INTESI GROUP

White Paper

Simplifying Digital Signatures for Life Sciences companies

How Intesi Group and Adobe Sign can help life sciences companies accelerating the drug approval process and comply with global regulatory requirements.

The FDA and EMA want pharmaceutical, biotechnology, and medical device companies to ensure that users applying electronic signatures understand and intend that their electronic signature is legally binding equivalent of their handwritten signature. Before an organization gives an individual an electronic signature, "the organization shall verify the identity of the individual".
Sponsors usually do this as part of their hiring process, when people read and hand sign a statement or policy that explains electronic signature, attesting the employee's understanding of the use of electronic signatures.
In response to these and other complex requirements affecting companies in the Pharmaceutical, Medical Device and Life Sciences sectors, Intesi Group and Adobe Sign have teamed up to offer a single solution for deploying simple, advanced and qualified electronic signature types across desktop, mobile and web devices, using both traditional and new cloud-based trust frameworks for online identity and trusted digital signatures.

This partnership enhances Adobe Sign, the market-leading signature platform, with the unique trusted certificate infrastructure of Intesi Group. As a result, Adobe Sign can be used to produce all kinds of signatures, including simple click to sign, multi-factor authentication, or the more rigorous certificate-based authentication that uses the new cloud-based digital signature standards to comply with the most stringent e-signature laws and regulations, including the EU's eIDAS Regulation, EMA and FDA 21 CFR Part 11.
Intesi Group digital certificates have been declared compliant by FDA, allowing the acceptance of digitally signed documents.

This gives Life Sciences companies the reassurance they need regarding:

• **Legal enforceability** – Intesi Group processes for identification and certificate issuance mean that customers can be certain who is behind the certificate.

• **Non-repudiation** – the access control and security features mean that the signatory is legally responsible for his actions.

• **Regulatory compliance** – fully compliant with European Medicines Agency, FDA, 21 CFR Part 11 requirements.

• **Strong Security** – two-factor authentication mechanisms based on certificates provide the highest level of assurance.

• **Global acceptance** – digital signatures based on Intesi Group certificates are accepted in USA and EU with the same legal effect as wet signatures.

Taking a drug from bench to bedside can cost $2.6bn according to the Tufts Center for the Study of Drug Development, from which $1.2bn is time costs.
A significant part of this sum is related to gathering, assembling, cross checking and analyzing data.
High quality data, without mistakes and inconsistencies, is fundamental for having FDA and European Medicines Agency approvals. But a world where Life Sciences and tech companies collide would be the shift for accelerating the new drugs approval, securing the clinical trials data.
Healthcare stakeholders including pharma, payers and providers embrace digital health in different ways, looking for technology-enabled solutions with focus on digital diagnostic tools and interest in regulatory approvals.

This paper looks at how Intesi Group are enabling organisations to rise to the challenge of digital transformation for 2021 and beyond in this highly regulated sector, improving pharma's productivity and reducing research costs and time. The benefits will be for everyone: pharma, digital health companies, providers, payers and, most importantly, patients.

Key takeaways

Put individuals first
Person-centered care values the whole individual including their privacy

Focus on value
Digital solutions that improve healthcare quality, efficiency, safety, affordability, effectiveness and access

Secure access to sensitive information
Support secure health information access, exchange, and use by individuals, caregivers, organizations with accountable processes

Global compliance
European Medicines Agency and FDA regulatory requirements, FDA21CFR Part 11, EU eIDAS Regulation, EU No.536/2014 Clinical Trials Regulation, GDPR, HIPAA

Choosing the right kind of electronic signature

Wherever they exist, paper documents introduce significant delay, error, and cost into the daily operations of life sciences companies. Deploying e-signature solutions can dramatically simplify communication both inside and outside a company and across a myriad of use cases:
Understanding which kind of signature solution is applicable in each of these use cases is an important first step for any company deploying electronic signatures.
A robust electronic signature policy can help a company ensure that signatures are used in ways that balance the need to comply with applicable laws and regulatory requirements, with the effort and complexityof deploying each solution.
Most companies will need to combine different kinds of signature across different business processes, based on their own internal risk assessment and compliance needs.
For many low risk situations, only a simple electronic signature solution may be required. In medium-risk situations, companies may require a second form of signer authentication. But in the most sensitive use cases, digital signatures – where signers use certificate-based digital IDs issued by trust service providers on accredited lists such as the Adobe Approved Trust List (AATL) and the European Union Trusted Lists (EUTL) - are essential for guaranteeing the highest levels of assurance for signer authentication and document integrity.

Until recently, companies that needed to rely on these certificate-based signatures have faced significant implementation challenges. That's because traditional token-based digital signatures have often been cumbersome to implement, requiring end users to have a piece of physical hardware such as a USB key or a smart card, and the organisations they work for to constantly maintain and renew their own library of digital certificates.
Recognizing the problem, Intesi Group worked with Adobe and other leading electronic signature technology providers under the banner of the Cloud Signature Consortium, a cross-industry standards development group, to deliver the world's first, open standard for cloud-based digital signatures. These new cloud-based digital signatures provide several benefits over traditional digital signatures:

• By removing the need for a locally-stored token, they enable anytime, anywhere signature solutions across desktop, web and mobile devices.
• They reduce the cost of IT governance for organisations that use certificates by delegating certificate management to trusted third parties.
• They eliminate compatibility and deployment limitations by making available a fully-documented API which allows a broad ecosystem of vendors to provide digital certificates and signing solutions.

In the following sections we will see how Intesi Group cloud-based digital signatures can help address several of the most critical use cases for companies in the Life Science sectors, achieving not just regulatory compliance but also enabling a significant reduction in the cost of clinical development, shorter study timelines, better user experience, and higher data quality.

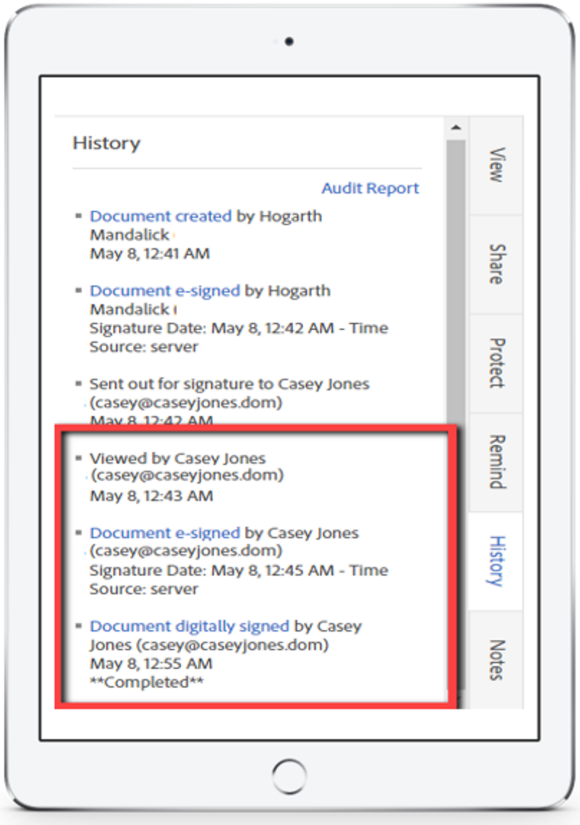
Maintaining Data integrity

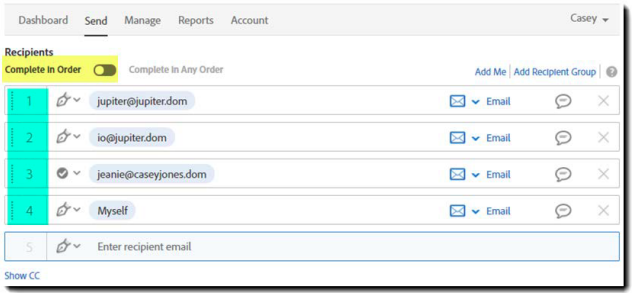
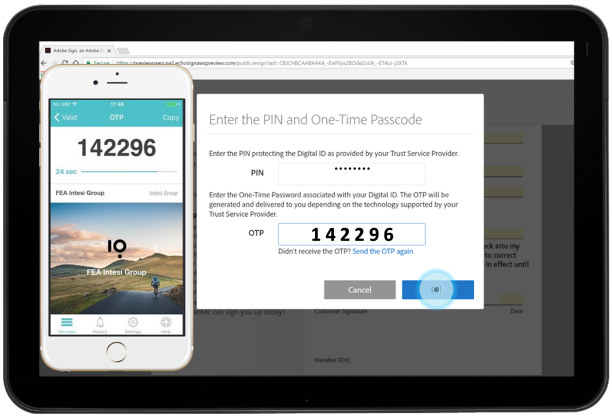
The process of developing a new drug is complex and involves significant commercial investment and risk. But over-focusing on clinical procedure and excellence in technical research without paying due attention to issues relating to data-integrity can have severe commercial consequences should non-conformity lead to research being invalidated.
In recent years, regulatory inspections have unearthed major problems relating to clinical study reporting, data management and monitoring. In fact, statistics show that **up to 30% of clinical trials are rejected by FDA because of data integrity-related violations** of
Guidelines for Current Good Manufacturing Practice (CGMP). Common violations include:
• Forms incorrectly signed by the study coordinator on the investigator's behalf (FDA forms, financial disclosure forms, protocols, Case Report Forms
• Missing Signature / delegation logs
(considered "essential documents" by the FDA).
• Forging of study-related documents by study staff
• Forging of signatures of sub-investigators and patients by study staff
• Forging of investigators' and patients'
signatures by study coordinators during the consenting, screening and follow-up process.
• Inappropriate signature practices of clinical investigators
• Pre-signed source documents (before patient data are entered on the documents).
• 53% clinical trials had issues with informed consent

Serious harmful effects of data fraud in clinical trials include potential harm to patients, negative public perception of the results of the trial in question, or broader damage to the clinical trial organization. These violations have led to numerous regulatory actions, including warning letters, import alerts, and consent decrees, and triggered updates to the Guidelines for Good Clinical Practice (GCP) by the International Council for Harmonization (ICH) under the new designation E6(R2) which have been adopted by both the FDA by the European Medicines Agency.
The ICH E6 (R2) guidelines provide an international ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve the participation of human subjects. Being compliant with this standard provides public assurance that the rights, safety and well-being of trial subjects are protected and that the clinical trial data are credible. Companies operating in this area need effective strategies to manage their data integrity risks based upon their process understanding and knowledge management of technologies and business models.
Intesi Group and Adobe Sign allow organisations to comply with EMA and FDA requirements regarding data integrity as laid out 21 CFR parts 210, 211, and 212, in line with CGMP guidelines. With audit trails, electronic certified copies of records, retention requirements, whether you sign with an electronic signature or digital signature, you can track the history of a document via the audit report which tracks “who, what, when and why” of signed documents and files.
Below are some of the key aspects of the EMA and FDA requirements with which organisations need to comply.

Requirement	Intesi Group/Adobe solution
SOURCE DOCUMENTS The investigator/institution should maintain adequate and accurate source documents and trial records that include all pertinent observations on each of the site’s trial subjects. **Source data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary (e.g., via an audit trail).**	Documents signed in Adobe Sign provide many levels of validation of the signers’ identity.: the signatories may be first identified by email for routing, may be required to authenticate themselves to access the document and, when digital signatures are used, will be required to apply a digital certificate which identifies them. 

Requirement	Intesi Group/Adobe solution
	When these signatures are applied to an electronic document, the document itself is sealed and no further changes can be made without invalidating the signature. In addition, Adobe Sign provides a complete audit trail that logs every change in the document and every step in the signing process.
ESSENTIAL DOCUMENTS Essential Documents are those documents that individually and collectively permit evaluation of the conduct of a trial and the quality of the data produced. These documents serve to demonstrate the compliance of the investigator, sponsor, and monitor with the standards of GCP and with all applicable regulatory requirements. A description is given of the purpose of each document, and whether it should be filed in either the investigator/institution or sponsor files, or both. It is acceptable to combine some of the documents, provided the individual elements are readily identifiable. **The sponsor and investigator / institution should maintain a record of the location(s) of their respective essential documents including source documents. The storage system used during the trial and for archiving (irrespective of the type of media used) should provide for document identification,**	By using PDF documents, organisations can maintain full control over their essential documents: • Adobe Sign allows for the routing of document for signature by multiple parties. • Adobe Sign supports version control requirements by providing an audit trail that registers relevant data including the IP Address and identity of each signatory, to provide a tamper-proof record of who has signed and when. • Adobe Fill & Sign functionality allows researchers to securely enter form data from within their current technology environment, reducing the risk of data error and providing a secure record of that data. • Using Adobe Acrobat DC and Adobe Sign, organisations can upload and combine multiple files including scanned papers., images and video. • PDF documents provide for easy document identification and searchability, whether stored in Adobe Document Cloud or through any of the out of the box integrations with multiple storage systems including Microsoft OneDrive, Microsoft Sharepoint, Dropbox, Box and many others. For a full list of integrations see https://acrobat.adobe.com/be/en/business/integrations.html#full Adobe Document Cloud services comply with industry best practices for logical and physical security, as assessed through SOC2 Type 2 reporting and through Adobe's ISO:27001:2013 certification. Once the final Intesi Group electronic signature is

Requirement	Intesi Group/Adobe solution
	applied to a document, the electronic document is certified by Adobe Sign using an electronic seal. This provides the assurance that the record originated in Adobe Sign, and that the content of the record including the signature has not been tampered with. In addition to that, a timestamp is applied which proves that the document existed at a point-in-time and that it has not changed since then.
AUDIT TRAIL For the FDA, an audit trail means a secure, computer-generated, time-stamped electronic record that allows for reconstruction of the course of events relating to the creation, modification, or deletion of an electronic record. An audit trail is a chronology of the "who, what, when, and why" of a record.	Adobe Sign creates a complete, tamper-proof Audit Trail of every event in the signing process. The audit trail is time-stamped by Adobe's own time-stamp trust service, which is regulated under the European eIDAS Regulation as a Qualified Trust Service. By default, the audit trail is visible to the originator of the signature throughout the process, and a final version is emailed to each party after the final document is signed and filed. 

Requirement	Intesi Group/Adobe solution
Control strategies must ensure that original laboratory records, including paper and electronic records, are subject to second-person review (211.194(a)(8)) to make certain that all test results are appropriately reported.	Adobe Sign allows users to create sequential signatures flows.Signers receive and sign the document in the order that their e-mail addresses were entered into the To: field. Once the last signer completes the signing process, then all parties receive a Signed & Filed e-mail with the signed PDFs attached. 
An electronic signature with the appropriate controls to securely link the signature with the associated record fulfills this requirement. This comports with part 11, which establishes criteria for when electronic signatures are considered the legally binding equivalent of handwritten signatures.	Each user is uniquely associated in Adobe Sign with an email address. The user's email address can only be associated with a single Sign account. Digital signatures are applied to documents using Intesi Group qualified cloud-based digital certificates. This is **the highest level of assurance for a digital signature, where the identity is uniquely linked to the signature, is legally enforceable and the signatory is legally responsible for his actions because of non-repudiable property.**
Firms using electronic signatures should document the controls used to ensure that they are able to identify the specific person who signed the records electronically.	Intesi Group qualified cloud-based digital certificates have cryptographic keys securely stored on a certified HSM. 

Requirement	Intesi Group/Adobe solution
	Access to certificates is protected by deploy a 2-factor authentication mechanism, assuring the strong security of the transactions. By using digital signatures on documents involved in Clinical trials, your company no longer need to have controls in place to ensure the identification of specific person who signed the records.
Electronic copies can be used as true copies of paper or electronic records, provided the copies preserve the content and meaning of the original data, which includes associated metadata and the static or dynamic nature of the original records. True copies of dynamic electronic records may be made and maintained in the format of the original records or in a compatible format, provided that the content and meaning of the original records are preserved and that a suitable reader and copying equipment (for example, software and hardware, including media readers) are readily available (§§211.180(d) and 212.110).	The PDF standard (ISO 19005-3) allows document creators to embed the contents of referenced data files directly within the body of the PDF. In this way, a document can contain both a human readable written narrative and underlying data. Such PDF files are fully self-contained, not requiring web access. These files also meet international standards for long-term archiving and may be digitally signed to assure that not only is the descriptive narrative of the PDF file intact, but that the embedded data likewise has not been tampered with.
When generated to satisfy a CGMP requirement, all data become a CGMP record. You must document, or save, the data at the time of performance to create a record in compliance with CGMP requirements, including, but not limited to, §§ 211.100(b) and 308 211.160(a). FDA expects processes to be	Form fields available in Adobe Sign can help standardize data collection, thus improving data quality and reducing errors in data entry. The pdf document can then be digitally signed to prevent modification. Adobe Sign provides an audit trail of the signing process, giving a tamper-proof seal to the data. The Adobe Sign service maintains electronic records on Adobe's servers during the record approval process and these records are encrypted at rest.

Requirement	Intesi Group/Adobe solution
designed so that quality data required to be created and maintained cannot be modified. For example, chromatograms should be sent to long-term storage (archiving or a permanent record) upon run completion instead of at the end of a day's runs. It is not acceptable to record data on pieces of paper that will be discarded after the data are transcribed to a permanent laboratory notebook (see §§ 211.100(b), 211.160(a), and 211.180(d)). Similarly, it is not acceptable to store data electronically in temporary memory, in a manner that allows for manipulation, before creating a permanent record. Electronic data that are automatically saved into tempo-rary memory do not meet CGMP documentation or retention requirements.	Records are uploaded to / downloaded from Adobe's servers via an encrypted tunnel. Documents may be extracted from the Adobe Sign portal as pdf files which are certified by Adobe using public key infrastructure. This provides assurance that the document originated in Adobe Sign and that the content of the record, including the signature, has not been tampered with. Adobe Sign offers long-term signature validation so that users can check the validity of a signature long after the document was signed. Users can embed the necessary information - the signing certificate chain, certificate revocation status, and timestamp during the signing process.

Securing legally valid Informed Consent

Obtaining the legally valid informed consent of clinical study participants or patients is one of the major ways in which digital signature technologies can benefit companies in the pharmaceutical, medical device & life sciences sectors.

Informed consent is a mandatory requirement for enrolling any person in a clinical trial. According to ClinicalTrials.gov, 316,844 studies are listed with locations in all 50 States and in 209 countries. An impressive number if we look back in 2000 when only 1,255 studies were registered. Traditionally, clinical trials are paper-based and focused on physical meetings, meaning higher costs reflected at the end in the price of the new drugs on the market.

When a clinical trial involves patients or researchers based in the EU, or if the end objective of the

the trial is to obtain approval from the European Medicines Agency to place the drug on the market in the EU, that trial will need to be conducted in line with prevailing EU legislation including the GDPR and the new EU Clinical Trials Regulation. This brings new requirements about the format, procedure for obtaining consent.

Key criteria where Intesi Group and Adobe Sign address the challenges of electronic informed consent, helping Life Sciences to stay compliant with EU Clinical Trials Regulation, GDPR and FDA Guidance for IRBs, Clinical Investigators and Sponsors can assist with compliance include:

Requirement	Intesi Group/Adobe solution
The written informed consent form and any other written information.... should be revised whenever important new information becomes available that may be relevant to the subject's consent. [...]. **The communication of this information should be documented.**	Adobe Sign can be configured to require explicit acceptance of Terms of Use (ToU) and Consumer Disclosure (CD) documents. These documents can be used to (i) define any other details pertaining to the relationship between researcher and subject (ii) to obtain explicit acknowledgement that consent can be provided electronically When any changes need to be communicated and accepted, Adobe Sign can help automate the sending of updated documentation to affected parties, confirm proof of opening and receipt, and record renewed consent via digital signature.
Prior to a subject's participation in the trial, the written informed consent form should be signed and personally dated by the subject or **by the subject's** legally acceptable representative, **and by the person who conducted** the informed consent discussion.	Adobe Sign allows users to create sequential signatures flows, involving more than one signer. Signers receive and sign the document in the order that their e-mail addresses were entered into the To: field. The audit trail provides timestamped information relating to the date and time of signing.
Prior to participation in the trial, the subject or the subject's legally acceptable representative **should receive a copy of the signed and dated written informed consent form** and any other written information provided to the subjects.	Adobe Sign enables researchers to send pdf documents containing all relevant information to subjects, to record receipt and opening of the information, and automate the collection of consent via digital signature.

Requirement	Intesi Group/Adobe solution
Consent should be given by a clear affirmative act establishing a freely given, specific, informed and unambiguous indication of the data subject's agreement to the processing of personal data relating to him or her, such as by a written statement, including by electronic means, or an oral statement.	Adobe Sign can be configured to require explicit acceptance of Terms of Use (ToU) and Consumer Disclosure (CD) documents. These documents can be used to (i) define any other details pertaining to the relationship between researcher and subject (ii) to obtain explicit acknowledgement that consent can be provided electronically
A copy of the signed consent form that includes the date when the eIC was signed shall be provided to the subject. Some form of the consent document must be available in a format that can be retained.	Adobe Sign delivers notifications to the signers, containing the link from where the signed consent form can be downloaded. The communication channel is secure, with restricted access. In this way is ensured the confidentiality regarding the subject's identity, study participation and personal information after the informed consent has been obtained, in compliance with GDPR, HIPAA
For the purpose of consenting to the participation in scientific research activities in clinical trials, the relevant provisions of Regulation (EU) No 536/2014 of the European Parliament and of the Council should apply (Regulation on Clinical Trials). In accordance with international guidelines, **the informed consent of a subject should be in writing**. When the subject is unable to write, it may be recorded through appropriate alternative means, for instance through audio or video recorders	This provision clarifies that video-based consent is not applicable in the context of clinical trials. Adobe Sign meets all relevant needs cited above relating to the provision of information to trial subjects, capturing written consent, communicating changes and documenting renewed consent.

Benefits

A simple calculation for a health care organization with around 19,500 consents per month and two pages per consent form at a $0.30 per page results in $140,400 per year. In addition to that we should consider the physical archiving cost, as these papers should be preserved for the entire period of the final drug or therapy on the market.

Conclusion

Data integrity is key to achieving compliance with the highly complex and rigorous regulatory requirements that apply to organisations operating in the pharmaceuticals, medical device and life sciences sectors. But, while compliance may be the driver, implementing the right digital signature solution can have many additional benefits, including a significant reduction in the cost of clinical development, shorter study timelines, better user experience, and higher data quality.
A robust electronic signature policy can help a company ensure that signatures are used in ways that balance the need to comply with applicable laws and regulatory requirements, with the effort and complexity of deploying each solution.
Adobe and Intesi Group offer a robust technology solution that provides a one-stop shop for regulatory compliant, anytime, anyplace electronic and digital signatures, and can help organisations in the pharmaceutical, medical devices and life sciences ecosystem stay ahead of constantly evolving regulatory requirements.

Engage with one of our specialists to find out how we can help your company to implement regulatory requirements for data and documents

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