

NextDocs Compliance with Key European Regulations

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1 Overview

Unlike the U.S. Food and Drug Administration, European Health Authorities do not have a single document that defines the authorities' position on electronic records and electronic signatures. That is, there is no single document that is the equivalent of Code of Federal Regulations, Title 21 - Food and Drugs, Part 11 - Electronic Records; Electronic Signatures.

NextDocs has been asked to provide a response to specific regulations that cover aspects of electronic records and electronic signatures. This paper provides a response to the requirements of four specific regulations:

- [Reflection Paper On Expectations For Electronic Source Documents Used In Clinical Trials](#) (EMA/505620/2007)
- [EMA Implementation Of Electronic-Only Submission And eCTD Submission: Questions And Answers Relating To Practical And Technical Aspects Of The Implementation](#) (EMA/596881/2007)
- [ICH Topic E 6 \(R1\) Guideline for Good Clinical Practice](#) (CPMP/ICH/135/95)
- [EudraLex: The Rules Governing Medicinal Products in the European Union Volume 4 Good Manufacturing Practice Medicinal Products for Human and Veterinary Use Annex 11: Computerised Systems](#), SANCO/C8/AM/sl/ares(2010)1064599

2 Reflection Paper on Expectations for Electronic Source Documents Used In Clinical Trials

Doc. Ref.: EMEA/505620/2007

Date: 17 October 2007

Status: Draft

In general, this document is not highly relevant to NextDocs systems due to the scope involved, which is stated to be:

1. Electronic Case Report Forms ((e-CRFs) e.g. laptop/desktop based programs or web based tools which may include a combination of original source records and data transcribed by re-keying from other sources).
2. Electronic patient diaries – e.g. palm-pilot instruments supplied to patients to record observations, rating scales, IMP use – this can be primary efficacy or supportive data.
3. Other instruments supplied to investigators or patients for recording of study data either by data entry or by automated capture of events such as biometric measures (e.g. psychometric scales, blood pressure, respiratory measures, ECG monitoring etc.)

Documents that are created in electronic data capture systems are not created or edited within NextDocs. However, it is possible that the final copies of these records would be archived within a NextDocs eTMF system. Table 1 provides responses to the specific requirements in that context.

Table 1 NextDocs and EMEA/505620/2007 Requirements

Requirement	NextDocs Response
An instrument used to, capture, source data shall ensure that the data are captured as specified within the protocol.	Not applicable to NextDocs as such instruments are not contained in or integrated with a NextDocs system.
Source data shall be Accurate, Legible, Contemporaneous, Original, Attributable, Complete and Consistent.	This would be the responsibility of the data capture process.
An audit trail shall be maintained as part of the source documents for the original creation and subsequent modification of all source data.	This would be the responsibility of the data capture process for all processing occurring before the document is finalized. Once the document is imported into the NextDocs system, audit trail records are created for associated events, which would normally be constrained to import, QC check to ensure that the record is a certified copy, and placement into an Approved status.
The storage of source documents shall provide for their ready retrieval.	Documents can be located with a NextDocs system via browsing or searching.
Source data shall only be modified with the knowledge or approval of the investigator.	It's not really possible to modify source data within a NextDocs system as raw data is not normally stored within the system. If data is contained within documents (such as an eCRF) it is protected as such documents are not edited within NextDocs.
Source documents and data shall be protected from destruction.	Documents are "locked down" once QC is complete to prevent destruction, although it is possible to apply records management policies and destroy documents in accordance with retention schedules.
The source document shall allow for accurate copies to be made.	Documents can be printed or exported by authorized users.
Source documents shall be protected against unauthorized access.	Access to the NextDocs system is controlled via user name and password and available only to authorized users.

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Requirement	NextDocs Response
<p>The sponsor shall not have exclusive control of a source document.</p>	<p>This would be up to the sponsor to enforce as far as granting access to the NextDocs system to investigators or allowing them to retain originals or certified copies.</p> <p>The NextDocs clinical portal allows for full participation of the investigator and other site personnel in accordance with their defined roles.</p>

3 EMEA Implementation of Electronic-Only Submission and eCTD Submission: Questions and Answers Relating to Practical and Technical Aspects of the Implementation

Doc. Ref.: EMEA/596881/2007 V0.5

Date: December 2008

This question and answer document aims to address the commonly-asked questions and provide guidance regarding technical and practical aspects of the EMEA's plans to implement electronic-only, and specifically eCTD-only, submission for the Centralised Procedure.

Most requirements in this document are controlled by electronic publishing systems that actually produce the electronic submission XML components and the final documents. As NextDocs manages source documents and their conversion to PDF format, there are a number of requirements that do pertain to NextDocs. These requirements are discussed in Table 2.

Table 2 NextDocs and EMEA/596881/2007 Requirements

Requirement	NextDocs Response
SUBMISSION TYPES Q3. Should correspondence be included in the eCTD?	The answer indicates that only the minimum amount of correspondence should be included. NextDocs regulatory systems out of the box include document types for all correspondence called for in EU Module 1.
FILE FORMATS Q1. What file formats are accepted or required within the eCTD for the Centralised Procedure by EMEA?	NextDocs handles all the specified file types and manages templates to enforce that the correct file types are used in document creation.
FILE FORMATS Q4. Are there any particular requirements for PDF documents submitted within the eCTD?	See separate NextDocs paper entitled "Generation of Compliant PDFs with NextDocs". All requirements that are possible to address during PDF generation (as opposed to those that must be addressed by the author such as margins).
FILE FORMATS Q5. Does EMEA accept the electronic application form in XML for the Centralised Procedure?	The XML eAF can be managed in NextDocs.
SECURITY Q2. Can I password-protect the eCTD submission, or individual files within the eCTD submission?	NextDocs has the capability to generate password-protected files, but this capability is disabled by default.
ELECTRONIC SIGNATURE Q1 What is the position of EMEA regarding the use of electronic signatures within the eCTD?	The answer indicates that "Advanced electronic signatures' are currently accepted in the EU as being legally equivalent to handwritten signatures (Directive 1999/93/EC3)." NextDocs provides advanced (digital) electronic signatures as a standard component.

4 ICH Topic E 6 (R1) Guideline for Good Clinical Practice

Doc. Ref.: CPMP/ICH/135/95

Date: July 2002

ICH E6 is an international ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve the participation of human subjects. Much of the standard discusses procedures to be followed around a clinical trial. Where those procedures call for documentation, that documentation is pre-defined in the NextDocs eTMF module based on the industry-standard DIA TMF Reference model, which was created based on the documents called for in E6 and other guidance documents.

I6 does not provide specific requirements around managing electronic records other than to touch on eCRFs, which are not created or updated within a NextDocs system.

NextDocs also provides the capability to require investigators or other personnel with access to the NextDocs system to acknowledge receipt of specific documents such as protocol amendments via workflow. For participants not having system access, acknowledgements can be received via email or other means and uploaded into the NextDocs system.

Table 3 provides responses to some of the record and report specific requirements in E6.

Table 3 NextDocs and CPMP/ICH/135/95 Requirements

Requirement	NextDocs Response
4.9.1 The investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor in the CRFs and in all required reports.	This is the responsibility of the investigator prior to these documents being uploaded into the NextDocs system.
4.9.2 Data reported on the CRF, that are derived from source documents, should be consistent with the source documents or the discrepancies should be explained.	This is the responsibility of the investigator prior to these documents being uploaded into the NextDocs system.
4.9.3 Any change or correction to a CRF should be dated, initialed, and explained (if necessary) and should not obscure the original entry (i.e. an audit trail should be maintained); this applies to both written and electronic changes or corrections (see 5.18.4 (n)). Sponsors should provide guidance to investigators and/or the investigators' designated representatives on making such corrections. Sponsors should have written procedures to assure that changes or corrections in CRFs made by sponsor's designated representatives are documented, are necessary, and are endorsed by the investigator. The investigator should retain records of the changes and corrections.	Corrections to the CRFs are not made within NextDocs.
4.9.4 The investigator/institution should maintain the trial documents as specified in Essential Documents for the Conduct of a Clinical Trial (see 8.) and as required by the applicable regulatory requirement(s). The investigator/institution should take measures to prevent accidental or premature destruction of these documents.	A NextDocs eTMF is pre-configured to manage trial documents and ensure their protection.
4.9.5 Essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period however if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.	Documents are "locked down" once QC is complete to prevent destruction, although it is possible to apply records management policies and destroy documents in accordance with retention schedules.
4.9.6 The financial aspects of the trial should be documented in an agreement between the sponsor and the investigator/institution.	This agreement is managed within a NextDocs eTMF system.

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Requirement	NextDocs Response
4.9.7 Upon request of the monitor, auditor, IRB/IEC, or regulatory authority, the investigator/institution should make available for direct access all requested trial-related records.	These records can be uploaded into a NextDocs system by site personnel or other designated personnel.

5 Good Manufacturing Practice Medicinal Products for Human and Veterinary Use: ANNEX 11 COMPUTERISED SYSTEMS

Doc. Ref.: SANCO/C8/AM/sl/ares(2010)1064599

Date: 30 June 2011

Status: Revision 1

In general, this document is highly relevant to NextDocs systems and their management of GMP documentation. NextDocs does not manage GMP data in its raw form.

Table 4 provides responses to some of the record and report specific requirements in GMP Annex 11.

Table 4 NextDocs and GMP Annex 11 Requirements

Number	Category	Requirement	NextDocs Response
1	Risk Management	Risk management should be applied throughout the lifecycle of the computerised system taking into account patient safety, data integrity and product quality. As part of a risk management system, decisions on the extent of validation and data integrity controls should be based on a justified and documented risk assessment of the computerised system.	This is a client responsibility.
2	Personnel	There should be close cooperation between all relevant personnel such as Process Owner, System Owner, Qualified Persons and IT. All personnel should have appropriate qualifications, level of access and defined responsibilities to carry out their assigned duties.	This is a client responsibility except in the case of NextDocs hosted clients. NextDocs maintains curriculum vitae and training records for our personnel responsible for hosted systems
3.1	Suppliers and Service Providers	When third parties (e.g. suppliers, service providers) are used e.g. to provide, install, configure, integrate, validate, maintain (e.g. via remote access), modify or retain a computerised system or related service or for data processing, formal agreements must exist between the manufacturer and any third parties, and these agreements should include clear statements of the responsibilities of the third party. IT-departments should be considered analogous.	For NextDocs hosted clients, these agreements are documented in contracts and Service Level Agreements (SLAs).

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Number	Category	Requirement	NextDocs Response
3.2	Suppliers and Service Providers	The competence and reliability of a supplier are key factors when selecting a product or service provider. The need for an audit should be based on a risk assessment.	NextDocs encourages our clients to audit our procedures and records.
3.3	Suppliers and Service Providers	Documentation supplied with commercial off-the-shelf products should be reviewed by regulated users to check that user requirements are fulfilled.	<p>NextDocs supplies a complete documentation suite including user requirements, design, and configuration specifications, user and administrator manuals, training materials, validation plan and report, installation qualification plan, scripts and report, operational qualification/performance qualification plan, scripts and report, risk assessment, and release notes.</p> <p>These materials are available during audit and also supplied at project initiation. They are updated based on specific client requirements and presented for review and approval.</p>
3.4	Suppliers and Service Providers	Quality system and audit information relating to suppliers or developers of software and implemented systems should be made available to inspectors on request.	NextDocs supports our clients by providing information they need to develop these reports.
4.1	Validation	The validation documentation and reports should cover the relevant steps of the life cycle. Manufacturers should be able to justify their standards, protocols, acceptance criteria, procedures and records based on their risk assessment.	NextDocs validation documents cover the complete lifecycle. We provide our justification during vendor audit.
4.2	Validation	Validation documentation should include change control records (if applicable) and reports on any deviations observed during the validation process.	This is part of NextDocs standard validation toolkit. It is a client responsibility to exercise change control and document deviations during validation.
4.3	Validation	<p>An up to date listing of all relevant systems and their GMP functionality (inventory) should be available.</p> <p>For critical systems an up to date system description detailing the physical and logical arrangements, data flows and interfaces with other systems or processes, any hardware and software pre-requisites, and security measures should be available.</p>	This is a client responsibility.

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Number	Category	Requirement	NextDocs Response
4.4	Validation	User Requirements Specifications should describe the required functions of the computerised system and be based on documented risk assessment and GMP impact. User requirements should be traceable throughout the life-cycle.	NextDocs provides a standard URS describing our out of the box systems. This URS is adapted to specific client requirements and traced into test scripts via a traceability matrix.
4.5	Validation	The regulated user should take all reasonable steps, to ensure that the system has been developed in accordance with an appropriate quality management system. The supplier should be assessed appropriately.	NextDocs develops software in accordance with a comprehensive, fully documented quality management system, and is NextDocs ISO 9001:2008 certified. We invite our clients to confirm our practices in a vendor audit.
4.6	Validation	For the validation of bespoke or customised computerised systems there should be a process in place that ensures the formal assessment and reporting of quality and performance measures for all the life-cycle stages of the system.	Not applicable - NextDocs systems are configured rather than customised.
4.7	Validation	Evidence of appropriate test methods and test scenarios should be demonstrated. Particularly, system (process) parameter limits, data limits and error handling should be considered. Automated testing tools and test environments should have documented assessments for their adequacy.	NextDocs performs this testing as part of product development, using both manual and automated testing. Our clients must determine the extent to which such testing should be repeated as part of their risk assessment and validation plan.
4.8	Validation	If data are transferred to another data format or system, validation should include checks that data are not altered in value and/or meaning during this migration process.	When data is migrated, such checks are normally specified as part of the migration plan.
5	Data	Computerised systems exchanging data electronically with other systems should include appropriate built-in checks for the correct and secure entry and processing of data, in order to minimize the risks.	Out of the box, NextDocs does not exchange data with other systems. It is possible to configure integrations with systems such as SAP using web services. If so, these checks would be part of the web services.
6	Accuracy Checks	For critical data entered manually, there should be an additional check on the accuracy of the data. This check may be done by a second operator or by validated electronic means. The criticality and the potential consequences of erroneous or incorrectly entered data to a system should be covered by risk management.	Not applicable - such data is not entered directly into NextDocs systems.
7.1	Data Storage	Data should be secured by both physical and electronic means against damage. Stored data should be checked for accessibility, readability and accuracy. Access to data should be ensured throughout the retention period.	This is a client responsibility except in the case of NextDocs hosted clients. NextDocs security procedures for hosted systems are described in SOP-1005-Security - Hosted Systems.

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Number	Category	Requirement	NextDocs Response
7.2	Data Storage	Regular back-ups of all relevant data should be done. Integrity and accuracy of backup data and the ability to restore the data should be checked during validation and monitored periodically.	Hosted NextDocs systems are backed up, with on-site archiving, on defined schedules. [See SOP-1004-Back Up and Monitoring - Hosted Systems.] For non-hosted systems, this is entirely a client responsibility.
8.1	Printouts	It should be possible to obtain clear printed copies of electronically stored data.	All NextDocs documents can be printed by authorized users. Printouts include electronic signatures where applied.
8.2	Printouts	For records supporting batch release it should be possible to generate printouts indicating if any of the data has been changed since the original entry.	Not applicable - such data is not entered directly into NextDocs systems.
9	Audit Trails	Consideration should be given, based on a risk assessment, to building into the system the creation of a record of all GMP-relevant changes and deletions (a system generated "audit trail"). For change or deletion of GMP-relevant data the reason should be documented. Audit trails need to be available and convertible to a generally intelligible form and regularly reviewed.	NextDocs includes a comprehensive audit log including entries for the creation, modification and deletion of all records. As NextDocs handles documents, not data, in general a reason for change is not required and would be handled if necessary as a change table within the document. Where appropriate, change requests must be created and approved in order to change effective documents. The audit trail is formatted for convenient viewing and can be exported to Excel for review. Establishing review procedures and schedules is a client responsibility.
10	Change and Configuration Management	Any changes to a computerised system including system configurations should only be made in a controlled manner in accordance with a defined procedure.	Hosted NextDocs systems are maintained under strict change control [SOP-1003-Change Management - Hosted Systems] and validated by the client with NextDocs' assistance as requested. For non-hosted systems, this is entirely a client responsibility.
11	Periodic evaluation	Computerised systems should be periodically evaluated to confirm that they remain in a valid state and are compliant with GMP. Such evaluations should include, where appropriate, the current range of functionality, deviation records, incidents, problems, upgrade history, performance, reliability, security and validation status reports.	This is a client responsibility.
12.1	Security	Physical and/or logical controls should be in place to restrict access to computerised system to authorised persons. Suitable methods of preventing unauthorised entry to the system may include the use of keys, pass cards, personal codes with passwords, biometrics, restricted access to computer equipment and data storage areas.	NextDocs requires username and password for entering the system and for applying electronic approvals or signatures. Developing and maintaining related procedures are a client responsibility. Physical access to hosted systems is tightly controlled.

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Number	Category	Requirement	NextDocs Response
12.2	Security	The extent of security controls depends on the criticality of the computerised system.	NextDocs works with our clients to determine the appropriate level of security controls.
12.3	Security	Management systems for data and for documents should be designed to record the identity of operators entering, changing, confirming or deleting data including date and time.	Data is not managed in NextDocs systems. For documents, this information is captured in the audit log.
13	Incident Management	All incidents, not only system failures and data errors, should be reported and assessed. The root cause of a critical incident should be identified and should form the basis of corrective and preventive actions.	This is a client responsibility. Incidents involving NextDocs software or hosted systems are reported through NextDocs support. NextDocs will then investigate and if possible resolve the incident.
14	Electronic Signature	Electronic records may be signed electronically. Electronic signatures are expected to: <ul style="list-style-type: none"> a. have the same impact as hand-written signatures within the boundaries of the company, b. be permanently linked to their respective record, c. include the time and date that they were applied. 	It is a client responsibility to ensure that electronic signatures have the same impact as hand-written signatures within the boundaries of the company. Signatures are bound directly to a specific version of a document and include the date and time of signature as well as the full name of the signer and the reason for signing.
15	Batch release	When a computerised system is used for recording certification and batch release, the system should allow only Qualified Persons to certify the release of the batches and it should clearly identify and record the person releasing or certifying the batches. This should be performed using an electronic signature.	Normally, batch release would not be done in NextDocs. If it were to be done so the system would require an authorized person (the Qualified Person) to perform the action and certify using an electronic signature. NextDocs would record the action in an audit log entry along with the name of the QP.
16	Business Continuity	For the availability of computerised systems supporting critical processes, provisions should be made to ensure continuity of support for those processes in the event of a system breakdown (e.g. a manual or alternative system). The time required to bring the alternative arrangements into use should be based on risk and appropriate for a particular system and the business process it supports. These arrangements should be adequately documented and tested.	This is a client responsibility except in the case of NextDocs hosted clients, where this is a shared responsibility captured in contracts and Service Level Agreements (SLAs).
17	Archiving	Data may be archived. This data should be checked for accessibility, readability and integrity. If relevant changes are to be made to the system (e.g. computer equipment or programs), then the ability to retrieve the data should be ensured and tested.	Archiving is not a standard part of a NextDocs project. Since archiving details would be client specific, this would have to be ensured on a client-by-client basis.

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NextDocs is the global leader in providing Microsoft SharePoint-based compliance solutions to life sciences organizations. It enables businesses in regulated industries to achieve compliance with FDA and other agencies while automating processes, improving efficiency and dramatically reducing costs.

NextDocs provides solutions for managing regulatory documents, SOPs, clinical documents as well as a full set of quality processes from CAPA to Complaints. NextDocs customers include pharmaceutical companies, Biotech firms, medical device manufacturers and contract research organizations.

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