



Product White Paper

ROSETTA Phoenix™ eCTD Viewer Desktop Edition by DoubleBridge Technologies, Inc. is the first and only high performance Windows desktop application that was released during the industry's early adoption of Electronic Common Technical Document (eCTD) standards and continues to be a popular choice among large and small life sciences companies. 10 of global top 20 pharmaceutical companies and/or their subsidiaries license ROSETTA eCTD solutions that includes ROSETTA Phoenix™ Desktop Edition, ROSETTA Phoenix Server™ and ROSETTA Pyramid™.

ROSETTA Phoenix eCTD software participated in multiple eCTD Tools Interoperability and Comparison Study (ETICS) projects that compared and analyzed various eCTD tool vendors' implementations of eCTD specifications. ETICS projects were conducted by volunteers of industry experts in eCTDs who (1) aimed to understand how eCTD software vendors interpreted eCTD specifications and guidance; and (2) made suggestions to regulatory authorities and standards-setting organizations to further improve eCTD specifications and guidance; and (3) promoted interoperability among eCTD vendors' tools. While many eCTD tool vendors that participated in ETICS projects mostly focused on the publishing of eCTD submissions, ROSETTA Phoenix was the only eCTD software that solely focused on the (read-only) viewing aspects eCTDs regardless what eCTD publishing software produced the eCTD submissions. The function and user interface designs of ROSETTA Phoenix eCTD Viewer have been engineered and optimized towards read-only users who don't necessarily need to know how eCTD submissions are produced. The result is a simple and friendly user interface that new users love without any training necessary while they enjoy behind-the-scenes performance-enhancing techniques that aim to boost the performance for large full lifecycle eCTD submissions.

In Greek mythology, a phoenix or phenix is a long-lived bird that is cyclically regenerated or reborn (Source: Wikipedia). ROSETTA *Phoenix* eCTD Viewer now enters its 11th year since its first generation. Each release of the software brings new features and support for new eCTD specifications as the standard evolves. First developed for a leading pharmaceutical company in 2005 and followed by a public release as freeware in 2007, ROSETTA *Phoenix* eCTD Viewer not only allows the viewing of eCTD submissions that are prepared in accordance with the latest versions of ICH and regional eCTD specifications but also, as importantly but often forgotten, eCTDs that were prepared in according to older specifications. Our first customer of the ROSETTA *Phoenix* eCTD Viewer, a global top 3 pharmaceutical company, continues to use the software as the enterprise standard for viewing eCTD submissions during their final stage of publishing eCTDs and after eCTD submissions are archived in their electronic archive, ROSETTA *Pyramid* (also developed by DoubleBridge).

ROSETTA *Phoenix* eCTD software supports the viewing of eCTDs prepared in accordance to ICH and regional eCTD specifications. Besides, certain eCTD submissions that do not strictly conform to these eCTD standards are tolerated by ROSETTA *Phoenix* eCTD viewer and can be viewed in the software. Because we participated in ETICS projects and understood how different eCTD publishing software might interpret regulatory authorities' guidance and specifications differently, ROSETTA *Phoenix* is able to detect and cope with some anomalies in such eCTD submissions, especially for early eCTD submissions that were created when the whole industry just started to adopt eCTDs. Besides common ICH eCTD specifications, ROSETTA *Phoenix* supports the following regional regulatory authorities' eCTD specifications:

- US Food and Drug Administration (FDA)
- European Medicinal Agency (EMA)
- Japan Pharmaceuticals and Medical Devices Agency (PMDA)
- Health Canada
- Switzerland SwissMedic
- Gulf Cooperation Council/Saudi SFDA
- Medicines Control Council (MCC) of South Africa
- Taiwan Food and Drug Administration
- Australian Therapeutic Goods Administration (TGA)

Key Features of ROSETTA *Phoenix* eCTD Viewer

Current View and Cumulative View

Although eCTD submissions are published one eCTD Sequence at time, all eCTD Sequences that belong to the same eCTD application are best to be viewed collectively so that all lifecycle management (e.g. addendum, deletions and replacements) of regulatory submission dossiers are all accounted for. The Cumulative View aggregates submission documents in all submission Sequences and display them in electronic Common Technical Document (CTD) content structure. The Current View works similarly as the Cumulative View except that under Current View, replaced or deleted documents are hidden. The Current View is the default view once an eCTD application/dossier is loaded in ROSETTA *Phoenix*. A user can easily switch between the Current View and Cumulative View by a single click.

Lifecycle Operations and Status

What makes eCTD a great advancement in the evolution of electronic submission formats is its ability to use lifecycle maintenance operations to indicate when a previously submitted document is appended or made obsolete during the lifecycle of a regulatory application. When a previously submitted document is appended, deleted or replaced, it is indicated by an intuitive lifecycle status icon in ROSETTA *Phoenix* Viewer. In addition, a user can access the full lifecycle of such dossier revision history by selecting the View Revisions menu option.

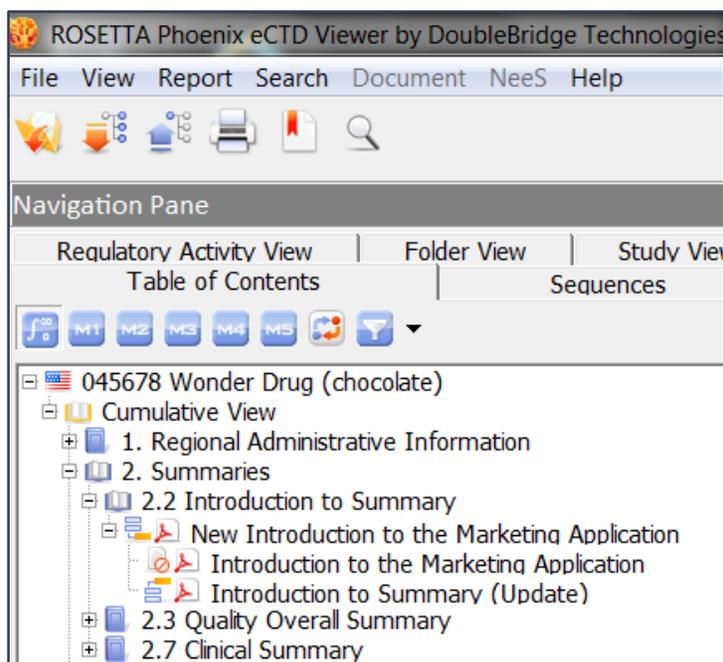


Figure: Cumulative View showing replaced document.

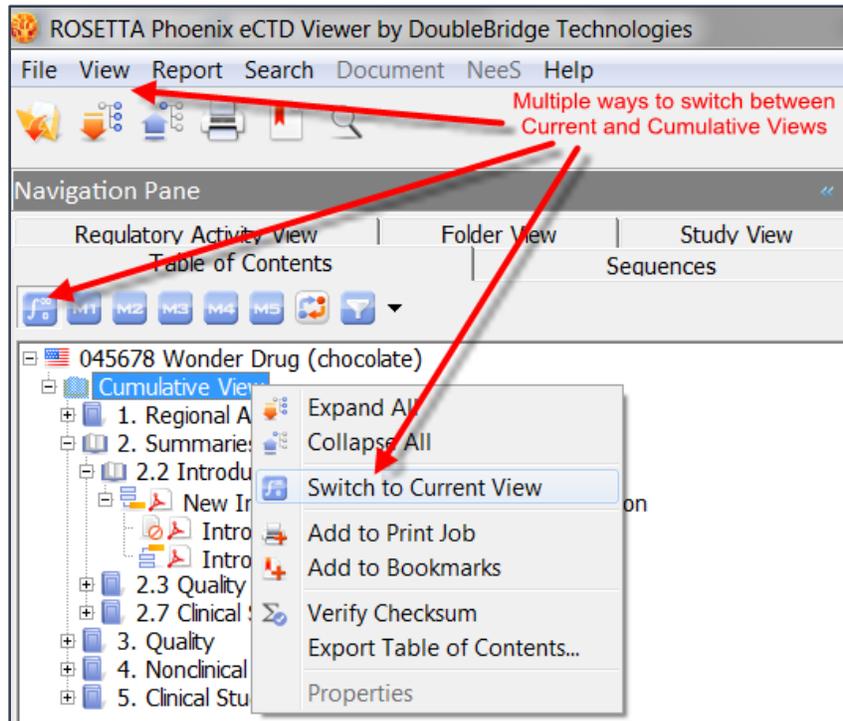


Figure: Multiple ways to switch between Current and Cumulative Views

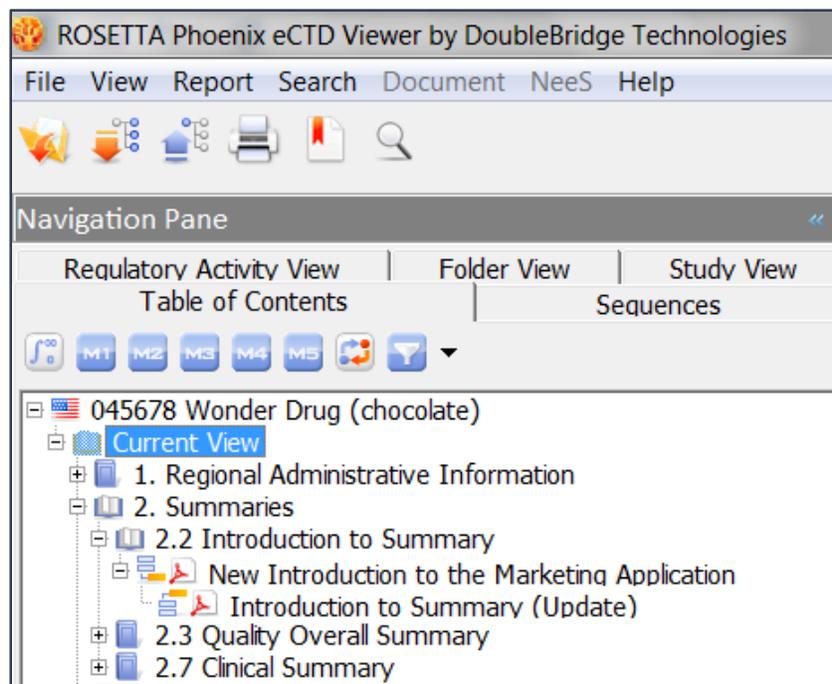


Figure: Current View showing only current documents

CTD Section Attributes

As defined by ICH's Common Technical Document (CTD) structure, certain sections of CTD content are repeatable – meaning they have the same CTD section headings but only differ in their specific subject matters. These sections include 2.3.S Drug Substance, 2.7.3 Summary of Clinical Efficacy, 3.2.S Drug Substance, 3.2.P Drug Product, and 3.2.P.4 Control of Excipients.

For example, in an eCTD submission, it can have one section 3.2.S Drug Substance for a substance made by Manufacturer X and another section 3.2.S for a substance made by Manufacture Y. In ROSETTA *Phoenix* Viewer, by default, repeating sections are displayed with their attributes appended to the section headings to distinguish them as shown:

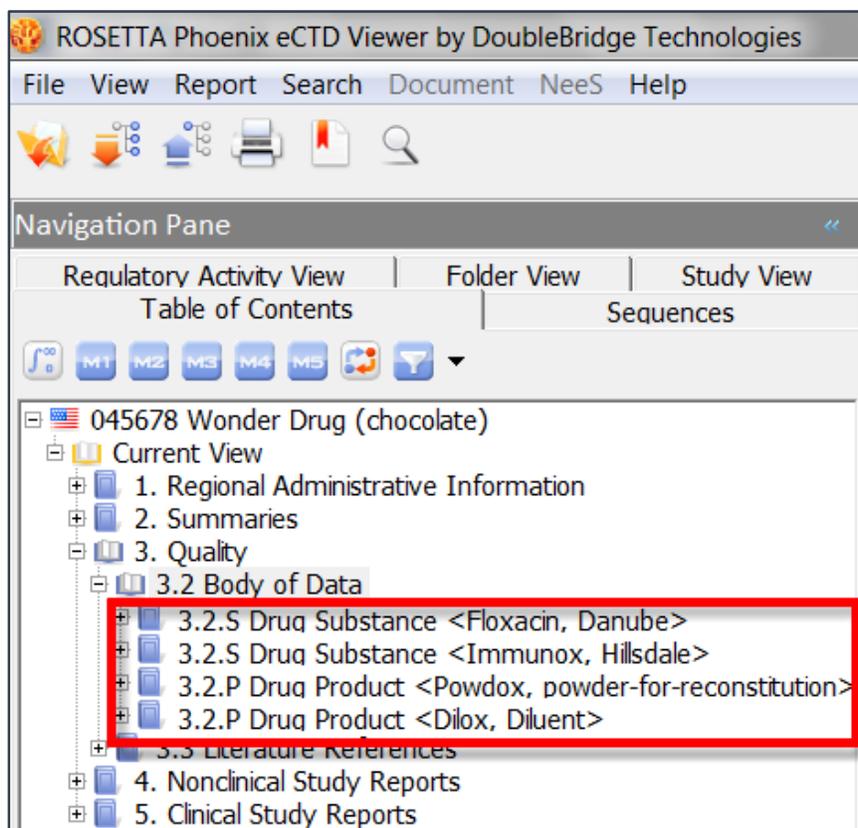


Figure: Repeating sections distinguished by attributes

Merging Repeating Sections

By default, repeating sections are displayed as separate sections so that users can better locate the documents they are looking for in an eCTD submission. However, there are cases where merging those repeating sections are desirable. One of such cases is the scenario when one company is acquired or merged with another and, as a result, the

ownership of the regulatory application is transferred to the acquiring company. Say, after a merger or acquisition, the manufacturer's name changes to the acquiring company's name. In such case, it's not desirable to display 3.2.S Drug Substance sections separately - one under the legacy company's name and another under the acquiring company's name as the manufacturers.

One advanced feature in ROSETTA *Phoenix* eCTD Viewer is an option to merge repeating sections. The capability to merge or separate repeating sections can be accessed from the View > Options menu options in ROSETTA Phoenix. When repeating sections are merged, the original section attributes are appended to the title of each document. This capability is designed to overcome a deficiency in the current eCTD standard that does not allow the modifications of attributes in previously submitted eCTD submissions.

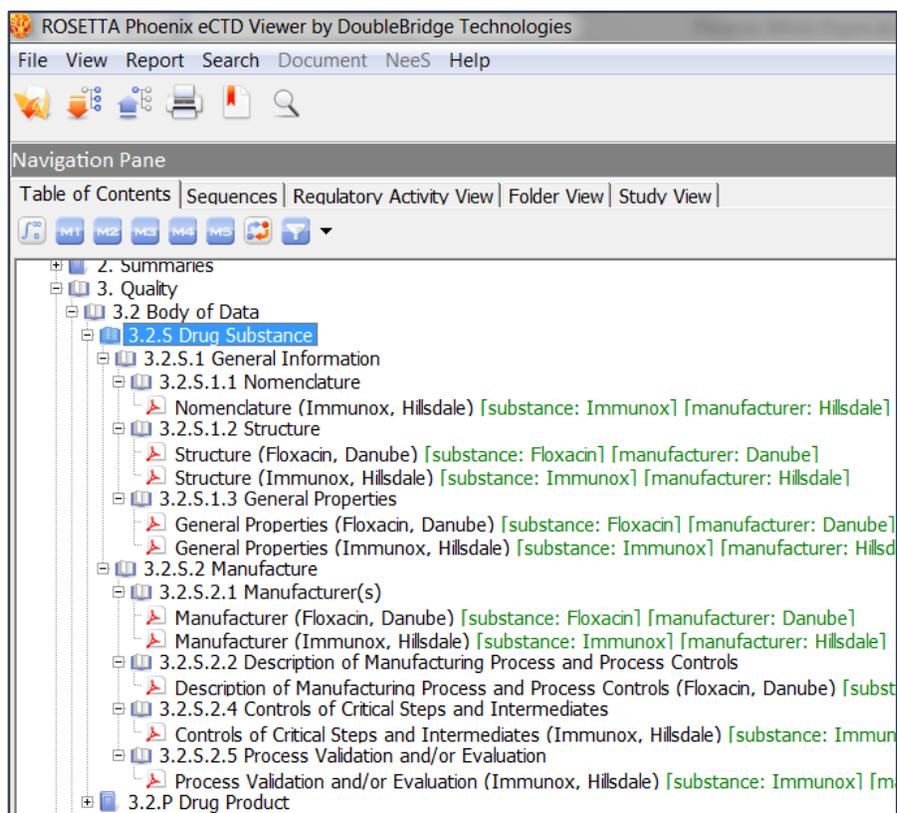


Figure: Merged Repeating Sections

Regulatory Activity View

A Regulatory Activity comprises one or more regulatory submission sequences that lead to a health authority's regulatory decision (e.g. Approval, denial, no objections, etc.) on a regulatory application. An NDA original application, an efficacy supplemental application and a variation that seeks a health authority's approval are examples of Regulatory Activities. A Regulatory Activity is usually a subset of the entire eCTD submission dossier. In eCTD terms, the submission sequences in a Regulatory Activity are related and their relationship is indicated in their eCTD metadata files as related sequences. ROSETTA *Phoenix* eCTD Viewer allows users to see specific Regulatory Activities under the Regulatory Activity View. The Regulatory Activity View allows users to focus on specific Regulatory Activities instead of viewing the entire dossier.

Sequence View and Metadata

One of the greatest advantages of eCTD submissions over paper submissions or other formats of electronic submissions, such as eNDA and NeeS, is the capability to submit the contextual information regarding regulatory activity of submissions in a format that is machine-readable to allow for process automation. Depending on regional eCTD specifications, such contextual or regulatory process information (aka metadata) may include application type and application number, submission type and submission date, submission sequence description, product and applicant information. A submission's metadata is displayed under the Sequence View in ROSETTA *Phoenix*. Users can navigate to the metadata of a submission sequence and drill down the metadata hierarchy as defined by regional eCTD specifications. The design is self-adapting to the underlining version of eCTD specifications under which a submission sequence was created. The navigation works seamlessly even if the submission sequences are prepared in accordance to different versions of eCTD specifications over the life time of an eCTD dossier.

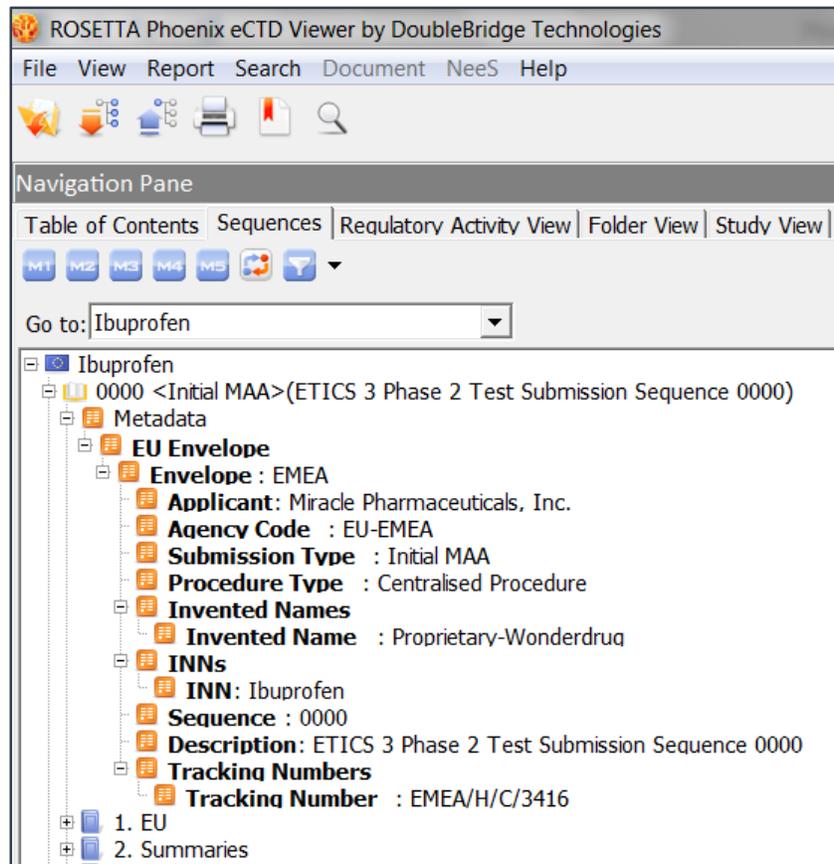


Figure: Metadata of an FDA eCTD sample

Folder View

The Folder View displays submission documents with the folder structure as they are stored on a file share or a local drive. This is the only view in ROSETTA *Phoenix* eCTD Viewer that shows users the physical location of files and their file names. It is also the only place where you can access ICH and regional backbone files, the MD5 checksum file and other utility files. These files are designed for computer-based processing but not for human eyes. Other viewing options in ROSETTA *Phoenix* eCTD Viewer hide these technical files and convert them to user-friendly presentations of the same information and, hence, shields users from complex technical implementation of eCTD.

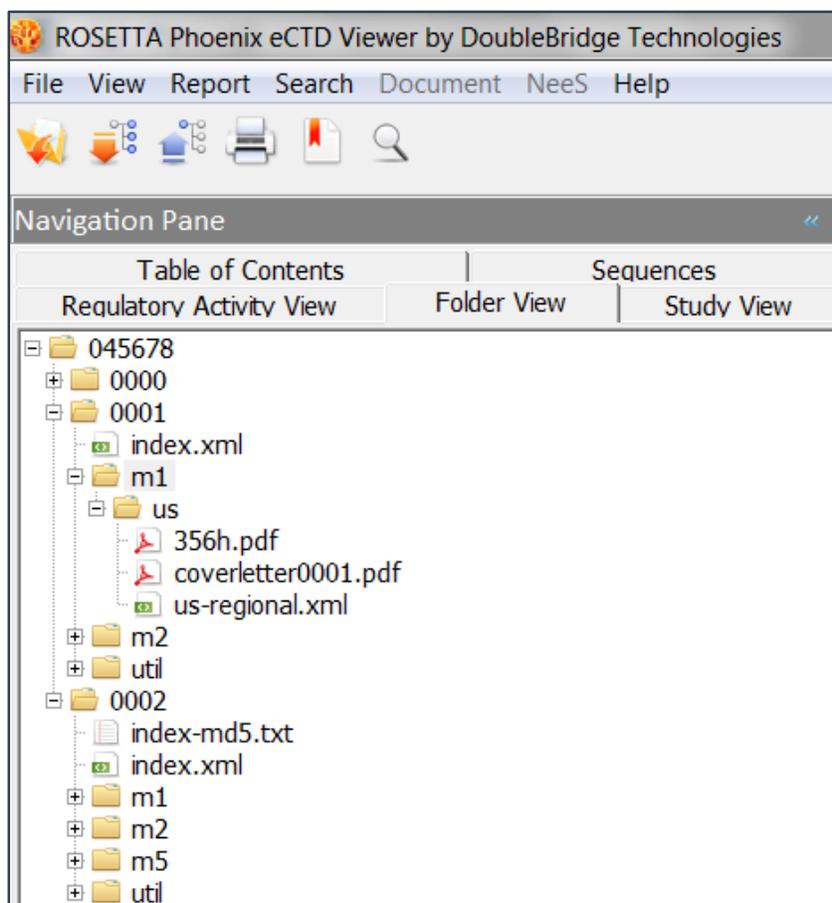


Figure: Folder View

Besides showing the physical folder structure of eCTDs, one subtle feature in ROSETTA *Phoenix* eCTD Viewer under the Folder View is its capability to indicate files that are referenced from multiple eCTD sections or eCTD Sequences.

Cross References

Another advanced feature in ROSETTA *Phoenix* eCTD Viewer is its capability to indicate an identical document content that has been “submitted” in or referenced from multiple eCTD sections or Sequences. eCTD specifications allow one physical copy of electronic content to be submitted once and referenced from different contexts of use (even from different submission sequences).

For example, in an eCTD submission Sequence, it may reference a non-clinical study of Single Dose Oral Toxicology in Wharf Rats in section 4.2.2.5 in one submission Sequence and reference the same study in section 4.2.3.1 in another submission Sequence.

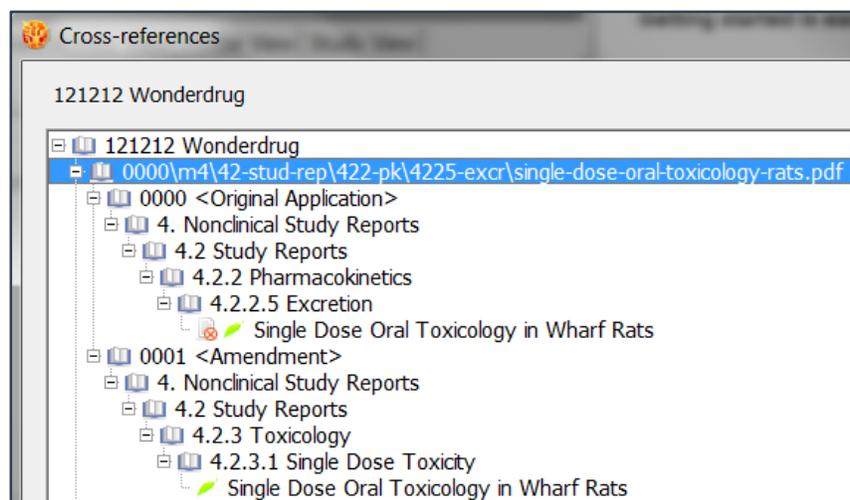


Figure: Cross-Reference Report

Health authorities encourage sponsors such “submission by reference” to eliminate redundant submissions of the exact content while allowing the navigation of such content in different contexts of use.

Besides the Cross-References Report shown above, ROSETTA *Phoenix* also indicates cross-referenced documents in its Table of Content View, Regulatory Activity View, Sequence View and Folder View. Cross-referenced documents are appended with additional information linking to the physical location of the file being referenced.

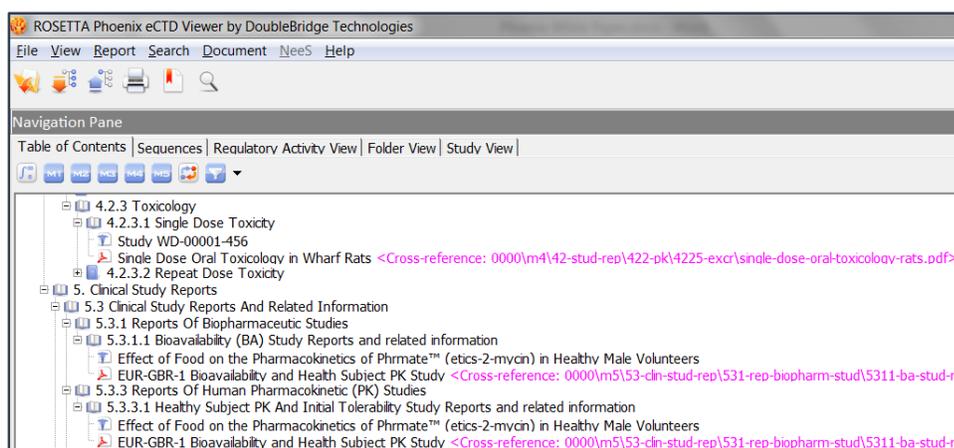


Figure: Cross-reference under Table of Contents View

Study View

ROSETTA *Phoenix* eCTD Viewer is the first such eCTD tools that fully explores the additional values of Study Tagging Files (STF) specifications defined by US FDA. STF defines content structure and metadata-tagging capability for non-clinical and clinical study reports. ROSETTA *Phoenix*

provides a Category View that organizes studies by their species, route of administrations and type of controls. It also provides a reporting capability for a comprehensive listing of all the studies in a submission dossier.

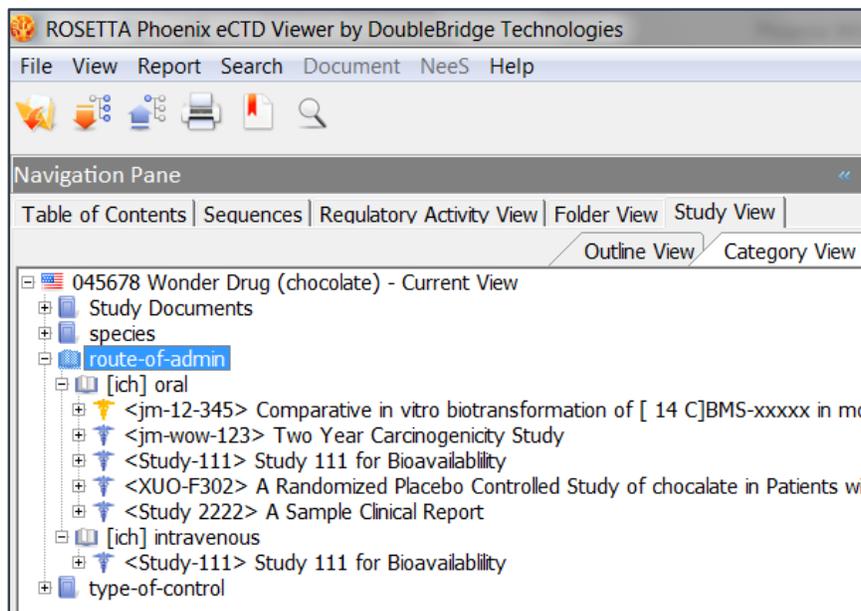


Figure: Study Category View

View Non-eCTD Electronic Submissions

Non-eCTD Electronic Submission (NeeS), is an electronic submission format that follows ICH's CTD content structure and folder hierarchy. NeeS is typically a transitional format accepted by many regional health authorities before the full embrace of eCTD. NeeS and eCTD differ in (1) A NeeS submission does not include the so-called eCTD backbone files that contain regulatory process metadata (e.g. submission type, application number); and (2) NeeS specifications mandate strict folder naming conventions and hierarchy. Even though ROSETTA *Phoenix* is mainly designed for viewing eCTD submissions, starting in version 4, it also supports the viewing of NeeS dossiers. ROSETTA *Phoenix* takes advantage of NeeS strict folder hierarchy and automatically creates the Cumulative View of NeeS dossier sequences so that submission documents for the same subject matters are co-located in their respective modules and folders (e.g. Module 3 Quality). Without the Cumulative View for NeeS, such documents would "scatter" across multiple sequence folders and make it difficult to navigate and comprehend the entire submission dossier.

Command Parameters

A hidden gem embedded in ROSETTA *Phoenix* eCTD Viewer Desktop Edition is its capability of accepting a command line parameter providing the folder path of an eCTD submission dossier. If the ROSETTA *Phoenix* application is launched with such parameter, the eCTD dossier will be loaded into the eCTD Viewer. This capability allows the creation and sharing of reports containing information of regulatory applications and hot links to view eCTD submissions in an organization without requiring report readers' knowledge of the locations of eCTD submissions.

Add Sequence

If your responsibility is to publish eCTD submissions, most likely, your previously submitted eCTD sequences and the one you are building but not yet finalized are co-located on either a file share or in an EDMS (e.g. EMC Documentum). This is perfectly good since you'd like to preview what the entire eCTD dossier would look like if the in-progress sequence were finalized and submitted to the health authority.

However, outside of the submission publishing group, users typically would only want to view the eCTD dossiers with submission sequences that have been submitted to the health authorities but not any sequence that is being built. Many of our customers license ROSETTA *Pyramid* and use it as the authoritative archive of submitted dossiers to provide broader access to the dossiers beyond the submission publishing group within their organizations. ROSETTA *Phoenix* eCTD Viewer gives you the best of both worlds by providing you the capability to load all submitted sequences from the official archive and add an in-progress sequence from a file share storing published eCTD outputs. This unique design shields Regulatory Affairs, Regulatory Operations and legal departments from seeing not-yet submitted sequences but, at the same time, provides submission publishing group the ability to preview the would-be, full lifecycle, cumulative view of an eCTD dossier if an in-progress eCTD sequence is finalized and submitted.

(ROSETTA *Pyramid* allows a life sciences company to archive eCTD submissions and other types of submissions and correspondence received from health authorities. Visit www.rosettaectd.com for details.)