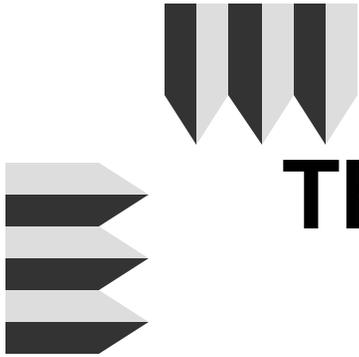
XI. RECORDS INSPECTION

A. FDA may inspect all records that are intended to support submissions to the Agency, regardless of how they were created or maintained. Therefore, systems should be able to generate accurate and complete copies of records in both human readable and electronic form suitable for inspection, review, and copying by the Agency. Persons should contact the Agency if there is any doubt about what file formats and media the Agency can read and copy.



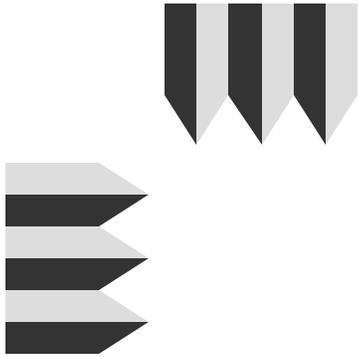
GCP's, GLP's, and GMP's

- “The Predicate Rule”



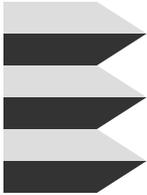
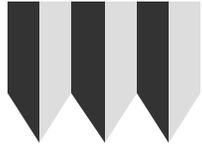
The Environmental Protection Agency Proposed Rule

- **40 CFR Parts 3, 51, et al.**
- **Establishment of Electronic Reporting: Electronic Records; Proposed Rule**
- **Federal Register / Vol. 66 No. 170**
- **21 AUG 2001**
- **Pages 46162 – 46195**



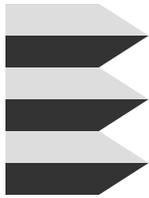
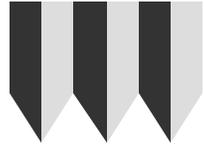
40 CFR 3, 51, et al. Instructors' Disclaimer

- **The following analysis is based upon a preliminary review of the proposed rule**
- **We quite probably have mis-interpreted the EPA intent in several places**
- **We've also quite probably have gotten several things just plain wrong**
- **We've only had two weeks, one of which included 11SEP2001**



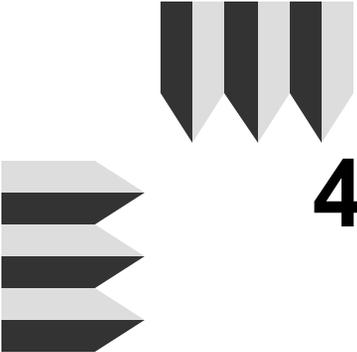
40 CFR 3 – Key Concepts

- **40CFR3 establishes, by definition, a distinction between electronic documents, and electronic records**
- **It defines the terms “electronic signature,” and “handwritten signature” but not “digital signature”**
 - **And much more broadly than 21CFR11**
- **It defines “third party system”**
- **Reference to the “Central Data Exchange”**



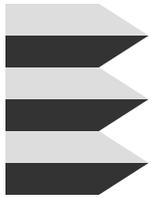
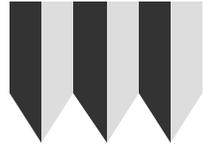
40 CFR 3 § 100 – Acceptable Electronic Records

- **Accurate and complete and that may not be altered without detection**
- **Accurate and complete without alteration for the entire retention period**
- **Accurate and complete copies in human readable and electronic form**
- **If signed, name of signer, date and time, and any “meaning” of the signature**
- **Protection from detaching, copying, or otherwise compromising e-sigs**



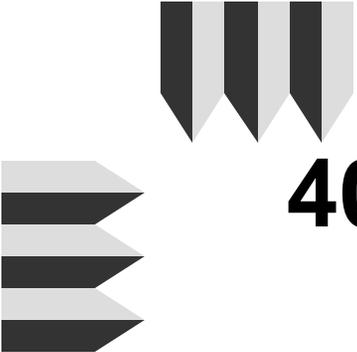
40 CFR 3 § 100 – Acceptable Electronic Records (cont.)

- **Secure, computer-generated, time-stamped audit trails of operator actions**
- **Record changes cannot obscure previously recorded information**
- **Retain audit trails for retention period**
- **Searchable and retrievable for reference and secondary uses:**
 - *“...inspections, audits, legal proceedings, third party disclosures...”*



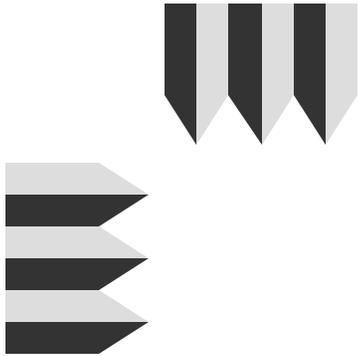
40 CFR 3 § 100 – Acceptable Electronic Records (Archiving)

- **Note that this is the largest section**
- **(9) Archive electronic records and documents in an electronic form which preserves the context, meta data, and audit trail, and, if required, must ensure that:**
 - **(i) Complete records can be transferred to a new system;**
 - **(ii) Related meta data can be transferred to a new system;**
 - **(iii) Functionality necessary for use of records can be reproduced in new system**



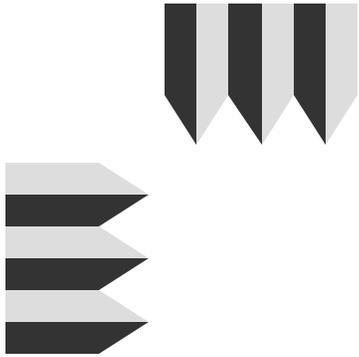
40 CFR 3 § 2000 – Acceptable “Receiving Systems”

- **This is specifically define for “electronic document receiving systems”**
- **“Electronic signature / certification scenario”**
 - **New concept of bilateral disclosure**
- **“Copy of record” concept / record**
 - **Evidence of bilateral disclosure**
- **Transaction record**
- **System archives**



40 CFR 3 § 2000 (f) Transaction Record

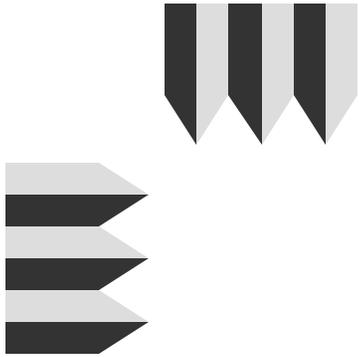
- **(1) The precise routing from the submitter's computer to receiving system;**
- **(2) The precise date and time (based on the system clock) of:**
 - **(i) Initial receipt of the electronic document;**
 - **(ii) Sending of electronic acknowledgment under paragraph (e)(2) of this section;**
 - **(iii) Copy of record created under paragraph (e)(3) of this section;**
- **(3) Copy of record as specified under paragraph (e)(3) of this section.**



40 CFR 3 § 2000 (g)

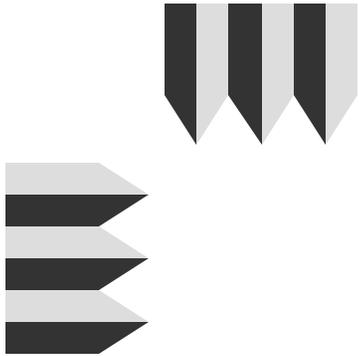
System Archives

- **(1) Maintain:**
 - **(i) The transaction records specified under paragraph (f) of this section, and**
 - **(ii) Records of the system on-screen interface displayed to a user under paragraph (e) of this section that can be correlated to the submission of any particular report (including instructions, prompts, warnings, data formats and labels, as well as the sequencing and functioning of these elements);**



40 CFR 3 § 2000 (g) System Archives (cont.)

- **(2) Maintain the records specified under paragraph (g)(1) of this section for at least the same length of time as would be required for a paper document that corresponds to the received electronic document, and in a way that:**
 - **(i) Can be demonstrated to have preserved them in their entirety without alteration since the time of their creation; and**
 - **(ii) Provides access to these records in a timely manner that meets the needs of their authorized users.**



Don't Forget the International Standards

- **MCA - Medicines Control Agency (UK)**
 - <http://www.open.gov.uk/mca/mcahome.htm>
- **Pharmaceutical and Medical Safety Bureau (Ministry of Health & Welfare - Japan)**
 - <http://www.mhw.go.jp/english/index.html>
- **The European Agency for the Evaluation of Medicinal Products (European Union)**
 - <http://www2.eudra.org/>
- **OECD - Organization for Economic Cooperation and Development**
 - <http://www.oecd.org>
 - <http://www.oecdwash.org/>



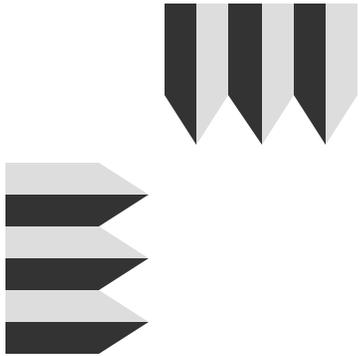
OECD - Environment Monograph No. 116

The Application of the Principles of GLP to Computerised Systems

Sec. 8. d) Standard Operating Procedures (SOPs)

Much of the documentation covering the use of computerised systems will be in the form of SOPs. These should cover but not be limited to the following:

- * Procedures for the operation of computerised systems (hardware/software), and the responsibilities of personnel involved.**
- * Procedures for security measures used to detect and prevent unauthorised access and programme changes.**
- * Procedures and authorisation for programme changes and the recording of changes.**
- * Procedures and authorisation for changes to equipment (hardware/software) including testing before use if appropriate.**
- * Procedures for the periodic testing for correct functioning of the complete system or its component parts and the recording of these tests.**
- * Procedures for the maintenance of computerised systems and any associated equipment.**
- * Procedures for software development and acceptance testing, and the recording of all acceptance testing.**
- * Back-up procedures for all stored data and contingency plans in the event of a breakdown.**
- * Procedures for the archiving and retrieval of all documents, software and computer data.**
- * Procedures for the monitoring and auditing of computerised systems**

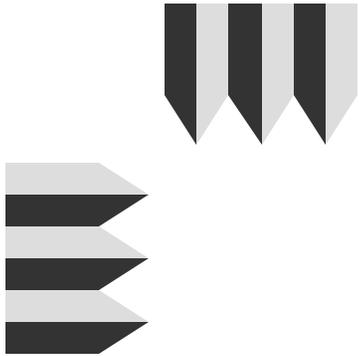


OECD Monograph No. 116 (cont.)

9. Archives

The GLP Principles for archiving data must be applied consistently to all data types. It is therefore important that electronic data are stored with the same levels of access control, indexing and expedient retrieval as other types of data.

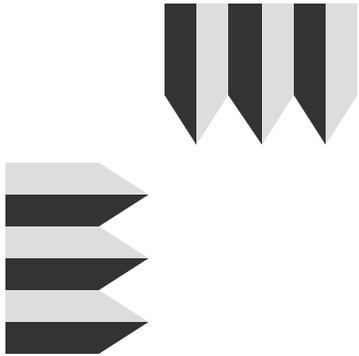
Where electronic data from more than one study are stored on a single storage medium (e.g., disk or tape), a detailed index will be required.



OECD Monograph No. 116 (cont.)

9. Archives

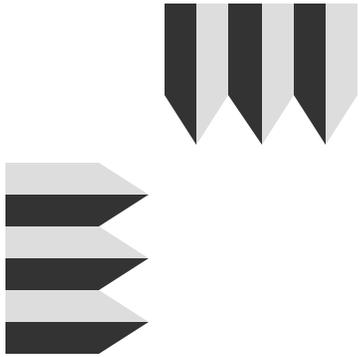
It may be necessary to provide facilities with specific environmental controls appropriate to ensure the integrity of the stored electronic data. If this necessitates additional archive facilities then management should ensure that the personnel responsible for managing the archives are identified and that access is limited to authorised personnel. It will also be necessary to implement procedures to ensure that the long-term integrity of data stored electronically is not compromised. Where problems with long-term access to data are envisaged or when computerised systems have to be retired, procedures for ensuring that continued readability of the data should be established. This may, for example, include producing hard copy printouts or transferring the data to another system.



OECD Monograph No. 116 (cont.)

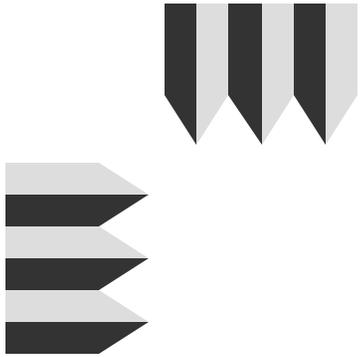
9. Archives

No electronically stored data should be destroyed without management authorization and relevant documentation. Other data held in support of computerised systems, such as source code and development, validation, operation, maintenance and monitoring records, should be held for at least as long as study records associated with these systems.

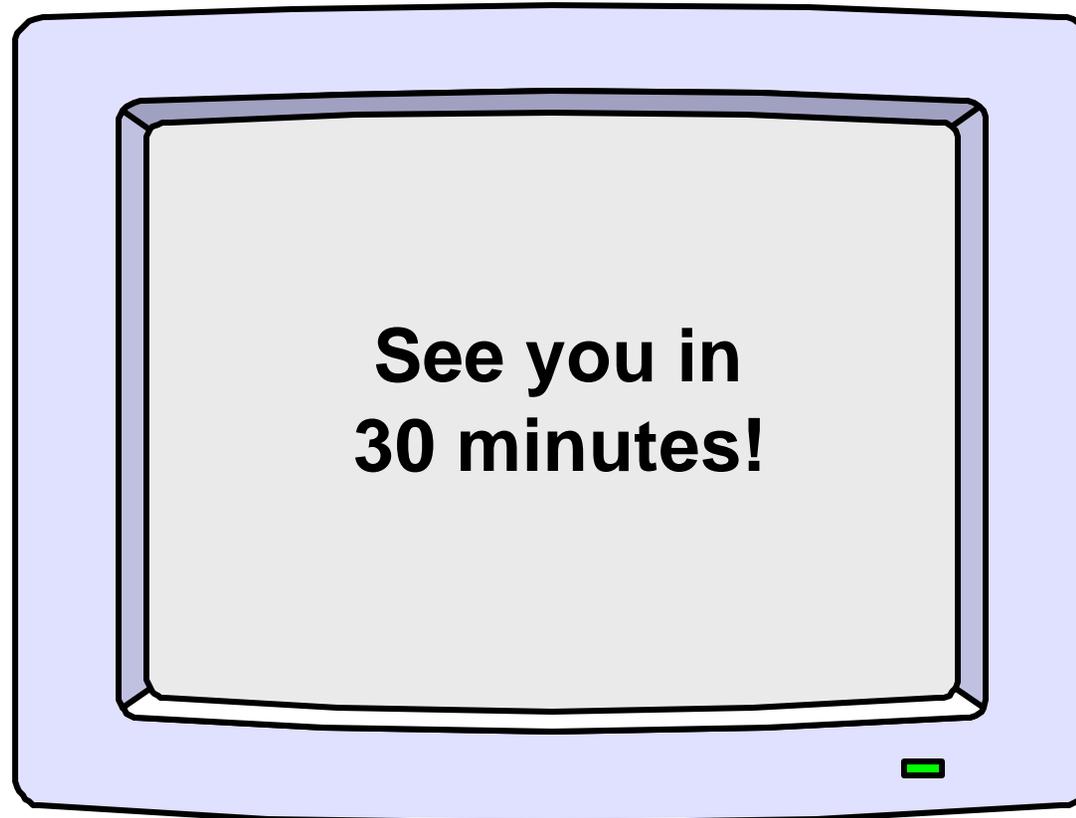


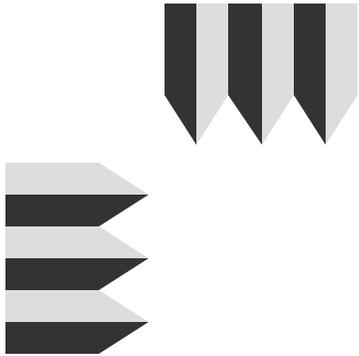
In Summary, The Regulators Require:

- **Qualified records as source documents**
 - **Audit trails, systems controls, etc.**
- **A chain of custody of the records**
 - **Authenticity == attributability + irrefutability**
- **Retention of the raw data, source records, authentication, and execution environment**
 - **For purposes of reconstruction**
- **Inspection-on-demand of all of the above at the sponsor and at the site**



Break Time!





Questions? Discussion?

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