REDUCING THE PAPER CLUTTER OF THE TMF

FRAMEWORK FOR THE DESTRUCTION OF PAPER

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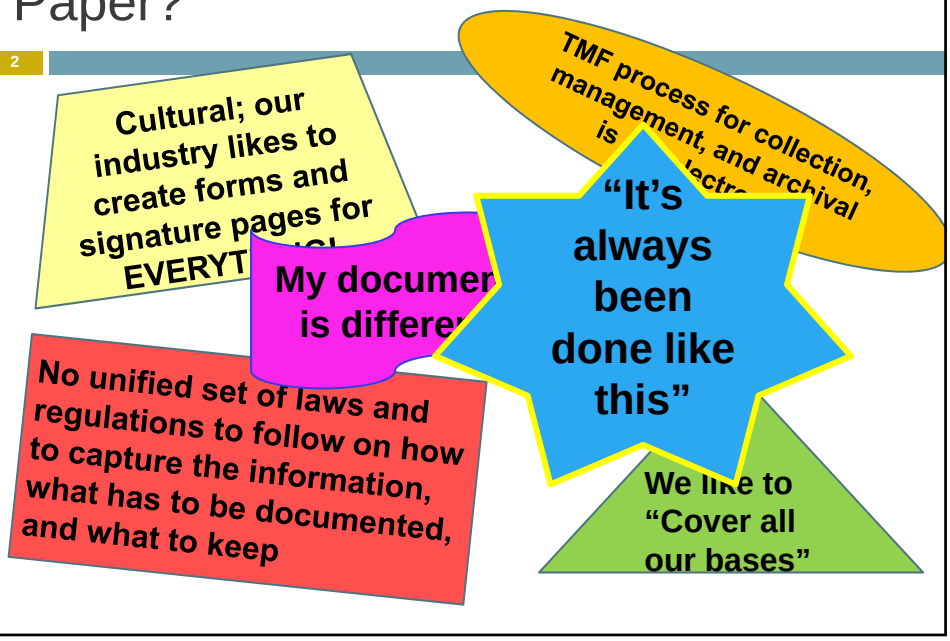
So Why is There Soooooooo Much Paper?



What "Paper" is Required by ICH Guidelines?

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- Actually paper isn't required.
- Nowhere is it stated that wet-ink signature must be obtained.
- Signature is required on the following TMF content per ICH E6 section 8:
  - Protocol/Amendments signature page – Sponsor
  - Protocol/Amendment signature page - PI/Institution
  - Signed agreements between Sponsor and Sponsor delegate, Signed agreements between PI/Institution and Sponsor or Sponsor delegate
  - Signed agreements between PI/Institution and regulatory authority, where applicable (ex Form FDA 1572)
  - Signed completed CRF forms, including any changes)

Eliminate the Creation of Paper and Copies

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Eliminate the Creation of Paper!

How do we do this?

Process, Process, Process

Eliminate the Complexity

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Eliminate need for signature

- No additional authentication other than text within the document that identifies it as a final, approved document
- Capture the approval of the document in a system audit trail.
  - This content will typically be those documents not requiring approval or where a robust process demonstrates that the final document is an approved one (e.g. completion of a process checklist or workflow)

Eliminate the Wet-ink signatures

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Eliminate creation of paper

- Incorporate the use of electronic and digital signatures
  - Digital signatures using one of the complex digital signature technologies that embeds the digital signature within the document (as per 21CFR11).
    - Authenticated Digital Signatures out to PI level
      - Digitally sign the protocol signature page and Form FDA1572

Eliminate the Collection & Creation

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- Eliminate the collection of paper documentation
  - Portals for sending and receiving electronic documents
    - electronic acknowledgements/audit trails
  - Assignment of where 'original' wet-ink is retained
    - Form FDA 1572 – original at site, electronic copy to sponsor
- Consider TMF documents in respect of the data they collect and an actual document that gets completed.

What can be Done with the Paper that is Created?

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- Within the Drug Information Association's SIAC for Document and Records Management, an yearly long effort has been organized to develop the critical requirements for a Framework for the Destruction of Paper.
  - *The initial scope of this effort is focused on GCP records in ICH regions of North America, Europe, and Japan.*

How many in this room has heard of this initiative? Any of you provide feedback on the draft?

Why is a Framework Needed at All?

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Documentation processes have changed from creating and managing paper documents into producing and managing documents in electronic formats.

The trend is that the remaining paper documents are scanned into a digital format and uploaded into an ECMS

This conversion process creates redundancy and duplication in the management of documentation in support of the business process

Why is a Framework Needed at All?

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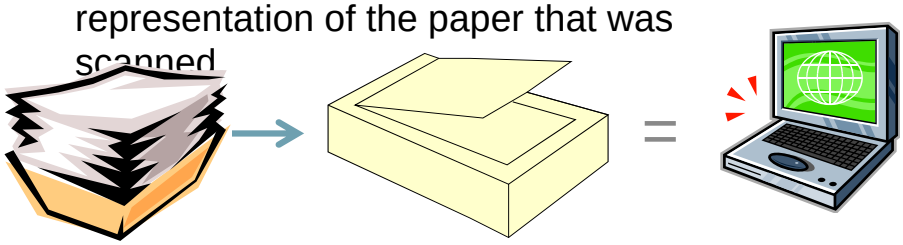
- Destruction of the scanned paper document necessitates a thorough examination of the requirements that confirm the electronic version is a complete and accurate representation of the paper that was scanned



Why is a Framework Needed at All?

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- Intention of this framework is to break through the reoccurring obstacles that have prevented our industry's confidence in this area for well over a decade
  - If the banking and transportation industries can do it so can the Pharmaceutical industry!

Who Created the Framework?

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- Voluntary contributions of the diverse special interest group professionals who provided their expertise and perspective on what is required for the act of paper destruction.

More than 40 professionals (all DIA members) from more than 25 pharmaceutical companies, contract research organizations, consultancies, and technical vendors.	The attention of participants was drawn to the non-commercial nature of this forum. This group has not been a forum for promotion of products, capabilities, or specific companies

Goal of the Framework

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Provide a single, unified interpretation of the applicable laws, regulations, and industry best practices that apply to a complicated, legally defensible, and regulatory compliant paper destruction process.

Position Statement

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When paper is created or collected, this framework recommends the destruction of that paper following a verified conversion of the document into a digital format, conditional on the following:

- A qualified organizational process is in place and monitored that ensures that the digitized copy is a complete and accurate representation of the paper version
- The digitized copy is placed in a validated electronic content management system
- A training plan covering the process flow and applicable SOPs has been created, is available within the organi-zation, and users have successfully completed the training

Framework – A Reference for our Industry

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- The framework is:
  - Non-binding in accordance with the DIA's scope and mission.
  - A reference for the industry and should not be considered mandatory, or a standard, but rather as an opportunity for harmonization across the industry.
  - Not endorsing or requiring any specific technology for implementation.

Five Perspectives within the Framework

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The 5 topic areas were based on perspective

- **Technology** – Specific requirements and capabilities of the system
- **Quality** – Validation of capture process and scan quality
- **Records Management** – Policies, procedures and practices
- **Regulatory** – Established health authority laws & regulations, and GCP, GMP and GLP standards
- **Legal** – Laws of evidence

Glossary

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- Term
- Alternate names
- Definition – as used within the framework
- Other legal and regional sources

Term	Certified Copy
Alternate Name(s)	Attested copy, Exemplified copy, Verified copy, Validated copy
Definition	A Certified Copy is a copy of original information that has been verified through a validated process, as an exact copy having all of the same attributes and information as the original.
Black's Legal Dictionary	A duplicate of an original (usually official) document, certified as an exact reproduction usually by the officer responsible for issuing or keeping the original.
ARMA	
North American Legislation	• "A Certified Copy is a copy of original information that has been verified, as indicated by a dated signature, as an exact copy having all of the same attributes and information as the original". FDA's Guidance for Industry Computerized Systems Used in Clinical Investigations (May 2007) • "a duplicate is a counterpart produced by the same impression as the original, or from the same matrix, or by means of photography, including enlargements and miniatures, or by mechanical or electronic re-recording, or by chemical reproduction, or by other equivalent techniques which accurately reproduces the original". Fed. R. Evid. 1001(4)
EU/MS Legislation	"Originals or copies certified after verification as being accurate copies" • EMA, ICH Topic E6 (R1) - Guideline for Good Clinical Practice, CPMP/ICH/135/95
Harmonized Guidelines	• "A certified copy is a copy of original information that has been verified as an exact (accurate and complete) copy having all of the same attributes and information as the original. The copy may be verified by dated signature or by a validated electronic process" • "An eCertified copy is a copy that is created through application of a validated process that is certified to preserve the information in the original. NOTE: an eCertified copy of an eSource document can also serve as a source document". CDISC Clinical Research Glossary Version 8.0, (Dec. 2009)
Japanese Legislation	Although the term of "duplicate" is not defined under the Japanese legislation, the Legal Terminology Dictionary (9th Edition) is stating as follows with respect to "duplicate": If a person prepares a document having the identical contents as the authenticated copy in addition to the authenticated copy in order to use it for purposes other than its primary purpose, the document is called a "duplicate." We could not find the definition of the term "certified copy" neither in the Japanese legislation nor the Legal Terminology Dictionary (9th edition). We could not find the definition of the term "record copy" neither in the Japanese legislation nor the Legal Terminology Dictionary (9th edition). "Authenticated copy" is one kind of a copy and means a copy which is prepared based on the original by an authorized person and which has the same effect as the original externally. Hiroshi Kaneko et al., horitsugaku-sho-jiten [The Dictionary of Law] (4th edition, comprehensively revised)(2008) at 320.

Process Diagrams

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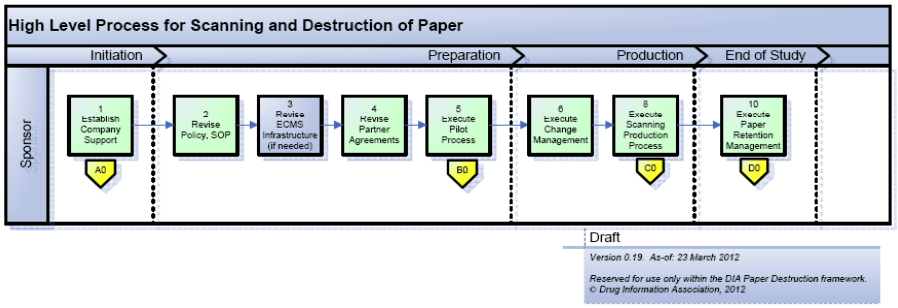

- Five sub-processes (note off-page (yellow) arrows)
- Includes potential collaboration with external partners
- Green boxes show where parameters have been associated with the process step

Process Diagrams (cont.)

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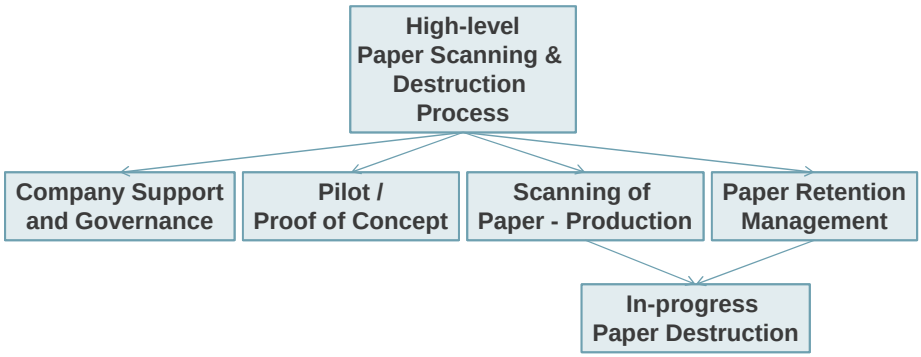
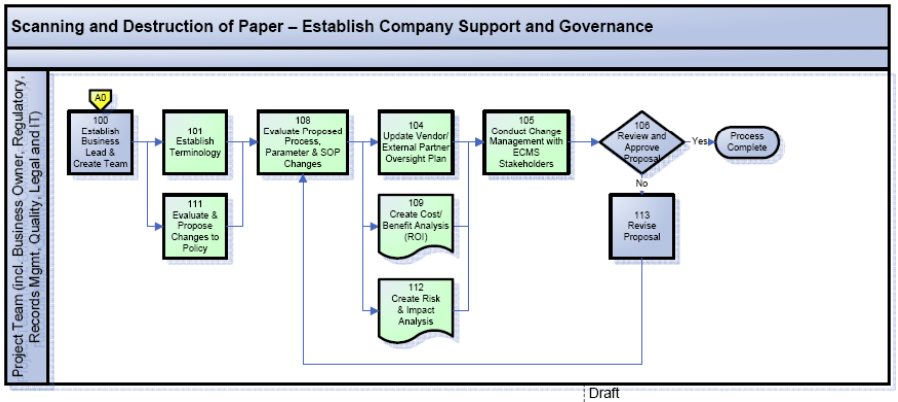
Process diagrams are hierarchical



Process Diagrams (cont.)

20



- Critical steps to acceptance
- Adaptation of process and SOPs to fit company culture

Parameters

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- Parameters were created for each of the 5 perspectives. Each parameter was created following a thorough assessment of the regulations, laws, guidance, and industry practices currently available.

- Most parameters include:
  - A statement of a requirement
  - An interpretation of the statement
  - A reference or bibliography of the content used to establish the statement (where available)
  - If pertinent, the process step(s) to which the parameter is applicable

Parameters (cont.)

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- What are the parameters?
  - Minimum requirements
  - Points to consider
  - Existing rules and guidelines that help justify including an action within your revised SOPs.
  - Recommendations

Parameters - Technology

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- Scope of the Technology Topic Team:
  - Provide guidance and recommendations to the team relating to the minimum technology requirements of the paper scanning system use of technology as it pertains to the destruction of paper documents associated to clinical trials.
    - Conduct a multi-industry assessment identifying key learning's and insights resulting from the process of migrating from a paper environment to an electronic environment and associated ramifications.
    - Conduct a review of the use of technologies in the pharmaceutical industry (Pharma, Bio, Device) as it relates to the primary objectives of team
    - Etc

Parameters - Technology

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T1:There are minimum requirements for scanner settings to scan and upload documents into an ECMS

T2:Optical Character Recognition (OCR) technology is utilized for both ease of content identification and increased search ability within ECMS

T3:Change management programs facilitate the successful migration from a paper format to electronic format in ECMS

T4:There are minimum requirements in electronic document formatting for the purposes of long term retention and future document reproduction capabilities

T5:There are core requirements to be followed in addressing the challenges of long term archiving

T6:Documents scanned or uploaded must be secured in a validated ECMS

Parameters - Technology

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T6 **Documents scanned or uploaded must be secured in a validated ECMS.**

INTERPRETATION

Companies scanning or uploading documents into an EDMS or ECMS must ensure that the system and repository is fully validated in compliance with 21 CFR Part 11[1] and GAMP5[2] standards. Refer to Quality Parameters Q1 & Q2 for additional information.

BIBLIOGRAPHY/REFERENCES

1. United States. Food and Drug Administration. *Electronic records; electronic signatures – Scope and Application, 21 CFR Part 11.* Aug. 2013. 17 Sep. 2011. http://www.fda.gov/downloads/RegulatoryInformation/Guidances/ucm125125.pdf
2. GAMP5. A Risk-Based Approach to Compliant GxP Computerized Systems. ISPE 2008.

PROCESS STEPS: 8, 105, 112, 204

Parameters - Quality

26

- Scope of the Quality Topic Team
  - Provide guidance on a quality focused validated process for scanning paper TMF documents to electronic format, to facilitate the destruction of paper

Parameters - Quality

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Q1:There should be a validated quality driven process for document scanning and uploading into an Electronic Content Management System (ECMS)

Q2:The authenticity of scanned images as certified copies must be established

Q3: There must be a documented quality driven process for destruction of paper documents and maintaining certified copies in an ECMS; in compliance with regulations and legal requirements Q4 : All training must be completed and documented

Q5: Third party requirements must be specified for when activities transferred to consultants and vendors

Q6 : Monitoring of quality must take place

Q7: It is critical to perform a risk assessment

Q8: The paper destruction process and certification of destruction requirements need to be defined by the company

Parameters - Quality

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Q7 **It is critical to perform a risk assessment**

INTERPRETATION:

A Risk Management and Mitigation plan should be established in a Paper Destruction pilot process.

- Milestones and considerations throughout the pilot, as well as at the end of the pilot to determine how to proceed with a Paper Destruction process are recommended.

This Risk Management and Mitigation Plan must align with company's risk management policies.

BIBLIOGRAPHY/REFERENCES:

1. "SO 31000:2009. Risk Management- Principles and Guidelines." International Organisation for Standardization <http://www.iso.org/iso/catalogue_detail?csnumber=43170>
Industry opinion and practice though not formally cited in the public domain

PROCESS STEPS: 112,201

Parameters - Records Management

29

- Scope of the Records Management Topic Team
  - Review industry standards including retention standards and overarching records management principles and guidelines, examples (not all-inclusive) of this are:
    - Establish minimum standards and principles
    - Media format and retention policy to keep electronic methods current (guidance)
    - Technology TT will determine the recommended mediums and methods
    - Policy for the management of the electronic media to keep current
    - Define electronic copy
    - Document ownership
    - Legal Hold
    - Handling of documents will need to follow regulatory guidelines

Parameters - Records Management

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RM1:Certain characteristics are required for the archiving, retrieval and retention processes involving electronic records. These are necessary to ensure authenticity, reliability, integrity and usability of the electronic records over the long-term

RM2: There are specific requirements for retaining both wet ink and electronic signatures. This interpretation provides an evaluation of which signatures are required by regulations and when procedures may suffice

RM3: A timeline for the discarding of the paper originals is dependent on following the appropriate procedures

RM4: Take risk parameters into account before deciding on a procedure to destroy paper

RM5: Access to electronic records must be facilitated continuously across time

RM6: There are essential business requirements that must be considered in creating a viable electronic archiving program

RM7: The risks associated with the reliability of electronically converted and stored documents must be assessed (as compared to paper)

RM8: There are numerous stakeholders surrounding the management of content.

RM9: Some document types must be identified as “Protected” in order to prevent the destruction of those paper documents

Parameters - Records Management

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RM 9 **Some document types must be identified as "Protected" in order to prevent the destruction of those paper documents.**

INTERPRETATION
The electronic rendition is authoritative and immediately effective upon approval. To manage the application of paper destruction rules, a risk-based approach should be used to identify each document type within the ECMS on how to apply those rules, based on the following:

- **Protected** - The paper document must be retained for reference according to an effective document retention policy.
- **Retain Until End of Study** - The paper document must be preserved during the conduct of the study, but may be destroyed following study closeout. Often, a Certificate of Destruction will be required upon completion.
- **Non-Protected** - Able to destroy the paper document while the study is in-progress.

It is possible to have exceptions to these definitions. Particular regions or markets may require special handling for a specific document type (e.g. xxxxxx) or characteristic (e.g. Japanese seals). A legal analysis will likely be required within a company to understand the extent of these exceptions.

A method should be devised to track changes to this Protected Document Types map so that investigations and audits can reference when a specific condition or policy on a document type is changed or determine what rule was in effect at the time of inquiry.

BIBLIOGRAPHY/REFERENCES
1. Industry opinion and practice though not formally cited in the public domain

PROCESS STEPS: 402, 502, 507

Parameters - Regulatory

32

- Scope of the Regulatory Topic Team
  - Ensure all topic teams' research is aligned with applicable regulations/guidelines for the eTMF paper destruction framework by performing the following:
    - Interpret applicable portions of the regulations/guidelines to determine if they support topic teams' deliverables
    - Identify the lack of clarity in regulations/guidelines, and provide recommendations to address gaps that prevent the industry from completely adopting the eTMF paper destruction framework, thus preventing the destruction of paper
    - Liaise with regulatory authorities throughout the development of the eTMF paper destruction framework to understand the practical and technical issues identified by authorities that must be addressed within the framework
  - Provide specific regulatory guidelines with interpretations and application to business & technology
  - Address the issue of eSignatures

Parameters - Regulatory

33

R1: For each record required to be maintained under predicate rules, you must determine in advance whether you plan to rely on the electronic record or paper record to perform regulated activities

R2: Create a company-wide inventory of your tools and assess whether they perform quality or business critical and determine if validation is necessary

R3: Ensure that computerized technologies meet, at minimum, applicable current requirements

R4: Ensure the organization's selected technology provides an audit trail for signatures that captures date, time, or the sequence of events in a particular instance. Sponsors should ensure appropriate use of electronic vs. digital signatures

R5: When used, time stamps must be implemented with a clear under-standing of the time zone applied

R6: Electronic Signatures

R7: An electronic certificate of authority signed by a credible and verifiable notary representative is required for each notarized electronic document

R8: Documented rules governing the conduct of parties using electronic signatures must be available

R9: Organization must adopt/create and train all employees on a corporate level policy detailing the use of electronic signatures.

R10: Address the concern for Japanese raised seals

Parameters - Regulatory

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R 10 Address the concern for Japanese raised seals.

INTERPRETATION

It is recommended that this document type is considered a "Protected Document" and maintained in its original form until technology solutions and guidance for authentic preservation is more feasible. In Japan, Hanko (or called Inkan) or a Japanese seal, is often required as proof of verification of a transaction or as an official acknowledgement of a situation or event, instead of using a hand-written signature. Based on the following – the Jitsu-In stamp is legally binding. Unknown how to determine the type of stamp; however, corporate use of Inkan is always legally binding and should be synonymous to wet-signatures. The Japanese are moving towards electronic signatures. As a result, both the Jitsu-In (corporate signature) and electronic signatures are used during official activities.

BIBLIOGRAPHY/REFERENCES

1. Japan. Law Concerning Electronic Signatures and Certification Services. May.2000. http://www.meti.go.jp/english/report/data/gesignconte.html. Sep.2011.

PROCESS STEPS: 108, 309, 311, 502, 506, 507

Parameters - Legal

35

- Scope of the Legal Topic Team
  - The Legal Topic team will define the North American (NA), European Union (EU) and Japanese (JPN) legal requirements for certifying electronic renditions of paper TMF documentation as equivalent to the original record; other jurisdictions are out of scope.
    - Only a sampling of EU member states will be included in scope.
    - Precedents and supporting citations will be limited to Clinical Trial area and other regulated industries or existing document processing examples where similar approach has been successful, e.g. mortgages, tax filing
    - Definitions will be limited to those found in the Paper Destruction Working Group Objectives xls under Legal.
    - Only a sampling of EU member states will be included in scope.
    - Etc.

Parameters - Legal

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L1:Once records exist, they may be sought as evidence in government inquiries, civil litigation, or criminal prosecution

L2: If a company maintains ECMS and scans documents and certifies them as the authoritative source, discovery of these documents "stand on equal footing with discovery of paper documents."

L3: The duty to preserve evidence in support of litigation holds extends to data compilations, computerized data and other electronically recorded information

L4: Electronic signatures and records are equivalent to paper signatures and records, and therefore are subject to the same legal scrutiny to determine authenticity

L5: A process that accurately reproduces or forms a durable medium for reproducing the original [paper], enables destruction of the original [paper] so long as the process is used in the regular course of business [Business As Usual].

L6: Destruction of original paper records should not be prohibited once a complete and accurate electronic rendition is made unless required by a predicate rule or other applicable legal requirement.

L7: Sponsors of a clinical trial must of the essential documents of this clinical trial. Records may be kept on magnetic or other media, thus including electronic document management systems (ECMS).

L8: Policies, procedures, and other quality and compliance documentation, including partner agreements, developed or modified to support the paper destruction process should be reviewed in light of applicable legal requirements. The implementation of a paper destruction process may entail the review of documentation beyond records management policies (e.g. vendor oversight SOP).

Parameters - Legal

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L 8

Policies, Procedures and other quality and compliance documentation, including partner agreements, developed or modified to support the paper destruction process should be reviewed in light of applicable legal requirements. The implementation of a paper destruction process may entail the review of documentation beyond records management policies (e.g. vendor oversight SOP).

INTERPRETATION
New governance documentation must align or include revisions to existing documentation to ensure alignment with enterprise records management principles and policies and to ensure such policies extend beyond the enterprise to any third party organizations conducting activities on behalf of the organization, including but not limited to CROs. Contracts and agreements must align with record keeping requirements of the enterprise to ensure the same quality is applied throughout the process regardless of which group is responsible for a particular activity in the paper destruction process.

BIBLIOGRAPHY/REFERENCES
1. Industry opinion and practice though not formally cited in the public domain

PROCESS STEPS: 1, 2, 4, 101, 108, 111, 112

Timeline for Creation

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Mar'11
- Commencement of Meetings
- Charter drafted

Dec'11
- Framework v0.4 ready for broad industry review

Feb '12
- Feedback collection period ended and team members reconvene to consider

Jun'12
- Version 1.0 release expected (dependent on feedback)

Where Do You Find the Framework?

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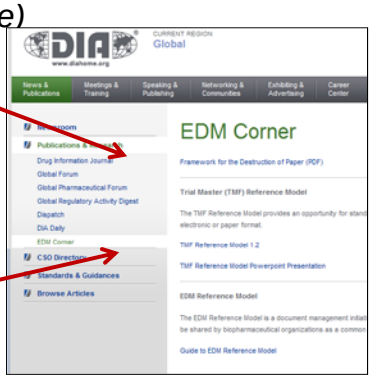
The framework will be released in June 2012

(and still draft so information in this presentation may change)

- Found now (draft) at: http://www.diahome.org/en/News-and-Publications/Publications-and-Research/EDM-Corner.aspx
- TMF Reference Model v1.2 can be found in the same location
  - V2.0 in later June



How to Use the Framework

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Is anybody at this meeting already using framework ?

REMEMBER…

- The framework is a set of guidelines and considerations for how to proceed
  - It is not an exact answer nor a prescription for success
- The framework requires careful consideration, decisions, and adoption within your own companies
  - Consider following the steps in the process diagrams to gain acceptance and prepare your organization

Continued Review and Feedback on the Framework is Critical!

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How might one organize review and collect feedback?

1. Determine core team (IT, Legal, Regulatory, QA, Records Management, Document Management, Clinical Operations, etc.) for evaluation of framework. Distribute framework to team representatives for their review
2. Schedule meetings to collect feedback
3. Input feedback into form(s) provided within the framework and email form(s) to the dedicated email address provided in the form

It is essential to the success of this framework that your suggestions, opinions, etc. be returned to the team. The feedback mechanism is described in the framework.

Feedback Form within the Framework

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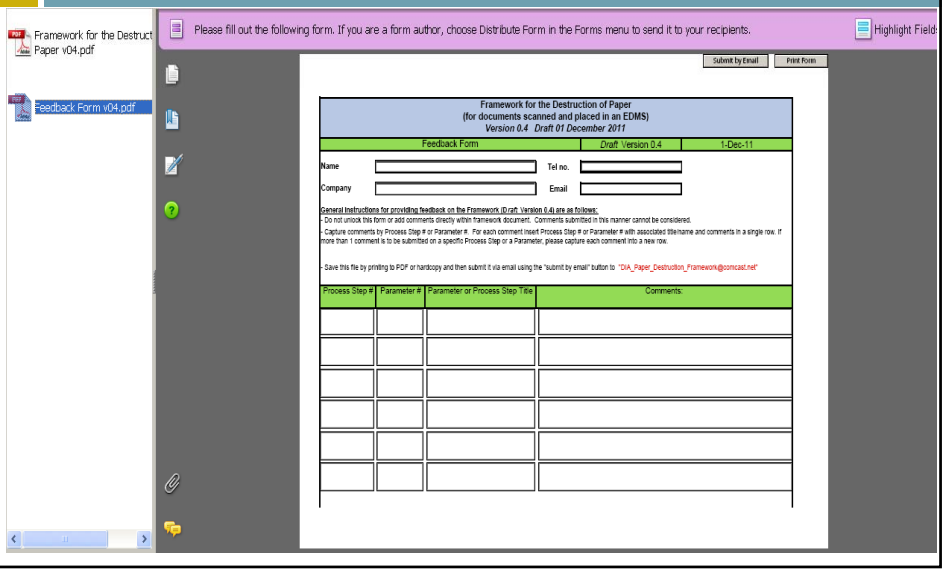

Thank You

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- Join the team to the update framework due to expanded use and Regulator feedback plus maybe expand to other regions of the world!
  - Contact Lisa Mulcahy at mulcahy67@comcast.net to get involved; no amount will be unappreciated.