Steps to Comply with the FDA's Binding Guidance on Electronic Study Data Submissions

On December 18th 2014, the FDA issued binding guidance regarding electronic submissions of nonclinical study data. This means that beginning in 2017, any organization making IND, NDA or BLA submissions of nonclinical studies will need to plan for, and be ready, to submit their studies in the required standardized digital format that is directly consumable by the FDA's NIMS review and analysis tool.

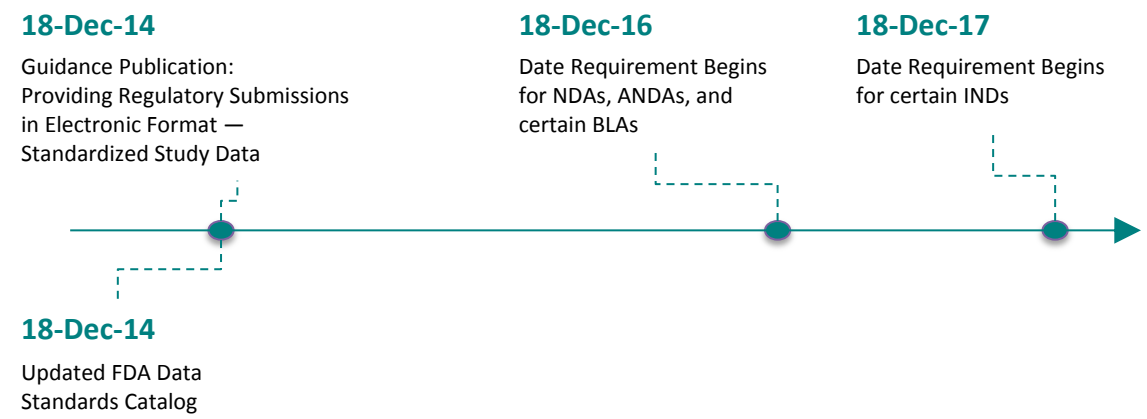
The links provided at the end of this white paper point to useful reference documents. These include the FDA guidance and technical specifications, as well as Agency presentations on the tools and processes they have in place to modernize regulatory reviews through the use of standardized data. The FDA uses their NIMS system to perform data fitness checks on submitted standardized studies and to present them to the medical reviewers.

NIMS is an implementation of the PointCross DSIMS™ product. PointCross Life Sciences has been working closely with the FDA for the past three years to prepare for this important change by:

- Implementing NIMS,
- Standardizing FDA selected studies from current NDA and IND submissions for review by FDA in NIMS
- Conducting clinics to orient reviewers on analyzing studies on NIMS under the FDA's JumpStart Nonclinical service.

To build an effective readiness plan for compliance, sponsors will need to involve internal business, IT, Data Management, Regulatory Affairs and external stakeholders, such as CROs and other service providers who participate in the data collection and submission processes. Compliance means that sponsor organizations must learn how to model studies into the FDA's implementation of the CDISC SEND exchange standard, create define.xml files, manage controlled terminologies, analyze study data like FDA reviewers, prepare study data review guides, and package data into the required submission structures. Quality assurance controls will need to be applied across the data preparation and submission lifecycle. Sponsors will need to work closely with qualified service and technology providers to rapidly establish new processes and tools in time to routinely submit SEND formatted data packages compliant with FDA specifications. Done correctly and in the right spirit this can be a transformational process that will shave costs, minimize risks for your organization and reduce time to market.

PointCross Life Sciences is providing this white paper as a blueprint to help you and your extended teams become compliance-ready by the following submission deadlines specified by the FDA:



Every Sponsor, be it a Pharmaceutical or a Biotechnology company, will have its own set of challenges to become compliant. Now that the FDA driven changes are law, we have applied our experience to advise and offer support to Sponsors in the change management required to implement the following recommended steps to achieve an orderly and risk free result. We have separated our recommendations for Sponsors who make frequent submissions (Medium and Big Pharma) from smaller Biotech and Pharma companies who are infrequent submitters.

Medium and Big Pharma Sponsors

Challenges

Most Sponsors have a combination of internal labs and external CROs conducting nonclinical studies needed for their development programs. The trend towards increased outsourcing of studies to CROs is likely to continue, providing both opportunity and challenges for all parties.

Today, we see two schools of thought amongst Sponsors:

1. Those that expect to be stewards of the study packages in SEND with NIMS compatibility. These companies plan to accept multiple streams of data from CROs and internal labs for final submission. Some of these incoming GLP data streams will be from the main CRO and some will arrive via specialized CROs that conduct histopathology, PK/TK or bioanalytical parts of the study. Depending on the situation, some data may be CDISC SEND packaged, while others may not. Those who subscribe to this approach will need to package content with various versions of SEND and Controlled Terminologies. This will require re-packaging the individual data streams for the study and preparing the overall define files before submission. This is not a trivial task, but keeping in mind that the Sponsor is accountable for the final submission, the onus is on the Sponsor to defend all of the study standardization decisions reflected in the submitted data package, including those made by their CROs. Companies should not underestimate the magnitude, risks and costs associated with this task. We constantly have seen over the past 2 years requests for remedial services from companies that have had many fitful starts and missteps with their service providers. By engaging early and taking proactive measures to tackle issues preemptively, costly delays to submissions can be avoided.
2. The second group comprises Sponsors that outsource all of their studies. They expect, or hope,

that their CROs will deliver SEND ready packages for submission and assume no intervention on the part of the Sponsor. This is a questionable strategy since Sponsors are accountable for their standardized data. Data validation failures found by the FDA may result in a Refusal to File (RTF) for your NDAs and BLAs. Consider de-risking your submission by having an experienced services firm curate the packages or standardize the studies as needed with guaranteed assurance that they will load into NIMS problem free. You may also consider gaining access to the same product to review your submissions and prepare for Agency Responses to Questions (RTQ).

In either case, Sponsors must seriously engage with their labs and CROs immediately to develop a data standards strategy that is ultimately bound in contracts, internal SOPs and tools. It is also important to mitigate risks by ensuring that the data in the submittable packages are:

- Consistent with the Study Reports;
- Validated and loadable into NIMS without getting bounced leading to a potential RTF; and
- Reviewable by the scientists such that they can quickly interpret and respond to the questions in the same context as the FDA reviewers who look at their digital data on NIMS.

Based on our experience, several internal stakeholders will need to be involved in the change management required for success, including:

- **Business** – These include Study Directors from Test Facilities, Toxicology Project Leaders involved with pre-submission reviews, and Scientists who may be called upon to help with responding to Agency questions. Some Sponsors are using this opportunity to define and streamline their interactions with their CROs so that protocols and their amendments are managed digitally from the outset. Additionally, there will now be a need to have better consistency in terminology and units to make it easier to be SEND compliant and to keep up with frequent updates of Controlled Terminologies from CDISC. A number of business decisions must be made regarding data that is included in the SEND submission. These are not always self-evident based on the study protocol or the study report, or even from the study data as-collected.
- **Data Management** – These stewards of the GLP data from internal and external sources will need to make sure that the study data complies either with the prevailing version of the SEND standard and FDA specific requirements, or that it is compliant to the one established for the submission depending on the Sponsor's SOPs. They will need to specify naming conventions like those for subject and group ID naming so that it is easier to merge converging streams of source data from LIMS extracts received from CROs or internal labs. Some Sponsors may choose to specify their preferred terms to all of their CROs and internal labs to ensure consistency across all of their submissions. They will also need to orchestrate the flow of these streams of data to ensure timely review and final packaging, and be actively engaged in reviewing and planning for changes driven by the evolution of SEND and updates to the FDA's submission specifications. For example, the current SEND 3.0 standard supports general toxicology and carcinogenicity standards; support for safety pharmacology is expected in early 2015 and reproductive toxicology will follow in the future.
- **IT** – Owners of the on premise installation or provisioning Cloud Service providers will be accountable for availability, security, 21 CFR Part 11 Compliance and exchange of data between internal and/or external networks. They also need to plan for a Development environment since the FDA's specifications and the SEND standards are evolving with new study types and data

fitness checks being added. The Development environment is essential for Sponsors who will need to have their own processes for data modeling, impact assessment and process stewardship. For on premise installations, there is also a need for Qualification and Production environments.

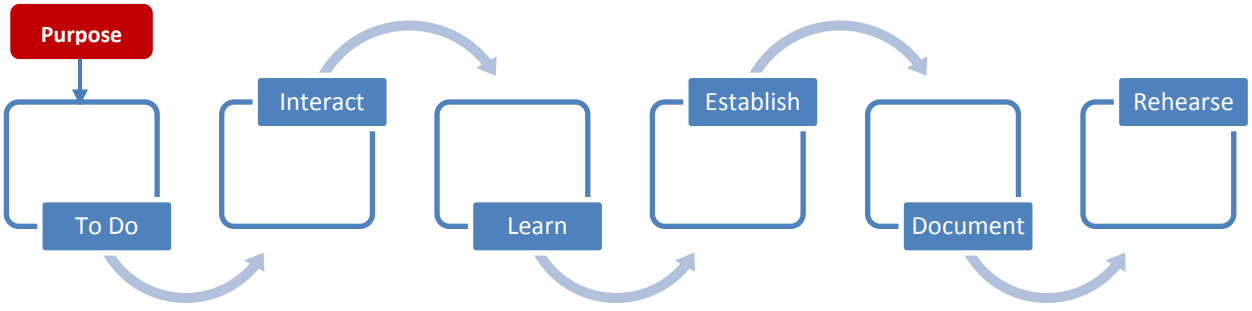
- **CRO Outsourcing** – this group within large Pharma organizations is typically responsible for managing MSA's (Master Service Agreements) with CROs and awards of study-specific contracts. They will need to update their contracts with CROs to ensure that deliverables are appropriately specified and that contractual obligations in regards to standardized datasets are met.
- **Quality Assurance** – These stakeholders must ensure that the systems being put in place are validated and they will need to ensure that compliance requirements are met. They will need to develop best practices in collaboration with the CROs and labs for data quality assurance from the sources, establish processes to ensure consistency with the internal requirements for how the study must be standardized with requisite traceability, and ensure that data sourced from GLP systems are managed in compliance with 21 CFR Part 11 controls.
- **Regulatory Affairs** – This is the group responsible for internal processes related to submission management. They typically prepare eCTD submission packages, manage Agency RTQ processes, and handle Agency communications both internally and externally.

Coordinating these stakeholders and establishing a coherent plan that can be executed within the required timeframe can be very complex and difficult without the right expertise in-house. Consider having an experienced consultant join your Steering Committee to help ensure that the plans are realistic and that best practices are applied.

The following are a series of process recommendations for SEND readiness and compliance with the FDA guidance and technical submission specifications, beginning with January 2015.

Steps to SEND Readiness

As a medium or large Sponsor with a series of IND, NDA and BLA submissions already planned, start by classifying them according to when they are due for submission. The goal is to manage change in a phased manner over the next 18 months with the following framework for each of the phases.



	For Studies Slated For Submission by August 2015	For Studies Slated For Submission by June 2016	Future Standardized Submissions
Purpose (Goals)	• Understand the FDA's implementation of the SEND standard and their review process • Identify and assess gaps between your data sources (internal & CRO) and submission requirements • Develop a plan to address standardization gaps • Identify new processes and SOPs that may need to be established • Determine changes to current processes and SOPs	• Assess readiness by performing a test submission to the FDA • Establish rules for terminologies, units, naming conventions and data merging • Implement standardization plan • Implement changes in processes and SOPs to meet standardization requirements and data flows with CROs and internal data providers • Develop plans to address future updates to controlled terminologies and SEND Implementation Guides	• Prepare SEND formatted studies using a validated solution • Review studies prior to submission, in the same way as the FDA • Establish a controlled process to assess, monitor and recommend policies to manage evolving changes to standards governing submissions
To Do	• Don't attempt to make any submissions in SEND format. • Select a few studies that are likely to be pivotal for reviewers. • Consider having PointCross Life Sciences standardize these studies to understand submission requirements, and for internal use to prepare for questions from the FDA. *Note:* The FDA may standardize them using their Jumpstart Nonclinical Service • Initiate discussions for SEND software and deployment decisions	• Select key pivotal single & repeat dose general toxicology for at least two species and carcinogenicity studies. Have them standardized by PointCross and obtain validated SEND packages. • Have CROs separately generate SEND datasets for the same studies • Implement a Development environment internally or on the Cloud for further preparation and test submissions • Prepare for your Validation and Production Environments	• Prepare SEND formatted studies using a Cloud hosted SaaS or on premise validated SEND solution • Have studies tested and validated. • View studies prior to submission to eliminate any surprise • Identify and implement change control procedures as needed
Interact	Establish a Working Group (WG) with internal stakeholders and all key CROs with external expertise in SEND and FDA's NIMS. Involve your LIMS providers. Have PointCross send you an experienced consultant to join your team and help you through the process.	WG develops rules on harmonizing Controlled Terminologies, Units, Naming Conventions, Define.xml and Study Design using standardized studies as the test bed	Close the development WG and establish a new Operational WG to assess, monitor and recommend policies to manage evolving changes to standards governing submissions
Learn	Have us conduct workshops or clinics using standardized studies to: • Learn about SEND standards and FDA rules for conformance and quality • Identify best practices in modeling studies • Understand the role of controlled terminologies • Learn how the FDA intends to review standardized data	Continue clinics and updates on latest FDA specifications, controlled terminologies, new SENDIG releases and FDA review updates	
Establish	Key areas for process changes and establish a detailed action plan with roles and responsibilities. PointCross can help with this process.	• Procedures for accepting interim and final study data uploads into internal GLP data stores • Curation processes for packaging and submission readiness. • Plan for SEND software and key implementation decisions on Cloud versus On-premise deployments	
Document	• Plan of action for the Initial Implementation Phase • New SOP requirements • Areas in SOPs that need change	• Changes in SOPs based on data flow between Sponsors and CROs. • Plans on managing future updates to standards, controlled terminologies, and FDA technical specifications and timelines	Qualification (Computer Systems Validation) documentation, Final SOPs including Change Control Procedures
Rehearse	Reviewing standardized studies through clinics with PointCross experts who run such clinics with FDA reviewers on NIMS	Perform test submissions into FDA	You are ready for routine SEND submissions.

Recommendations for Submissions in next 6-8 months from January 2015

For submission dates within the next 6-8 months, do not attempt to prepare them in SEND format using any specific system. It can be a distracting diversion. However, remember that the FDA does select studies they consider pivotal and have them standardized so that they can be reviewed in NIMS under their JumpStart Nonclinical program. This has been going on since mid-2013.

We are under contract with the FDA to standardize studies currently submitted into NIMS compatible digital form. We standardize and load these studies into NIMS, and conduct study focused training clinics in NIMS for medical reviewers. What we recommend for readiness to answer any questions on contemporary submissions is to select pivotal studies and have them standardized.

1. Note that data standardization does add time to submission review cycles. To play it safe, consider only standardizing pivotal general toxicology studies, and studies that have PK/TK and histopath findings as well as carcinogenicity studies in parallel without interrupting existing submission processes.

2. The benefit of standardizing these studies is to reduce time to respond to questions from the FDA. It can also reduce time and risk particularly on NDA submissions. More importantly, it will help you identify FDA submission requirements that can inform your standardization strategy.

Recommendations for Submissions beyond 6-8 months from January 2015

Studies contained in such submissions are the on-ramp to being compliant in the long run. For these studies consider the following steps:

1. Select studies (key general toxicology studies, and studies that have PK/TK and histopath findings as well as carcinogenicity studies) that have been completed and standardize them to be submission ready.
2. Include some ongoing studies with one or more CRO partners.
3. Establish a collaborative team consisting of your data management staff, CRO representative, and an expert who has experience with SEND standards, implementations and submissions.
4. Define a way of working with CRO partners to receive SEND data sets including identifying the best practices of what needs to be included in the SEND package, how the study must be modeled for the purposes of standardized presentation and to comply with the FDA's implementation of the SEND standard and technical specifications.
5. While steps 1-3 are underway, long term decisions need to be considered about (a) how to merge multiple study components from internal or external sources; and (b) how to package, validate, and view standardized studies. Examples of these include studies where one part is done by a CRO and the other in-house, or where the entire study is outsources to multiple CROs. These data need to be merged into a uniform representation for submission to the FDA.

These standardized studies should then be used to draw lessons that can be applied to SOPs and future study data management. In addition, these studies can be used to send test submissions into FDA along with other expected documentation such as the Study Data Reviewer's Guide (SDRG) and the Study Data Standardization Plan (SDSP). Then develop a long-term strategy, operational readiness, and tactics for ensuring the establishment of a reliable, high quality data flow from all captive sources. Specific steps should include:

1. Developing rules on harmonizing Controlled Terminologies, units, naming conventions, Define.xml files and study definitions using standardized studies as the test bed.
2. Establishing procedures for accepting interim and final study data uploads into your internal GxP data stores and curation processes for packaging and readying the submission.
3. Standardizing an approach to prepare SDRG's and SDSP's and developing new SOPs around them.
4. Planning for SEND compliance software and making key decisions on Cloud versus On-premise installation.
5. Documenting changes in SOPs based on data flow between Sponsors and CROs and planning how to manage future updates to FDA specifications of the SEND standard and to Controlled Terminologies.
6. Determining the Quality Assurance strategy.

Collaborating with experts who have valuable experience, knowledge and insights gained from working with the FDA, and with data standardization programs can ensure a successful outcome.

Recommendations for Submission Readiness by Mid 2016

By late 2015, Sponsor Data Managers should be exercising their updated SOPs while Quality Assurance is validating the SEND solution with the assistance of IT and Data Management staff.

Expect new updates to the SEND standard by then and establish an Operational Working Group to monitor, evaluate and recommend policies to manage evolving changes to the standards and FDA specifications governing submissions. Continued interactions with CROs and other solution and service providers are necessary to ensure that they are keeping abreast of these new developments and target timelines for compliance with FDA specified timelines and requirements.

Small Pharma and Bio-Techs with sporadic IND/NDA submissions

The challenges for this group of sponsors are very different from those of the bigger Sponsors who have multiple IND and NDA submissions in a year. Here, the costs and time required for change management may be beyond current internal resources, and the investment in hiring the necessary expertise in-house may not be justifiable. Additionally most, if not all, of the studies are likely done by outsourced CROs.

- You may not have sufficient leverage over your CROs or Partners to enforce desired timelines. Additionally, you may not have in-house expertise to attain the competency in SEND compliance and keep up with changes to the standards and the FDA's specifications.
- We recommend a simple and pragmatic approach in this case: Have the studies standardized by a competent service provider.
- Your service provider can standardize the data and provide a submittable SEND package that is certified for conformance to CDISC SEND and the FDA's nonclinical validation rules. Such a provider can also work with partner CROs to establish the right SOPs for all of the studies

outsourced to them, and serve as a valuable resource to support pre-submission study data reviews and readiness for RTQ's.

Common Challenges

Nonclinical studies are conducted to meet the defined protocols by collecting data through multiple, dispersed LIMS systems, sites and even beyond organizational boundaries. This dispersed data collection situation poses some common challenges in complying with the FDA's requirements for 'standardized' data. It is imperative that Sponsors review existing process and assess impacts in the following areas:

- What data 'do you' and 'don't you' collect?
    - The new requirements do require submission of data that may not currently be collected electronically. For example, modeling the study design using Trial Sets, Trial Elements and Trial Arms must be done in extensive detail. This is very different from the standard way that Sponsors have thought about their studies in the past.
- How will you aggregate data from multiple nonstandard sources and standardize these data streams with a repeatable process prior to submission?
    - Sponsors use multiple LIMS systems that are dispersed to support the needs for in-life, clinical pathology, pathology, PK/TK, and reproductive toxicology data.
    - Even internal LIMS Systems probably don't use the same conventions for naming subjects, trial groups or day counting. Sponsors may very well have site-specific differences if studies are done at different locations. The same is true for many CROs.
    - Parts of a study may be outsourced across multiple CROs with different systems and levels of expertise ranging from no knowledge of SEND to proficiency with the standard but not necessarily with FDA requirements. Likewise, parts of a study may be conducted by a sponsor and the rest by one or more CROs.
    - Partner CROs likely do not use the same version of controlled terminologies as those implemented in existing LIMS systems for the studies they are conducting.
    - It will be important to start communicating the standards and FDA specific requirements early on in the study design stage across all the participating organizations (internal and CROs) to avoid last minute surprises when studies are being prepared for submission.
- How will you trace provenance of the submitted data to the raw GLP data when subjected to an audit?
    - Carefully determine in advance the QA controls that you need to put in place.
- Do you ensure that your tabular data in the study reports is consistent with the SEND representation of the same study data?
    - The standards do not require consistency today. However, the future cost in time when responding to questions from regulatory agencies or the increased time for regulatory review due to differences in terminology between the study reports and the submission, should be considered.

  - There are potential savings in creating a uniform way to source data from the LIMS extracts for both SEND submissions as well as study reporting. The difficulties in getting the various data sources and their organizations can be logistically challenging.

- How will you stay abreast with evolving standards and FDA rules governing submissions?
  - The SENDIG 3.0 today supports only single-dose general toxicology, repeat-dose general toxicology, and carcinogenicity studies.
  - SENDIG 3.1 is now under review and once published in early 2015, it will incorporate respiratory and cardiovascular testing done during safety pharmacology studies.
  - CDISC Controlled Terminology Group publishes 3 or 4 updates a year.
  - The FDA will periodically issue updates to their technical specifications, when new standards and specifications will be supported, and when older ones will be retired.
- How do you ensure that you have reviewed the 'standardized data' prior to submission?
  - Evaluate how the 'representation of the data' impacts the existing scientific review process.
  - The FDA will send their questions and refer to extracts from the NIMS reviewer tool. How quickly can these views be re-constructed so that the specific data and the context of their question can be understood before responding?

References

1. Guidance for Industry - Providing Regulatory Submissions in Electronic Format — Standardized Study Data
2. Study Data Technical Conformance Guide v2.0
3. FDA Specific SEND Validation Rules
4. CSC Update: A Demonstration of JumpStart, the New FDA Platform of Tools and Processes for Product Review – Presentation at PhUSE Annual CSS 2014 by Lilliam Rosario, PhD., Director, Computational Science Center, CDER, FDA
5. How JumpStart Works – Food and Drug Administration
6. FDA NIMS Overview
7. PointCross DSIMS Overview