Phone: +1 833 366 6887
Email: contact-us@ennov.com
Website: en.ennov.com

White Paper

Going Paperless: The Current Regulatory Landscape and Best Practices for Creating Certified Copies

Best Practices for Creating and Certifying Electronic Trial Master File (eTMF) Copies in Compliance with FDA and EMA Guidelines

Sponsors and CROs adopt electronic Trial Master File (eTMF) systems for a variety of reasons, but the usual goal is to reduce the cost, time, and risk associated with maintaining a compliant TMF. The more processes can become 100% electronic, the greater the benefit.

However, many documents still originate in paper form (often with handwritten signatures) and are scanned into the eTMF. Ideally, the paper would be discarded at that point so that it would not have to be transferred to an archive location and maintained for a retention period. This reduces cost and effort related to the production, handling, tracking and storage of paper documents.

This is no easy feat. Normally, the paper document remains the official record unless specific steps are created to create a certified copy. This white paper examines the regulatory requirements, processes and best practices around defining a certified copy process with the goal of eliminating retention of paper wherever possible.

What is a Certified Copy?

A Certified Copy is defined by the FDA as:

"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." [i]

The EMA provides a slightly different definition:

"A certified copy is a paper or electronic copy of the original document that has been verified (e.g. by a dated signature) or has been generated through a validated process to produce an exact copy having all the same information, including data that describe the context, content and structure, as the original." [ii]

The main difference between these definitions is that the FDA only mentions certifying by signature, while EMA allows certifying through signature or by using a validated process. In fact, few organizations actually collect a signature and instead consider completion of a certifying step to be sufficient.

When is a Certified Copy needed?

According to the European Medicines Agency:

"The ICH GCP guideline requires that copies (irrespective of the media used) in the eTMF that irreversibly replace originals should be certified copies of the original. Any transfer or conversion (e.g. digitisation or printing), which does not fulfil the criteria for a certified copy, is not suitable to replace an original file." [iii]

At the TMF Summit conference in 2018, Andrew Fisher, an inspector representing the UK's Medicines & Healthcare products Regulatory Agency (MHRA), provided additional guidance:

"Certified copy requirements have evolved in the current guidance. A certified copy is not required if the original paper is kept. The current EMA guidance in draft clarifies that if an original document exists elsewhere e.g. in the ISF and a copy is needed in e.g. the Sponsor File, this copy does not need to be certified as the original still exists." [iv]

What do you have to do to Certify a Copy?

The EMA provides a high-level description of the certification process:

A process should be in place for risk-based QC checks of certified copies, before destruction of the originals. It is recommended that the QC checks include the following quality features:

- Congruency of the information contained between original and certified copy
- Accuracy of the metadata attributed to the document (when applicable)
- Accuracy of file name, including that it is marked as an updated version of an already existing document
- Quality of the image (suitable resolution to allow readability as per the original, legibility and reproduction of color — when the color gives meaning and legibility of wet-ink signatures or annotations and handwriting in general etc. (when applicable))
- The eTMF audit trail associated with the document (when applicable)
- Approval of the certification process (when applicable) [v]

Note that this means that a user certifying a copy must have access to the original. Usually, this means that certification must be done at the time of submission to the TMF, as users involved in a Quality Control (QC) process normally do not have access to paper originals.

Andrew Fisher (MHRA) elaborated on what is needed in a certified scan process:

"Process should be validated, with a level of ongoing QC to confirm the process and those doing the process must be trained. There is no need to sign and date a certified copy if a validated process was followed. It is up to each organization to decide what the process will be." [vi]

What about the Destruction of Paper?

The EMA specifically addresses destruction of original documents after digitisation and transfer: "Sponsors and investigators/institutions should ensure that essential documents are not destroyed before the end of the required retention; however, creation of certified copies, meeting the requirements outlined in section 5.1 to an eTMF repository (either during the trial or for archiving) could enable earlier destruction of the originals." [vii]

The FDA takes a similar position: "Original data: For the purpose of this guidance, original data are those values that represent the first recording of study data. FDA is allowing original documents and the original data recorded on those documents to be replaced by copies provided the copies are identical and have been verified as such (see FDA Compliance Policy Guide # 7150.13)." [viii]

The Special Interest Area Community for Document and Records Management within the DIA created a framework for the process and parameters concerning the destruction of paper documentation. This process is documented in the Framework for the Destruction of Paper[ix], a detailed and meticulously researched document that establishes recommendations for the legal and regulatory basis for the destruction of paper records. The 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 the digitized copy is a complete and accurate representation of the paper version;
- The digitized copy is placed in a validated ECMS; and
- A training plan covering the process flow and applicable SOPs has been created, is available within the organization, and users have successfully completed the training.

FDA vs EMA: Comparison Table of Certified Copy Requirements

	FDA	EMA
Definition	Verified copy with dated signature	Verified copy with signature or validated process
Certified Copy Requirements	Copies must irreversibly replace originals	Copies must irreversibly replace originals
Access to the Original	User certifying copy must have access to original	User certifying copy must have access to original
QC Checks	Process in place for risk-based QC checks before destruction of originals	Process in place for risk-based QC checks before destruction of originals
Training Requirements	Process must be validated and those involved must be trained	Process must be validated and those involved must be trained

What are some Good Practices around Certifying Copies?

- Review the Framework for Destruction of Paper. This document can help guide you through the decisions needed for certification and destruction of paper.

- Have a written policy and procedures. Your organization should define when and how copies must be certified, and when paper copies of certified records can be destroyed. This is reinforced by the FDA, who states: "Sponsors and other regulated entities should have written procedures to ensure consistency in the certification process." [x]

- Validate your process. Define validation requirements for your certification process and be prepared to show evidence that you have tested and confirmed the process.

- Make sure everyone is trained. Provide (and document) training for record submitters that covers the certification process and the process for destroying paper.

- Reduce the need for certification. Whenever possible, avoid the need to certify by obtaining electronic originals,reducing signatures or replacing with electronic signatures, avoiding handwritten notations, and leaving original documents at the location that produced them (such as sites or ethics boards).

- Only certify what is needed. There is no need to certify documents that are created as electronic originals, or when the original is retained elsewhere such as in an Investigator Site File (ISF) or regulatory document management system (for example, a signed protocol).

- Destroy paper afterwards. Paper that is retained even when a certified process is in place may raise questions.According to Andrew Fisher of the MHRA, "A certified copy can replace an original paper which can then be destroyed. If the original has not been destroyed, the MHRA may ask why. If you certify copies and then don't destroy the originals, are you confident you have a certified copy because what is rationale for keeping the paper? Not necessarily a finding, but would need explanation on why you would still be keeping the paper originals. Inspectors may want to look at the paper." [xi]

[i]U.S. Department of Health and Human Services Food and Drug Administration Office of the Commissioner (OC), Guidance for Industry Computerized Systems Used in Clinical Investigations, May 2007, 8.
[ii]European Medicines Agency, Guideline on the content, management and archiving of the clinical trial master file (paper and/or electronic), 06 December 2018, 11.
[iii] Ibid, 11.
[iv]Andrew Fisher, MHRA Inspector, TMF Questions & Answers, ExL Events 7th TMF Summit, London, UK October 2018, 4.
[v] European Medicines Agency, 11.
[vi] Andrew Fisher, 5.
[vii] European Medicines Agency,
[viii] USDA FDA, 2.
[ix]DIA Document and Records Management (DRM) Community, FRAMEWORK FOR THE DESTRUCTION OF PAPER, version 2, 18 January 2019.
[x] U.S. Department of Health and Human Services Food and Drug Administration, Use of Electronic Records and Electronic Signatures in Clinical Investigations Under 21 CFR Part 11 – Questions and Answers Guidance for Industry, June 2017, 9.
[xi] Andrew Fisher, 4.