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PDFs Done Right: The Statistical Programmer's Guide to Flawless Regulatory Submissions

Srivathsa Ravikiran and Sri Raghunadh Kakani, Agios Pharmaceuticals

ABSTRACT

In the pharmaceutical industry, regulatory submissions require meticulous preparation to ensure compliance with stringent guidelines. A key component of this process involves preparing Case Report Tabulation (CRT) packages, which include critical PDF documents such as annotated case report forms (aCRF), define.pdf, the study data reviewer's guide (sdrg.pdf), and the analysis data reviewer's guide (adrg.pdf). These documents play a pivotal role in Module-5 submissions, where consistency, quality, and technical accuracy are imperative for smooth health authority reviews.

This paper outlines a standardized framework for optimizing PDF deliverables used in CRT packages. Specifically, we focus on enhancing the quality and compliance of the PDFs generated within programming for submission.

Our proposed approach integrates the use of the Lorenz eValidator™ to evaluate and validate PDFs according to the technical attributes mandated by FDA guidelines and other regulatory agencies. Additionally, Adobe Acrobat Pro™ is employed to resolve any identified issues, ensuring that the PDFs meet submission standards and are ready for review. This method minimizes last-minute adjustments, enhances efficiency, and mitigates the risk of non-compliance.

To support statistical programmers, we offer a comprehensive checklist and toolkit based on industry best practices. This resource aims to streamline the preparation process, reducing technical issues in the final submission package. Through real-world case studies, we demonstrate the importance of adhering to standardized PDF preparation techniques and how these practices facilitate seamless reviews by health authorities.

By adopting this framework, organizations can achieve greater efficiency, regulatory alignment, and confidence in their CRT submissions.

INTRODUCTION

Regulatory submissions in the pharmaceutical industry demand stringent adherence to format and technical specifications to ensure smooth review by health authorities. A critical component of these submissions is the Case Report Tabulation (CRT) packages, which include key PDF deliverables such as annotated case report forms (aCRF), define.pdf, the study data reviewer's guide (sdrg.pdf), and the analysis data reviewer's guide (adrg.pdf). These PDFs are central to Module-5 submissions within the electronic Common Technical Document (eCTD) and must meet rigorous quality standards. Non-compliance—such as non-embedded fonts or broken hyperlinks—can lead to delays or rejection, making precision essential for statistical programmers.

This paper presents two detailed approaches to prepare submission-ready PDFs: an automated method using Lorenz eValidator for compliance checks and a manual method with Adobe Acrobat Pro for direct fixes. By addressing common challenges like inconsistent page layouts and font issues, we offer step-by-step guidance to streamline PDF preparation. Both approaches integrate automation tools and best practices to minimize errors and ensure readiness for health authority review.

OVERVIEW OF PDF PREPARATION PROCESSES

To create submission-ready PDFs for CRT packages, statistical programmers can choose between two distinct processes: one leveraging Lorenz eValidator for automated validation and another relying on manual techniques with Adobe Acrobat Pro. Below is an overview of each process, followed by a flowchart Figure 1 summarizing the workflows.

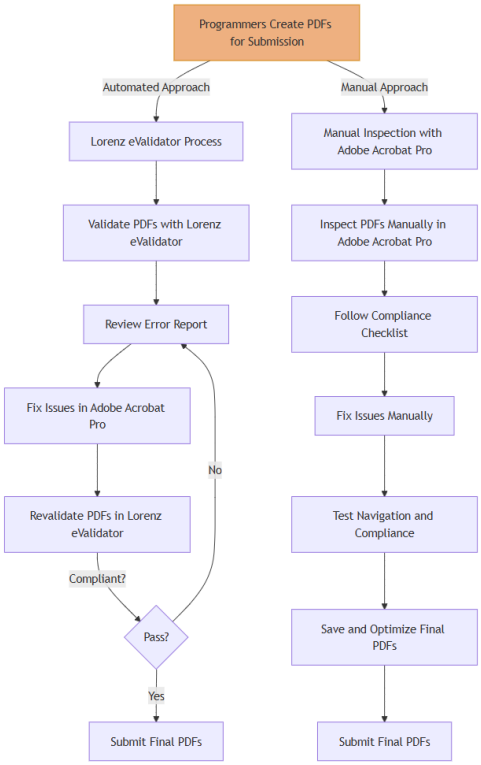
Process Using Lorenz eValidator:

This automated approach begins with PDFs from statistical programming created towards submission. The PDFs are then validated using Lorenz eValidator, which checks compliance against FDA eCTD standards. The tool generates a report flagging issues like non-embedded fonts or broken bookmarks. Programmers review the report, prioritize PDF-related errors, and use Adobe Acrobat Pro to fix them—embedding fonts, repairing links, or optimizing file size. The corrected PDFs are revalidated in Lorenz eValidator to confirm compliance before final submission. This method excels in efficiency for large submissions by automating error detection.

Process Without Using Lorenz eValidator:

In this manual approach, PDFs from statistical programming created towards submission are directly inspected using Adobe Acrobat Pro. Programmers follow a predefined checklist to verify compliance with FDA standards—checking PDF version, font embedding, page numbering, bookmarks, and file size. Issues are fixed manually within Adobe Acrobat Pro (e.g., embedding fonts via Preflight, adjusting bookmarks), and the PDFs are tested for navigation and compliance. Final PDFs are saved as optimized versions, ready for submission. This method offers hands-on control, ideal for smaller teams or single-document fixes.

Figure 1 Workflow for PDF Preparation Using Automated and Manual Approaches



This dual-process framework provides flexibility, balancing automation with manual precision.

BACKGROUND

PDFs submitted as part of CRT packages must adhere to technical guidelines outlined by regulatory agencies such as the FDA. These guidelines ensure that documents are accessible, navigable, and compatible with electronic review systems. According to the FDA Portable Document Format (PDF) Specifications, key requirements include:

1. PDF Version and Format Compliance:
    - Save in versions 1.4, 1.5, 1.6, or 1.7.

- PDF/A and PDF/X formats are not acceptable.
- Enable Fast Web View for improved loading times and accessibility.

2. Font and Text Requirements:
   - Embed all fonts (subset embedding acceptable).
   - Use black font color; blue permitted for hyperlinks.
   - Ensure legibility in grayscale printing.
   - PDFs must be text-searchable, especially for Modules 1, 2, and 3 administrative documents.
   - No hidden text in the PDF rendition.
3. Page Formatting and Structure:
   - Maintain correct, consistent page orientation (no tilting required).
   - Use Letter (8.5 x 11 inches) or A4 size throughout.
   - Align margins to submission standards.
   - Start pagination at 1, using consecutive Arabic numerals.
4. Bookmarks and Hyperlinks:
   - For documents with a Table of Contents (TOC): Provide bookmarks and hyperlinks for each TOC item, including tables, figures, references, and appendices.
   - For documents without a TOC: Bookmark headings, tables, figures, and appendices.
   - Collapse bookmarks by default, following TOC structure up to four levels.
   - Hyperlinks: Use blue text or thin rectangles, link to correct destinations, set magnification to “Inherit Zoom,” and use relative paths with forward slashes for internal links.
   - External web links (e.g., www.fda.gov) must be plain text, not hyperlinked.
   - Ensure no broken, inactive, or corrupt bookmarks/hyperlinks.
5. Security and Compliance Settings:
   - No password protection or security restrictions (all permissions “allowed”).
   - Retain original security settings for health authority forms.
   - PDFs must match source file content, including navigational aids.
   - Some agencies require tracked changes versions.
6. Image and Scanning Requirements:
   - Scan photographs, gels, and karyotypes at 600 dpi.
   - Scan other images (e.g., handwritten notes, chromatograms) at 300 dpi.
7. Initial View and Navigation Settings:
   - With bookmarks: Set Initial View to “Bookmarks Panel and Page.”
   - Without bookmarks: Set to “Page Only.”
   - Use “Default” for Page Layout and Magnification.
8. Prohibited Elements:
   - No JavaScript, dynamic content (audio, video, effects), embedded attachments, 3D content, or PDF annotations (except Module 1, section 1.15).
9. File Size Limitations:

- Limit single PDFs to 100 MB.

Adhering to these specifications ensures CRT deliverables are compliant, optimized, and navigable, reducing rejection risks and enhancing review efficiency. (U.S. Food and Drug Administration, 2016)

INTRODUCTION TO LORENZ EVALIDATOR

Lorenz eValidator is a standalone client application designed to verify the technical readiness of regulatory submission documents, including Case Report Tabulation (CRT) PDFs, before submission to health authorities. It ensures compliance with eCTD (electronic Common Technical Document) and non-eCTD validation requirements, reducing the risk of rejection due to technical deficiencies.

Key Features and Benefits:

- Automated compliance checks that run predefined validation rules based on global health authority requirements, such as FDA, EMA, and Health Canada.
- Validation profiles that offer region-specific criteria, such as US eCTD (FDA) - Validation Criteria 4.4.
- Error classification with three severity levels:
    - Green (Pass): No issues detected.
    - Yellow (Warning): Minor issues that may not impact compliance.
    - Red (Error): Critical issues that must be resolved before submission.
- Detailed reports that generate structured HTML validation reports with corrective action steps.
- Flexible licensing options available in Basic (Free), ONE, and Enterprise versions, each offering different levels of functionality.

This automated validation approach helps statistical programmers ensure PDFs meet regulatory expectations, reducing manual quality control efforts and streamlining submission workflows.

DOWNLOADING, INSTALLING, AND RUNNING LORENZ EVALIDATOR

Step 1. Downloading Lorenz eValidator

Lorenz eValidator is available as free or subscription-based software from:

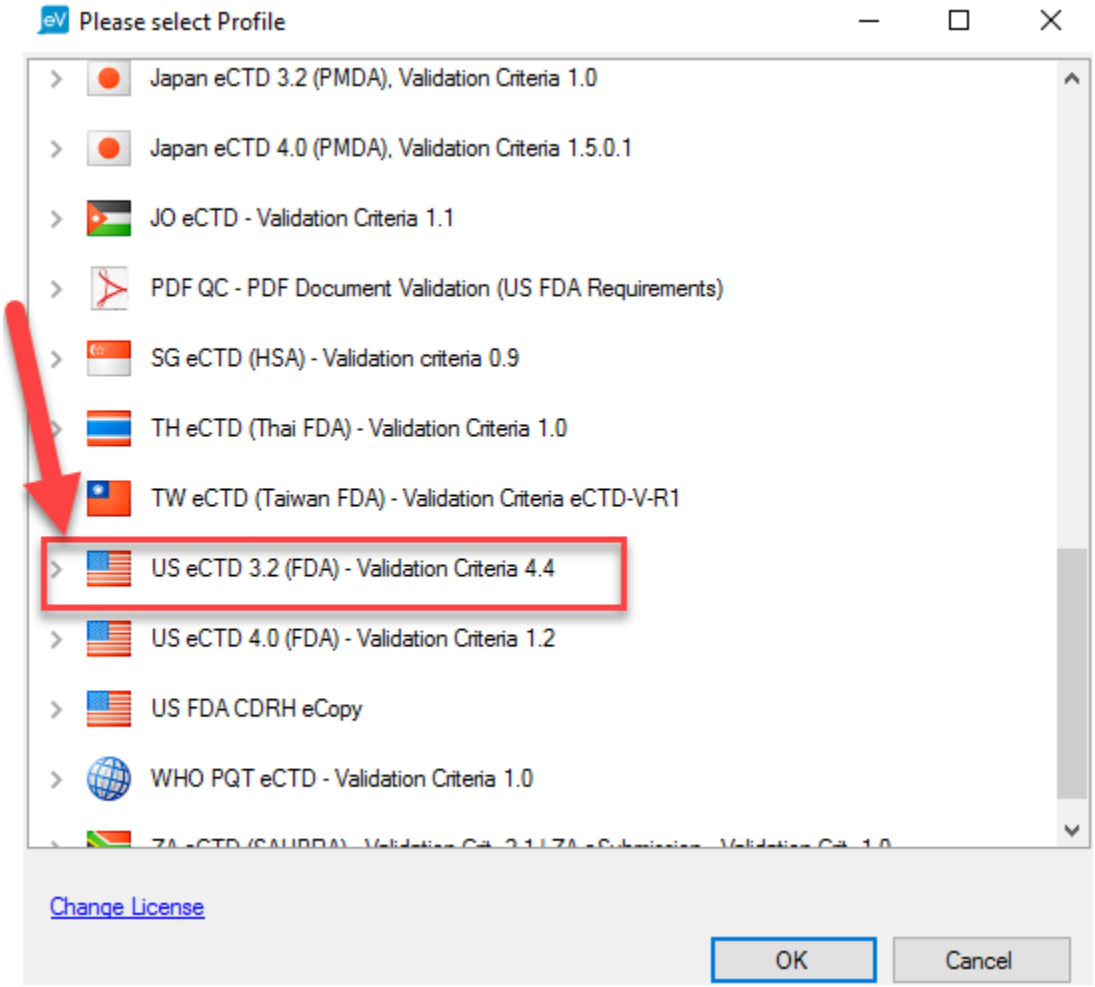
- The Lorenz Life Sciences Group website.
- Internal organizational repositories.

Install on a desktop (Windows 10 or macOS 11, 4 GB RAM minimum) following prompts.

Step 2. Selecting a Validation Profile

- Open Lorenz eValidator from the Start menu.
- Choose “US eCTD (FDA) - Validation Criteria 4.4” for FDA submissions Figure 2. Note: The first profile selected locks to the computer due to licensing restrictions.
- Click OK to apply.

Figure 2 Selecting the US eCTD 3.2 (FDA) Validation Profile (Criteria 4.4) in Lorenz eValidator.



Step 3. Configuring Report Settings

- Specify a root folder for validation reports; subfolders auto-organize results.
- Uncheck “Automatic Profile Detection” if no regional Module 1 is available to avoid errors.

Step 4. Running a Validation Report

- Place PDFs in a designated folder.
- In Lorenz eValidator, click “Select Submission,” browse to the folder, and click “Select Folder.”
- Click “Start Validation”; approve numeric folder prompts if prompted.
- Report is ready when the green bar disappears.

INTERPRETING AND NAVIGATING THE VALIDATION REPORT

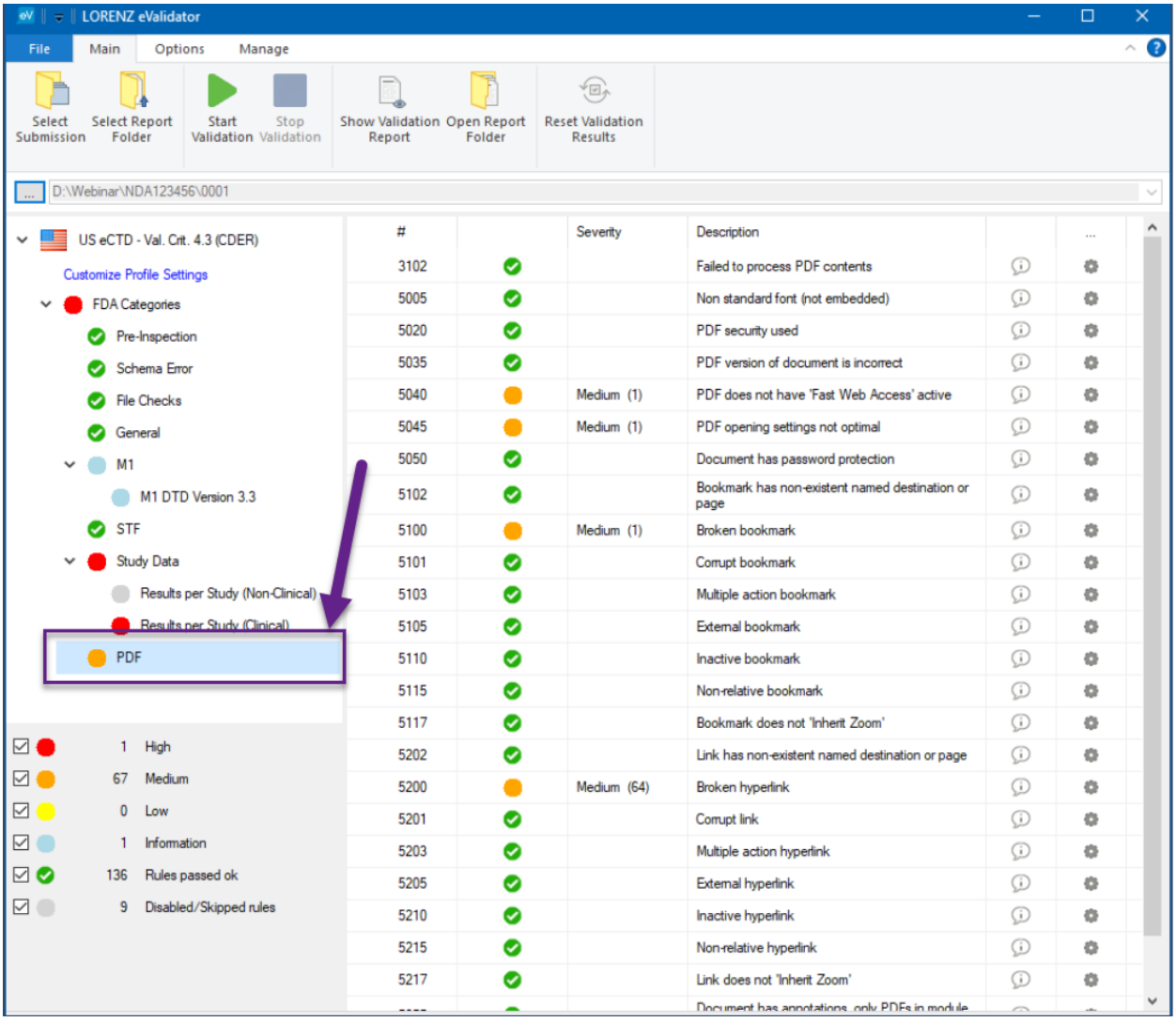
Understanding Validation Findings

The report categorizes validation results into three severity levels Figure 3:

- Green (Pass): No issues detected; the document meets compliance.
- Yellow (Warning): Minor issues that may not impact the submission but should be reviewed.
- Red (Error): Critical issues requiring resolution to avoid rejection.

For statistical programmers, focus on PDF-related findings. Ignore errors related to XML files, folder structure, or metadata, as they fall outside CRT programming scope.

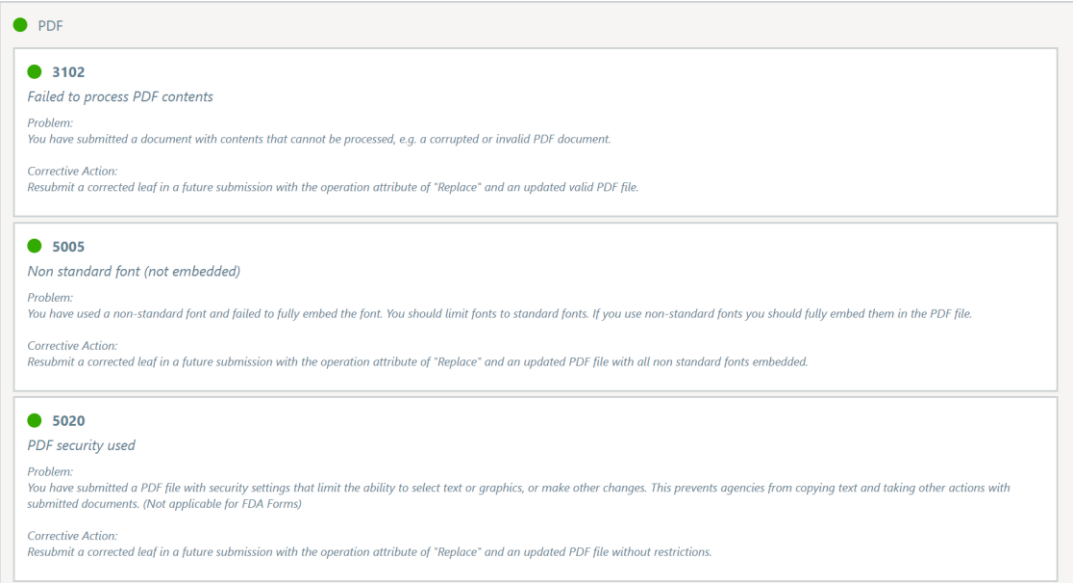
Figure 3 PDF-related validation issues identified in Lorenz eValidator, highlighting medium-severity warnings under the PDF section of the report.



Navigating the Report

- Click the severity column for issue details and correction guidance. See Figure 4 for sample of issue description.
- Ignore findings outside the purple box (not mandatory).
- View all findings via “Show Validation Report” or “Open Report Folder.”

Figure 4 Sample issue details from Lorenz eValidator, accessed by clicking the severity icon. The display includes the issue code, description, and corrective action guidance.



Saving and Exporting the Report

- Reports generate in HTML (eVReport.html).
- Convert to PDF: Open in a browser, use Adobe PDF Add-on.
- This step bridges automated detection to actionable fixes.

FIXING COMMON ISSUES IDENTIFIED IN LORENZ EVALIDATOR REPORTS

Once the validation process is completed using Lorenz eValidator, programmers need to resolve issues flagged in the report to ensure compliance.

Table 1 Corrective actions for common PDF issues identified during Lorenz eValidator validation, with step-by-step guidance for checking and resolving findings using Adobe Acrobat Pro.

Lorenz Issue ID	Issue Description	How to Check	How to Fix (Adobe Acrobat Pro)
3102	Failed to process PDF contents (corrupt or invalid file)	Attempt to open the PDF in Adobe Acrobat	Open Adobe Acrobat Pro → File > Save As > Choose PDF format → Resave the document and replace the corrupted file.
5005	Non-standard font (not embedded)	Open File > Properties (Ctrl+D) → Click on Fonts Tab	Open Tools > Print Production > Preflight → Expand PDF Fixups → Select Embed missing fonts → Click Analyze and Fix.
5020	PDF security settings enabled	Open File > Properties (Ctrl+D) → Go to Security Tab	Open File > Properties > Security → Set Security Method to No Security → Save the file.
5035	Incorrect PDF version	Open File > Properties (Ctrl+D) → Check PDF Version	Open File > Save As Other > Optimized PDF → Select an accepted version (1.4–1.7).

Lorenz Issue ID	Issue Description	How to Check	How to Fix (Adobe Acrobat Pro)
5040	'Fast Web Access' not enabled	Open File > Properties (Ctrl+D) → Check Fast Web View	Open File > Save As Other > Optimized PDF → Enable Fast Web View under PDF settings.
5045	PDF opening settings not optimal	Open File > Properties (Ctrl+D) → Check Initial View Settings	Open File > Properties > Initial View → Set Navigation Tab to Bookmarks Panel and Page or Page Only if no bookmarks exist.
5050	Document has password protection	Try opening the file in Adobe Acrobat	Open File > Properties > Security → Remove password protection and resave.
5055	Document contains annotations	Open Tools > Print Production > Preflight → Check for annotations	Open Tools > Print Production > Preflight → Select Flatten annotations and form fields → Click Analyze and Fix.
5057	Document contains no text (scanned image only)	Attempt to select text in the document	Open Tools > Scan & OCR → Click Recognize Text → Apply OCR to convert scanned text.
5100	Broken bookmark	Click each bookmark to verify it directs to a valid section	Right-click Bookmark → Select Set Destination → Choose the correct section.
5101	Corrupt bookmark	Try opening the file and using bookmarks	Delete the corrupt bookmark and recreate it manually.
5102	Bookmark links to non-existent page	Click on each bookmark and verify it leads to a valid section	Right-click Bookmark → Select Set Destination → Choose the correct page.
5103	Multiple action bookmark	Open Tools > Edit PDF > Link to check multiple actions	Remove additional actions, keeping only one per bookmark.
5105	External bookmark (web or email link)	Review all bookmarks for external links	Remove or update external bookmarks to link within the document.
5110	Inactive bookmark	Click on each bookmark and verify its functionality	Delete and recreate non-functioning bookmarks.

Lorenz Issue ID	Issue Description	How to Check	How to Fix (Adobe Acrobat Pro)
5115	Non-relative bookmark	Open File > Properties > Advanced and check bookmark settings	Ensure bookmarks use relative linking instead of absolute paths.
5117	Bookmark does not 'Inherit Zoom'	Open Bookmark Properties	Set Zoom Setting to Inherit Zoom for consistency.
5200	Broken hyperlink	Click each hyperlink to verify functionality	Right-click Hyperlink → Select Edit Link → Update the destination.
5201	Corrupt hyperlink	Check the hyperlink properties	Delete and recreate corrupt hyperlinks.
5202	Hyperlink points to a non-existent page	Click on each hyperlink to ensure it leads to a valid page	Update hyperlinks to point to correct pages.
5203	Multiple action hyperlink	Open Tools > Edit PDF > Link	Remove extra actions and retain only one per hyperlink.
5205	External hyperlink	Review hyperlinks for external references	Remove external hyperlinks or replace them with text-based references.
5210	Inactive hyperlink	Click each hyperlink to confirm it is functioning	Delete and recreate inactive hyperlinks.
5215	Non-relative hyperlink	Open File > Properties > Advanced and check hyperlink settings	Convert absolute hyperlinks to relative hyperlinks.

By systematically addressing these issues using Adobe Acrobat Pro, programmers can ensure that PDFs generated in statistical programming meet submission-ready standards. This structured approach minimizes compliance risks and ensures smoother regulatory review processes.

For programmers who lack access to Adobe Acrobat Pro, Adobe Reader can still be used to verify bookmarks, hyperlinks, security settings, and document properties. However, most modifications, such as fixing font embedding, correcting bookmarks, and adjusting document security settings, require Adobe Acrobat Pro or other specialized tools.

FIXING PDF ISSUES WITHOUT USING LORENZ EVALIDATOR

For teams without Lorenz eValidator, a manual approach with Adobe Acrobat Pro ensures compliance. Below is a checklist:

Table 2 Checklist of manual PDF compliance checks and corrective steps for common issues encountered in regulatory submissions, using Adobe Acrobat Pro in the absence of Lorenz eValidator.

Issue	How to Check	How to Fix (Adobe Acrobat Pro)
PDF Version Compliance	File > Properties (Ctrl+D) → Check PDF Version	File > Save As Other > Optimized PDF → Set to 1.4, 1.5, 1.6, or 1.7
Fonts Not Embedded	File > Properties (Ctrl+D) → Click on Fonts Tab	Tools > Print Production > Preflight → Expand PDF Fixups → Select Embed missing fonts → Click Analyze and Fix
Page Numbering Errors	Manually review pagination for consistency	Tools > Organize Pages > Page Labels → Set Start Number to 1
Bookmark/Hyperlink Issues	Click each bookmark and hyperlink to ensure they direct to the correct destination	Right-click Bookmark → Set Destination / Right-click Hyperlink → Edit Link
Bookmark Issues (broken bookmarks, inactive bookmarks, bookmarks pointing to non-existent pages, bookmarks not set to 'Inherit Zoom', bookmarks triggering multiple actions, bookmarks with external or non-relative destinations)	Open the Bookmarks pane (left sidebar). Click each bookmark to confirm it navigates to the correct destination. Right-click > Properties to inspect the assigned actions and target.	1. Right-click the bookmark and choose Set Destination. 2. Navigate to the correct page and view in the document. 3. Before clicking Set Destination, ensure the Inherit Zoom option is checked to meet regulatory requirements. 4. If the bookmark has multiple actions: Right-click > Properties > Actions tab → Remove any extra actions, keeping only Go to a page view. 5. For bookmarks pointing to external or non-relative paths: Delete and recreate the bookmark with an internal or relative destination (e.g., ../appendix.pdf). 6. For broken, corrupt, or inactive bookmarks: Delete the existing bookmark, navigate to the correct section, and create a New Bookmark, then set its destination.
Hyperlink Issues (broken hyperlinks, inactive hyperlinks, hyperlinks pointing to non-existent pages, hyperlinks not set to 'Inherit Zoom', hyperlinks triggering multiple actions, hyperlinks with external or non-relative destinations)	Use the Select Tool (Tools > Edit PDF > Select Tool). Click each hyperlink in the body of the document to ensure proper navigation. Right-click > Edit Link to review destination and properties.	1. Right-click the hyperlink and select Edit Link. 2. Choose Go to a page view in the dialog box (if not already selected). 3. Navigate to the correct page and zoom level, then click Set Link. 4. Ensure the Zoom option is set to Inherit Zoom for consistent viewing behavior. 5. For hyperlinks with multiple actions: Right-click > Edit Link > Actions tab → Remove all actions except Go to a page view. 6. For external or non-relative hyperlinks (e.g., absolute file paths or web links): Replace with plain text or adjust to use a relative path as needed. 7. If a hyperlink is broken or inactive: Remove the link and recreate it using Tools > Edit PDF > Link > Add/Edit Web

Issue	How to Check	How to Fix (Adobe Acrobat Pro)
		or Document Link, then configure as described above.
Fast Web View Not Enabled	File > Properties (Ctrl+D) → Check if Fast Web View is enabled	File > Save As Other > Optimized PDF → Enable Fast Web View under PDF settings
Security Restrictions	File > Properties (Ctrl+D) → Go to Security Tab	File > Properties > Security → Set Security Method to No Security
File Size > 100 MB	File > Properties (Ctrl+D) → Check File Size	File > Save As Other > Optimized PDF → Compress images and remove unnecessary elements
Annotations Present	Tools > Print Production > Preflight → Check for active annotations	Tools > Print Production > Preflight → Select Flatten annotations and form fields → Click Analyze and Fix
Page Orientation Errors	Manually review the document for incorrect page orientation	Tools > Organize Pages → Select pages → Use Rotate Tool
Image Quality Issues	File > Properties > Description → Check image resolution	Ensure images are scanned at 300 dpi (standard) or 600 dpi (gels/karyotypes) before inserting into the PDF

PROCESS

- Open PDFs in Adobe Acrobat Pro.
- Manually verify each checklist item.
- Adjust settings, test navigation, and save as optimized PDFs.
- This manual method offers precision and control, suitable for smaller teams or single documents.

CASE STUDIES

LORENZ EVALIDATOR APPROACH

A Phase III trial's define.pdf had non-embedded fonts (Issue 5005). Lorenz eValidator flagged it in minutes; Adobe Acrobat Pro fixed it in 30 minutes, and file was processed by regulatory for submission versus a prior two-week delay.

MANUAL APPROACH

An adrg.pdf with broken bookmarks was manually reviewed and corrected in Adobe Acrobat Pro over two hours, avoiding resubmission to the regulatory and saving time in overall submission process.

CONCLUSION

This paper presents two approaches for preparing submission-ready PDFs: an automated method using Lorenz eValidator and a manual method using Adobe Acrobat Pro. By following the outlined workflows and checklists, teams can ensure compliance with regulatory standards, minimize submission delays, and improve overall efficiency. Depending on resources and project scale, teams can opt for automation for large-scale submissions or manual corrections for targeted adjustments.

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U.S. Food and Drug Administration. (2024, October). *STUDY DATA TECHNICAL CONFORMANCE GUIDE .* Retrieved from U.S. Department of Health and Human Services: https://www.fda.gov/media/153632/download

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RECOMMENDED READING

For further guidance on regulatory PDF specifications and compliance requirements, refer to the following document:

U.S. Food and Drug Administration. (n.d.). Portable document format (PDF) specifications. U.S. Department of Health and Human Services. Retrieved from https://www.fda.gov/files/drugs/published/Portable-Document-Format-Specifications.pdf

CONTACT INFORMATION

Your comments and questions are valued and encouraged. Contact the author at:

Srivathsa Ravikiran
Agios Pharmaceuticals
Srivathsarkiran@gmail.com

Sri Raghunadh Kakani
Agios Pharmaceuticals
raghunadhkakani46@gmail.com

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