Paper PP21

Automation of Submission Packages Quality Checks

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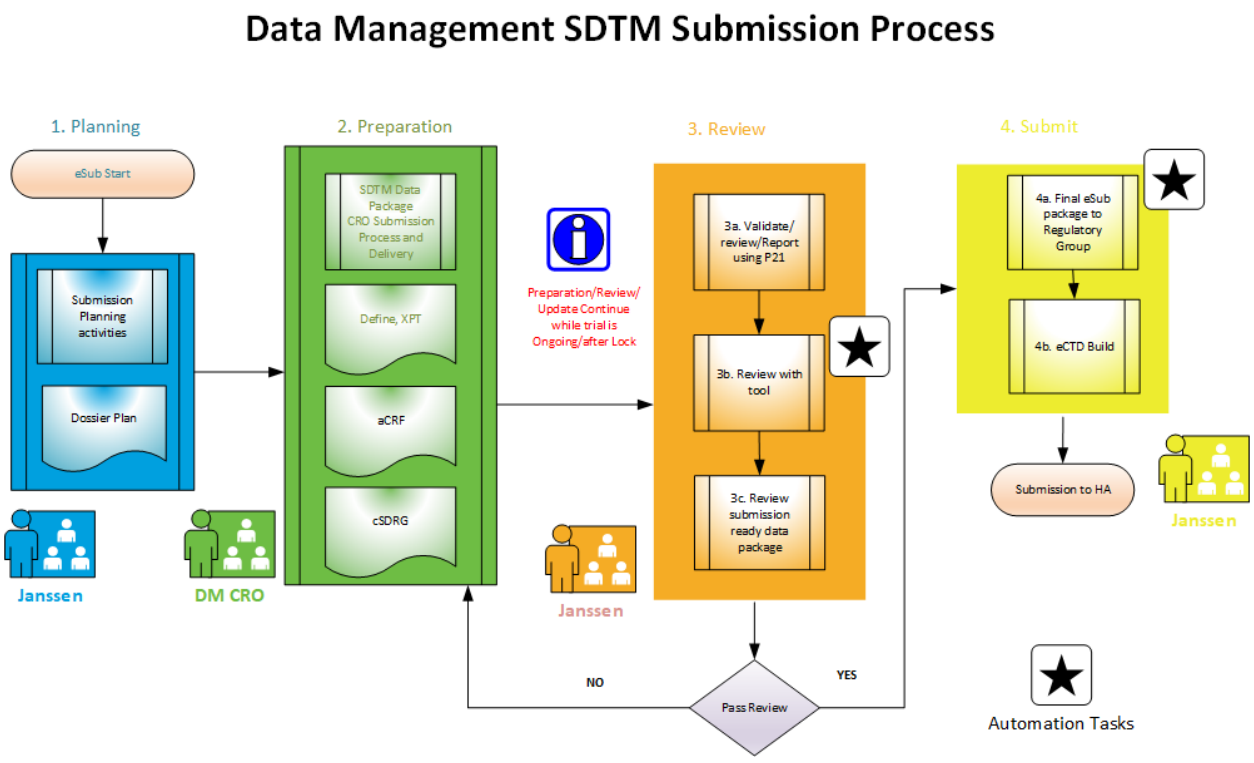
ABSTRACT

This paper introduces the automation tool for quality & compliance checking of clinical trial data submission packages to regulatory agencies. Up until now, submission packages were manually checked in the form of QC checklist for correctness, completeness and compliance to regulatory guidelines. This can be laborious and tedious job, with the possibility of human error. This automated tool acts as final gateway check or vetting tool before sending to regulatory/publishing group to build the eCTD. This also automates tedious work like checking all hyperlinks in PDF and XML files. By automating the checking and delivery of submission packages, handshaking between regulatory/publishing and data management/stat programming departments is also clear without any confusion across different therapeutic areas, functions (DM, STAT) and packages (SDTM, ADaM etc.).

INTRODUCTION

At Janssen, Data Management (DM) activities are outsourced to DM CROs. The DM CROs are contracted to deliver SDTM to Janssen during the trial conduct and to prepare the SDTM submission package after database lock.



When the SDTM package is ready for submission to health authorities, there are multiple aspects and attributes that need to be checked, and this was, up until recently, a completely manual process using QC checklists.

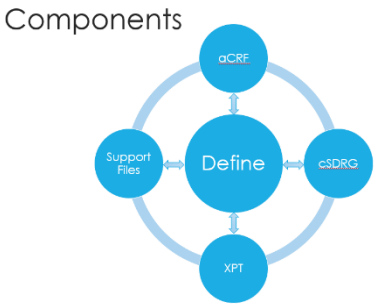
Some of these checks are time-consuming, for example checking the hyperlinks and bookmarks in define XML are working and pointing to the correct location or ensuring that PDF document attributes comply with the latest guidelines from health authorities. This tool automates the items listed in the Janssen QC checklists and submission package compliance can now be verified at the click of a button, reducing human error and time needed for review.

For example, if the submission responsible were to review a submission that includes 68 packages (multiple studies all including SDTM, ADaM, BIMO, etc.), and if each package review takes approximately 4 hours, it would take a total 34 business days to complete the review. This tool can perform the same review in a couple of minutes per package which cuts down the review time significantly. If the package is not submission ready the automated tool will produce a report of errors and halt the delivery to the Janssen regulatory group. The checking can be repeated as many times as needed until the package is submission ready.

Once the package is submission ready and no more errors occur, this tool also automates the delivery of the submission package to the Janssen regulatory group network server for building eCTD. This automation streamlines eCTD folder creation and will also protect the eCTD integrity by disabling the functions to re-update the package in the regulatory server without updating eCTD.

SCOPE

Submission package attributes need to follow specific guidelines from regulatory health authorities to ensure documents meet PDF specifications. In addition, submission packages include many components that are all interlinked as shown in the SDTM package components diagram below, and these links need to be verified for completeness and correctness:



This tool will check these attributes and links. Please find below some examples of checks performed by the tool:

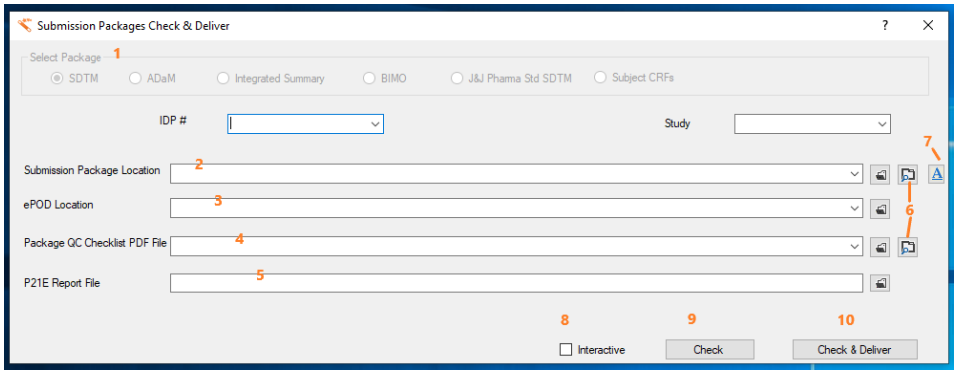
- Checks PDF files follows FDA's PDF specifications
- Checks all files submitted follow FDA's Specification for File Format Types Using eCTD Specifications
- Checks all files submitted follow FDA's Study Data Technical Conformance Guide
- Checks submission package follows Janssen specifications
- Cross-component checks – e.g., number of XPT files in Define vs. actual number of physical files
- Ensures correct order of SDTM package preparation: 1. Define 2. P21E validation 3. CSDRG 4. QC Checklist
- In case of split datasets, ensures sub-folder with split datasets are present
- Checks that only the following file types are present: XML, XSL, CSS, GIF, XPT, PDF
- Checks PDFs are bookmarked and ensures all hyperlinkings are working correct.
- Creates only necessary eCTD folders applicable to the study

Note, this tool does not check compliance to CDISC standards.

PROOF OF CONCEPT

This tool was designed as part of a proof of concept (PoC) to automate the QC checklists used for manual review of submission package attributes and interlinks, to create eCTD folder structure in the regulatory group server, and to copy the package to this location, once all validations have passed. This tool is designed to work as an interactive tool as well as in batch mode. In the interactive mode, each issue is reported individually, and the user needs to correct the issue to proceed further. In the batch mode, all the errors found are reported together in a single report and there is an option to export the report to an Excel format to enable distribution to CRO or other stakeholders. The tool can be run as often as needed by a reviewer. It tracks audit history and measures quality metrics by logging the usage.

GUI

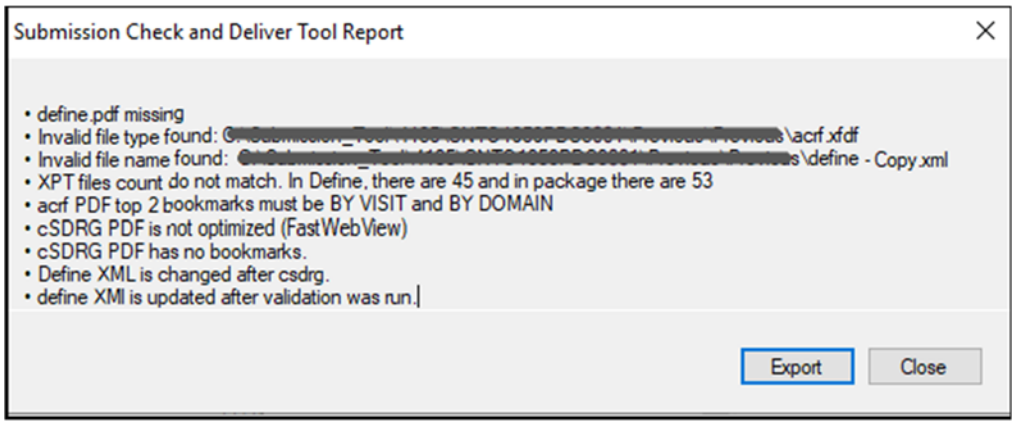


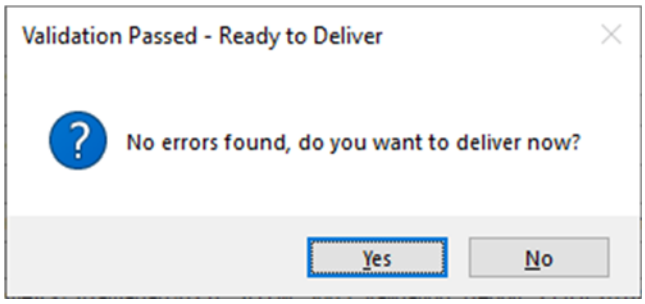
1. Submission package selection
2. Data management clinical data repository package location
3. Regulatory group drop zone location
4. Signed manual QC checklist electronic file
5. CDISC compliance validation report
6. Preview submission package in desktop
7. Check hyperlinks & bookmarks
8. Option to run in batch mode
9. Option to check only without delivering to internal regulatory group
10. Option to check and deliver the package to internal regulatory group

IMPLEMENTATION

As Janssen currently uses Windows 10 PCs, this PoC was developed in Windows .NET framework, uses PDF APIs to read and check PDF files and is designed to be independent of any Data Management Environment (DME) or Statistical Computing Environment (SCE) platforms. Most of the programming used in this tool is file processing and operating system functions using Windows file system calls/interface. All submission packages are processed on Windows network drives. This prototype also reads P21E validation reports in MS Excel format to cross check items and time stamps using MS Component Object Model (COM) technology.

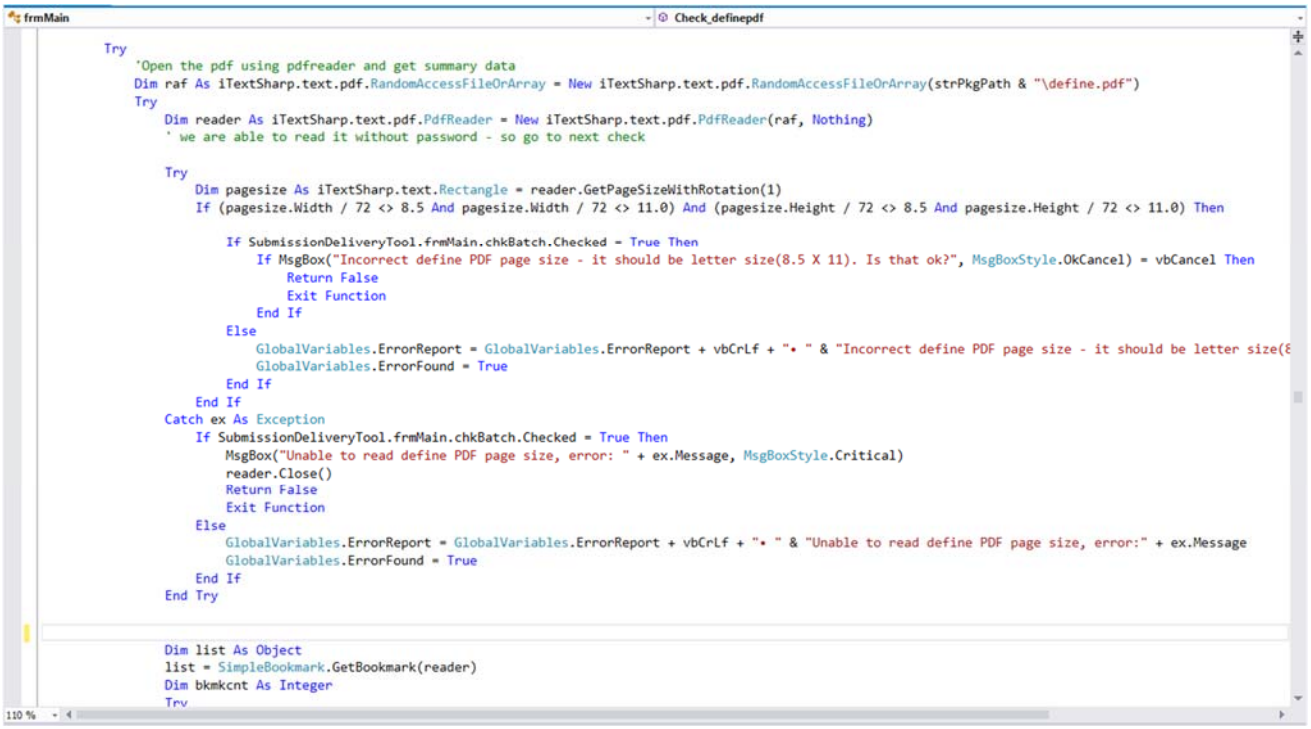
EXAMPLE RUNS



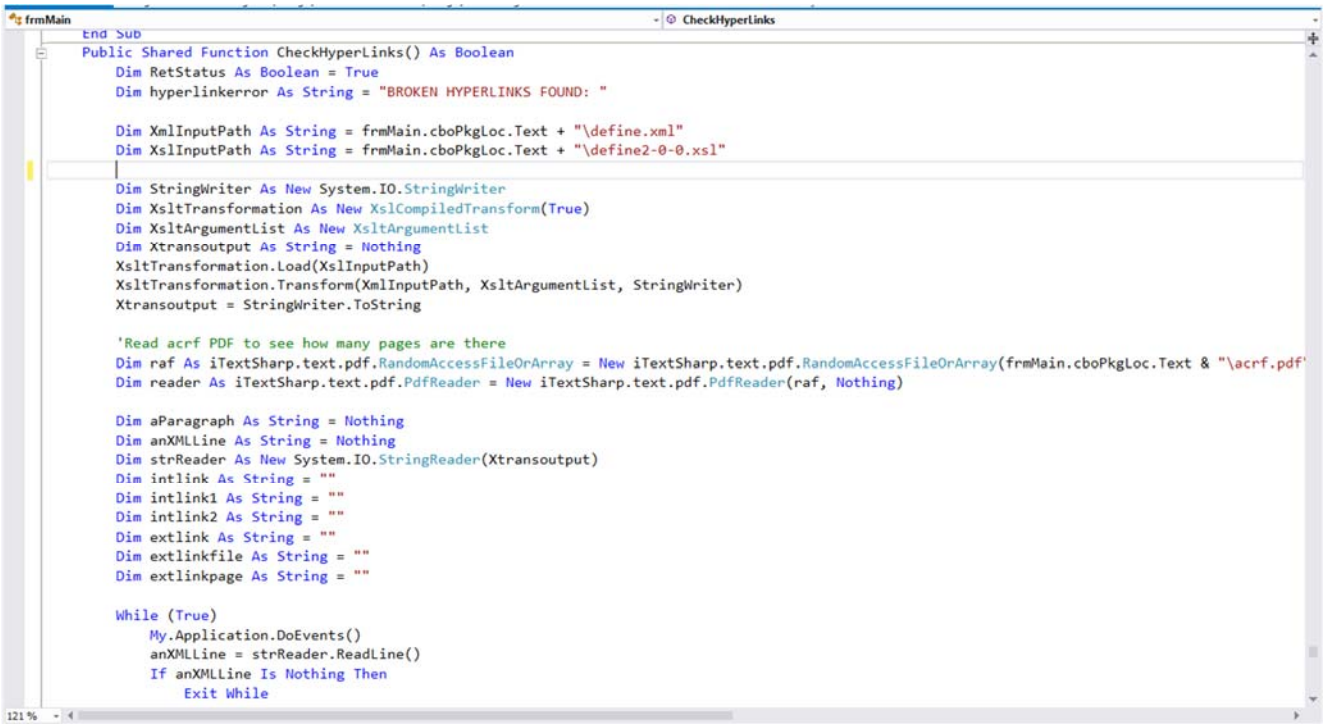


.NET SOURCE CODE

This automation tool can be implemented in any languages that can employ API calls and OS file/system functions, like Java, Python, C#, etc. Below is a snippet of code used in VB .NET to read PDFs:



Below is a snippet of code to read and check XML file:



CONCLUSION

This proof of concept shows that submission package review can be fully automated, and the sponsor can deliver timely and quality submission packages for faster approval. Other submission packages like Subject CRFs, ADaM, and BIMO can also be added to this automation. Further enhancements are being considered such as adding more challenging checks, PDF hyperlink cognitive checks, and use of Robotic Process Automation (RPA).

REFERENCES

- FDA, Providing Regulatory Submissions In Electronic Format – Standardized Study Data – Guidance for Industry
- FDA, Portable Document Format (PDF) Specifications – Technical Specifications Document – Guidance for Industry
- FDA – Study Data Technical Conformance Guide – Technical Specifications Document – Guidance for Industry
- FDA, Specifications for File Format Types Using eCTD Specifications – Guidance for Industry
- Janssen SDTM Submission Packages' QC Checklists and Job Aids

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