The Revised eCTD Guidance Document
CAPRA Symposium, February 21, 2006

E-Review

Modernizing Canada's regulatory submission system for therapeutic products.

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Outline of Presentation

- **Revision history of the guidance document**

- **Structure and content of the guidance document**
    - Combining three filing formats in one document
    - Reorganizing the document
    - Terminological issues

- **Two kinds of structure**

- **Steps in the preparation of submissions in eCTD format**

- **Life cycle management**

- **Other refinements**

- **Key messages**

Revision History of the Guidance Document

- **Overview of the Development of Guidance Document**

    – Release of draft guidance document for consultation spring 2004

    – Final guidance document posted spring 2005 (co-submission filing format only)

    – Revised guidance posted as a draft for consultation (January 2006)

- **Consultation**

    – Summary of WGES recommendation (January 2005)

Three Documents in One

- **Cover Three Filing Formats in One Document**

  – Co-submission, Hybrid, Electronic-only

- **Rationale for Combining Three Filing Formats**

  – One document to maintain (Health Canada perspective)

  – One document to keep current with (industry perspective)

  – Continual refinement as experience gained by both

Three Documents in One (cont'd)

- **Terms**

    – Varieties v. filing formats; staged v. structured approach

- **Common vs. Unique to Filing Format**

    – Structure and Content, Technical Requirements, Filing Process

    – Implementation Considerations

Reorganizing the Document

- **Structural Changes**

  - New section on Filing Formats

  - Brings together congruence of submissions, legal issues

  - Introduction of filing formats and table to cross-reference

- **New Content**

  - Material added to cover filing formats

  - Material added on life cycle management

Terminological Issues

- **Examples**

  - Sample vs. submission

  - Additional information and subsequent submission

- **Need for Standards**

  - Document, file, leaf element, and so on

  - Inconsistency in terminology used by ICH

  - Indication of another level of ambiguity

Two Kinds of Structure

- **Folder Structure**

  – Folder structure: organizing unit for computer operating system

  – Means of storing, saving, viewing, accessing files

- **eCTD Structure**

  – eCTD structure: the representation of a collection of files through its organization in XML backbone

  – Leaf files do not equal leaf elements

Two Kinds of Structure (cont'd)
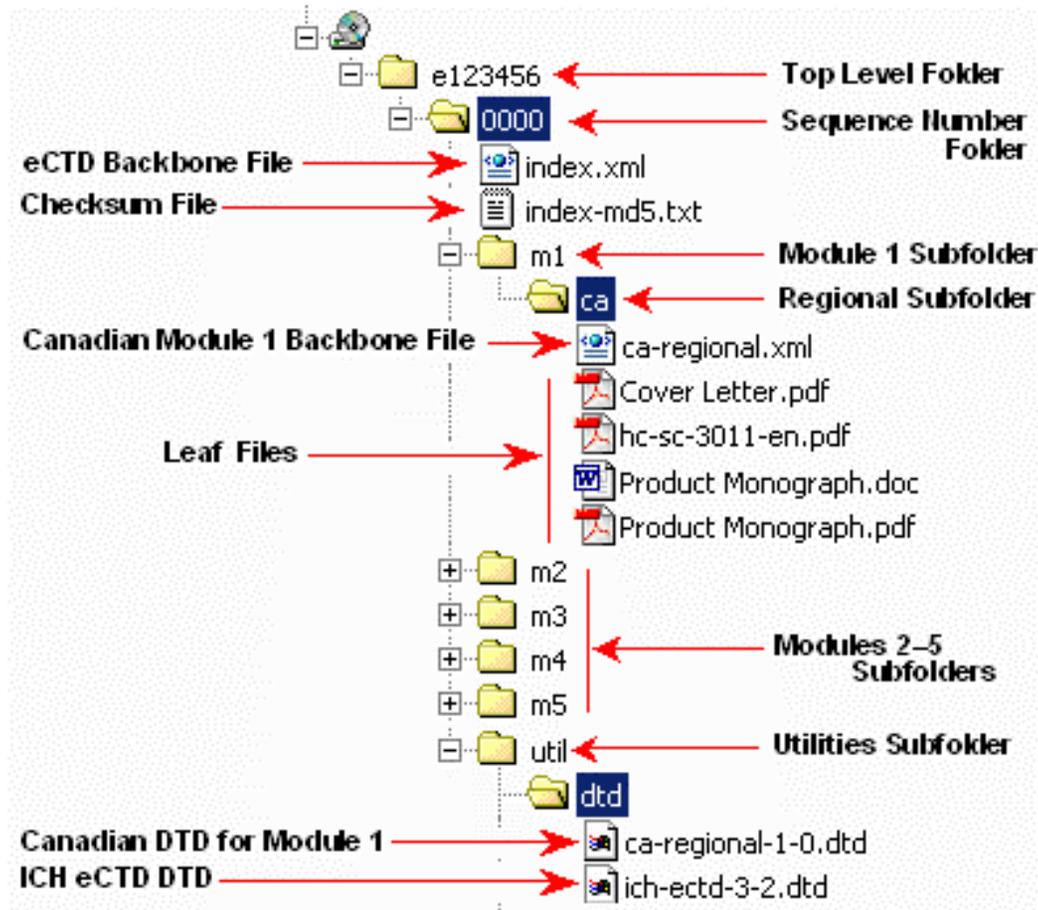
- **Terminology**

  - Folder structure does not equal eCTD structure

  - Sorting out what belongs to each of type of structure and using consistent terms for document, leaf, file, and so on
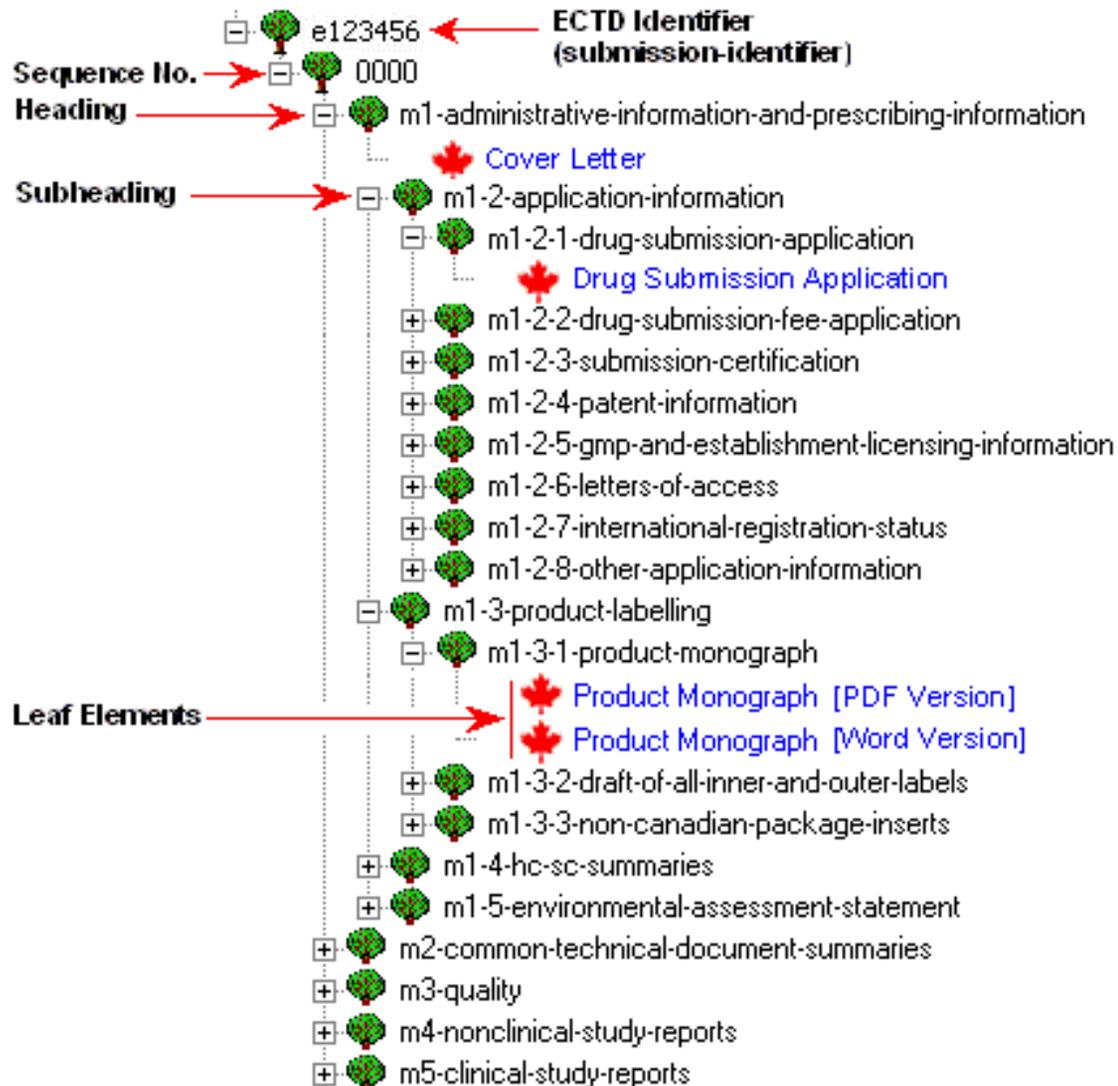
- **Conceptual Issues**

  - What is meant by a "document" in eCTD structure?

  - Important to be aware of conceptual issues when you're building a submission in eCTD format

Folder Structure

eCTD Structure

ECTD Identifier (submission-identifier) → e123456

Sequence No. → 0000

Heading → m1-administrative-information-and-prescribing-information

Cover Letter

Subheading → m1-2-application-information

m1-2-1-drug-submission-application

Drug Submission Application

m1-2-2-drug-submission-fee-application

m1-2-3-submission-certification

m1-2-4-patent-information

m1-2-5-gmp-and-establishment-licensing-information

m1-2-6-letters-of-access

m1-2-7-international-registration-status

m1-2-8-other-application-information

m1-3-product-labelling

m1-3-1-product-monograph

Leaf Elements → Product Monograph [PDF Version]

Product Monograph [Word Version]

m1-3-2-draft-of-all-inner-and-outer-labels

m1-3-3-non-canadian-package-inserts

m1-4-hc-sc-summaries

m1-5-environmental-assessment-statement

m2-common-technical-document-summaries

m3-quality

m4-nonclinical-study-reports

m5-clinical-study-reports

Steps in the Preparation of Submissions in eCTD Format

- Hold Technical Pre-submission Consultation

- File eCTD Sample

- Verify eCTD Sample

- Correct Errors and File Corrected Sample

- Obtain eCTD Identifier

- File Submission in eCTD Format

- Verify Submission in eCTD Format

- Correct Errors and File Corrected Submission in eCTD format

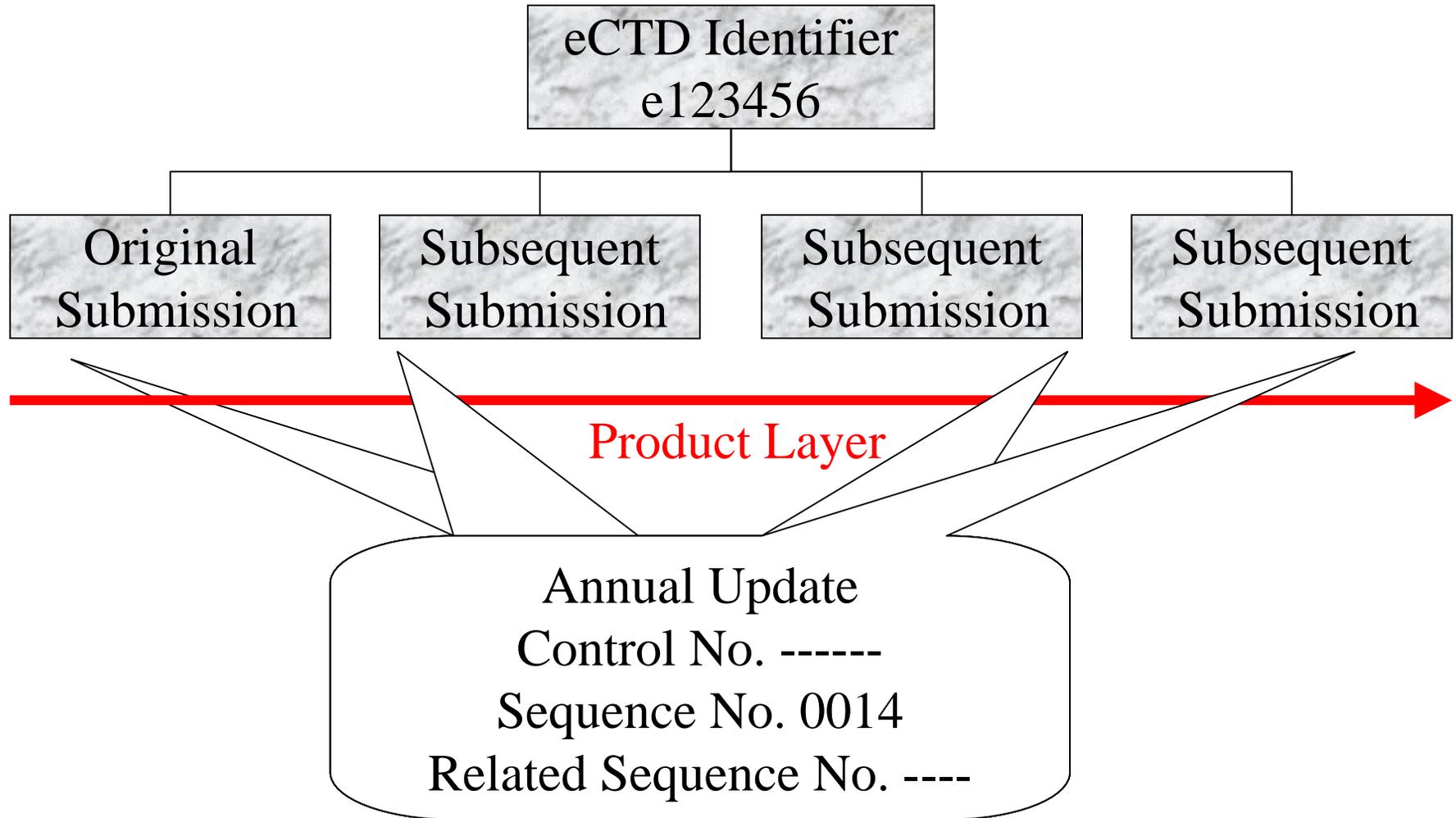- Upload Submission in eCTD format to Server
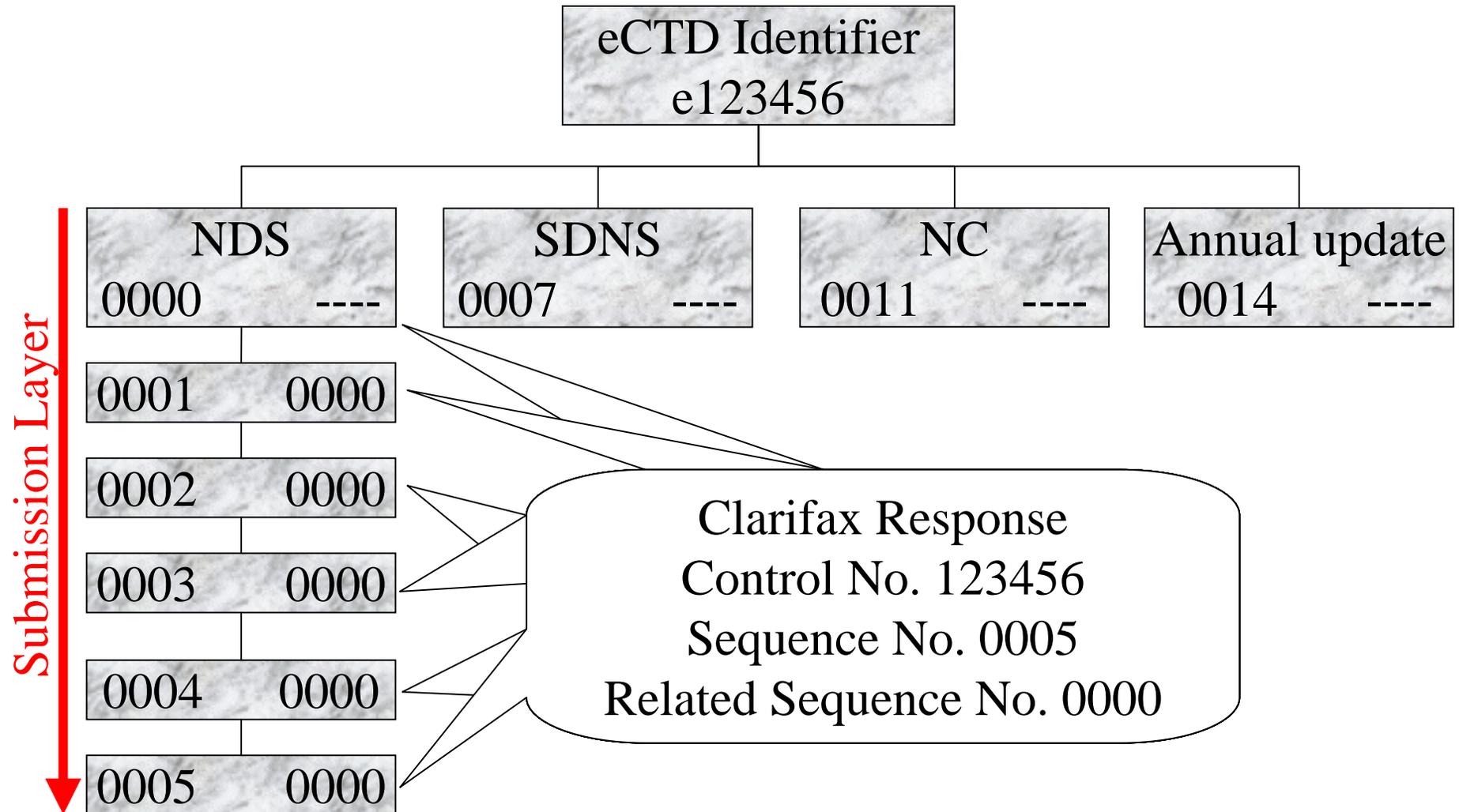
Life Cycle Management

- **Once in eCTD, Stay in eCTD**

  - Applies regardless of filing format

  - ICH standards enable life cycle management

- **Three Layers for Life Cycle Management**

  - Drug product layer

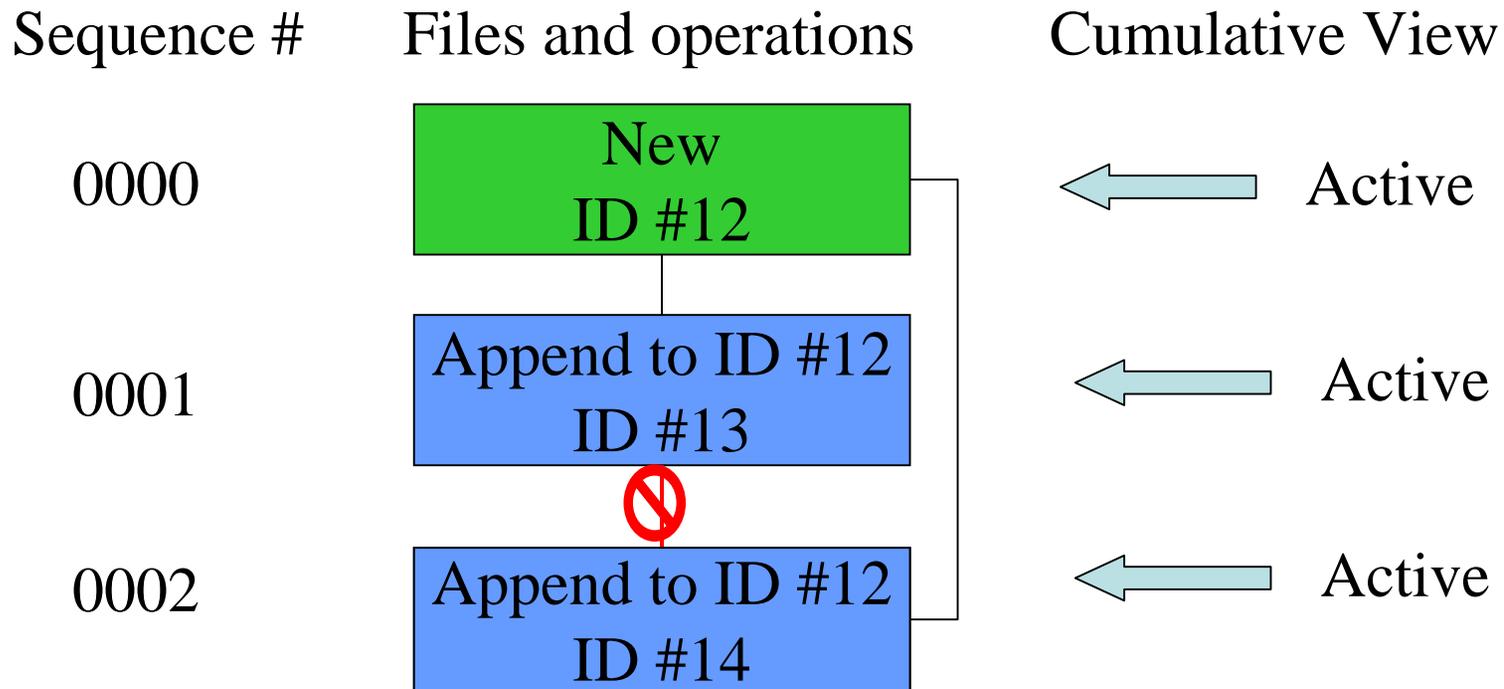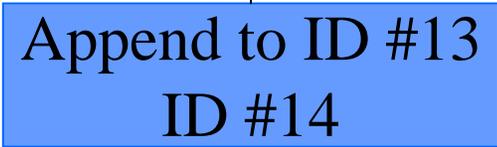 - Submission layer

  - Document layer

Product Life Cycle

```
                    ┌─────────────────────┐
                    │  eCTD Identifier    │
                    │  e123456            │
                    └─────────────────────┘
```

| Original Submission | Subsequent Submission | Subsequent Submission | Subsequent Submission |

Product Layer

Annual Update
Control No. ------
Sequence No. 0014
Related Sequence No. ----

Submission Life Cycle

Document Life Cycle

Sequence #

0000 — New

0001 — Delete, Replace, Append

0002 — Delete, Replace, Append, Delete, Replace, Append, End

Document Life Cycle Scenario #1 & 2 Append

Sequence #	Files and operations	Cumulative View

0000 — New ID #12 (green) — ⬅ Active

0001 — Append to ID #12 ID #13 (blue) — ⬅ Active

0002 — Append to ID #12 ID #14 (blue) — ⬅ Active

Document Life Cycle Scenario #3 Append

Sequence #	Files and operations	Cumulative View
0000	New ID #12	⟵ Inactive
0001	Replace ID #12 ID #13	⟵ Active
0002	Append to ID #13 ID #14	⟵ Active

Document Life Cycle Scenario #4 Append

Sequence #	Files and operations	Cumulative View
0000	New ID #12	⟵ Reactivated
0001	Replace ID #12 ID #13	⟵ Active ?
0002	Append to ID #12 ID #14	⟵ Active
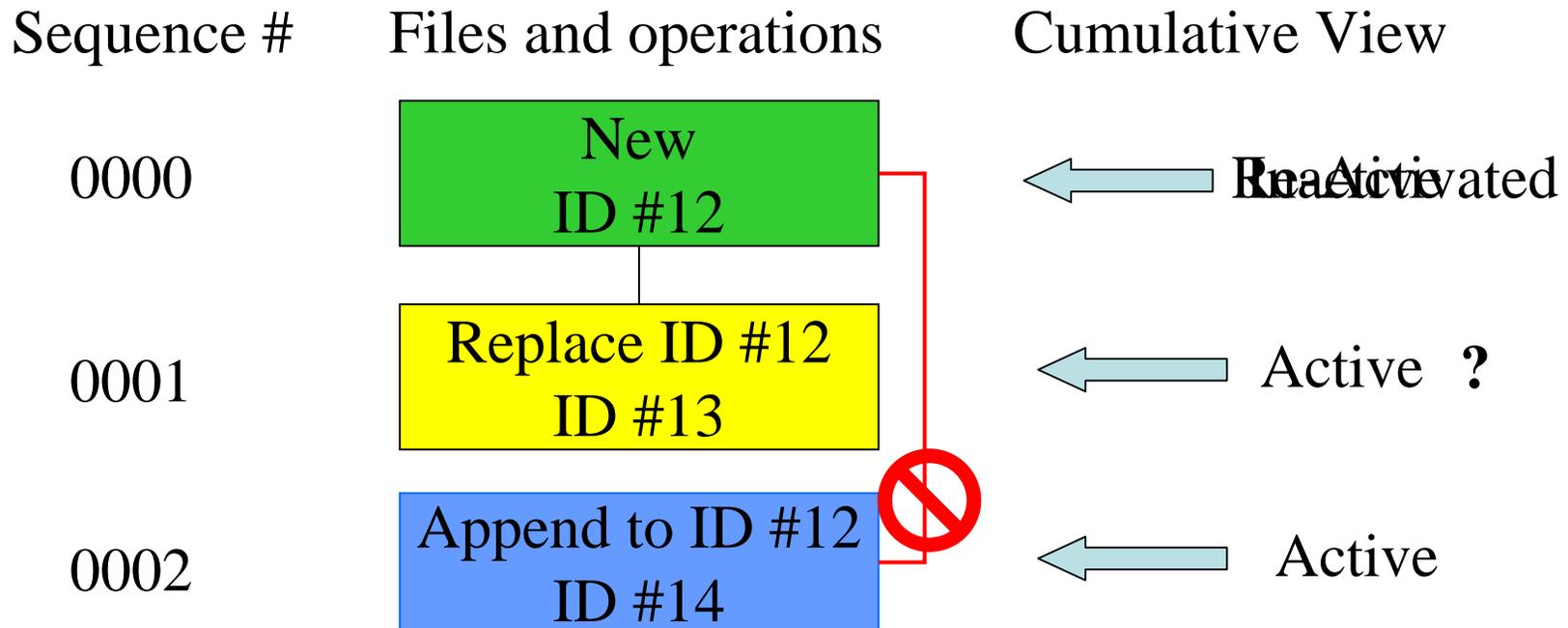
Not Recommended

Document Life Cycle Scenario #1 & 2 Replace

Sequence #	Files and operations	Cumulative View

0000 — New ID #12 ← Inactive

0001 — Replace ID #12 ID #13 ← Inactive

0002 — Replace ID #12 ID #14 ← Active
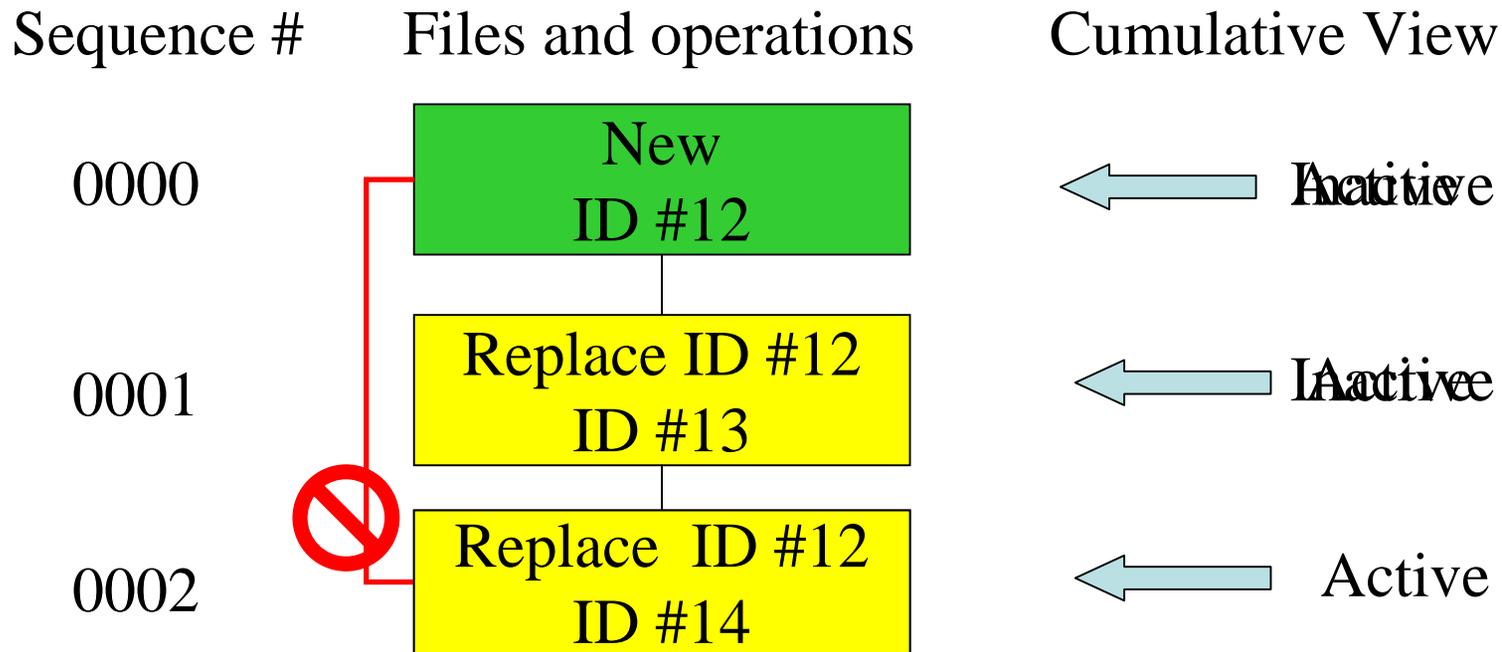
Not Recommended

Document Life Cycle Scenario #3 Replace

Sequence #	Files and operations	Cumulative View
0000	New ID #12	⬅ Active
0001	Append to ID #12 ID #13	⬅ Active
0002	Append to ID #12 ID #14	⬅ Inactive / Active
0003	Replace ID #14 ID # 15	⬅ Active
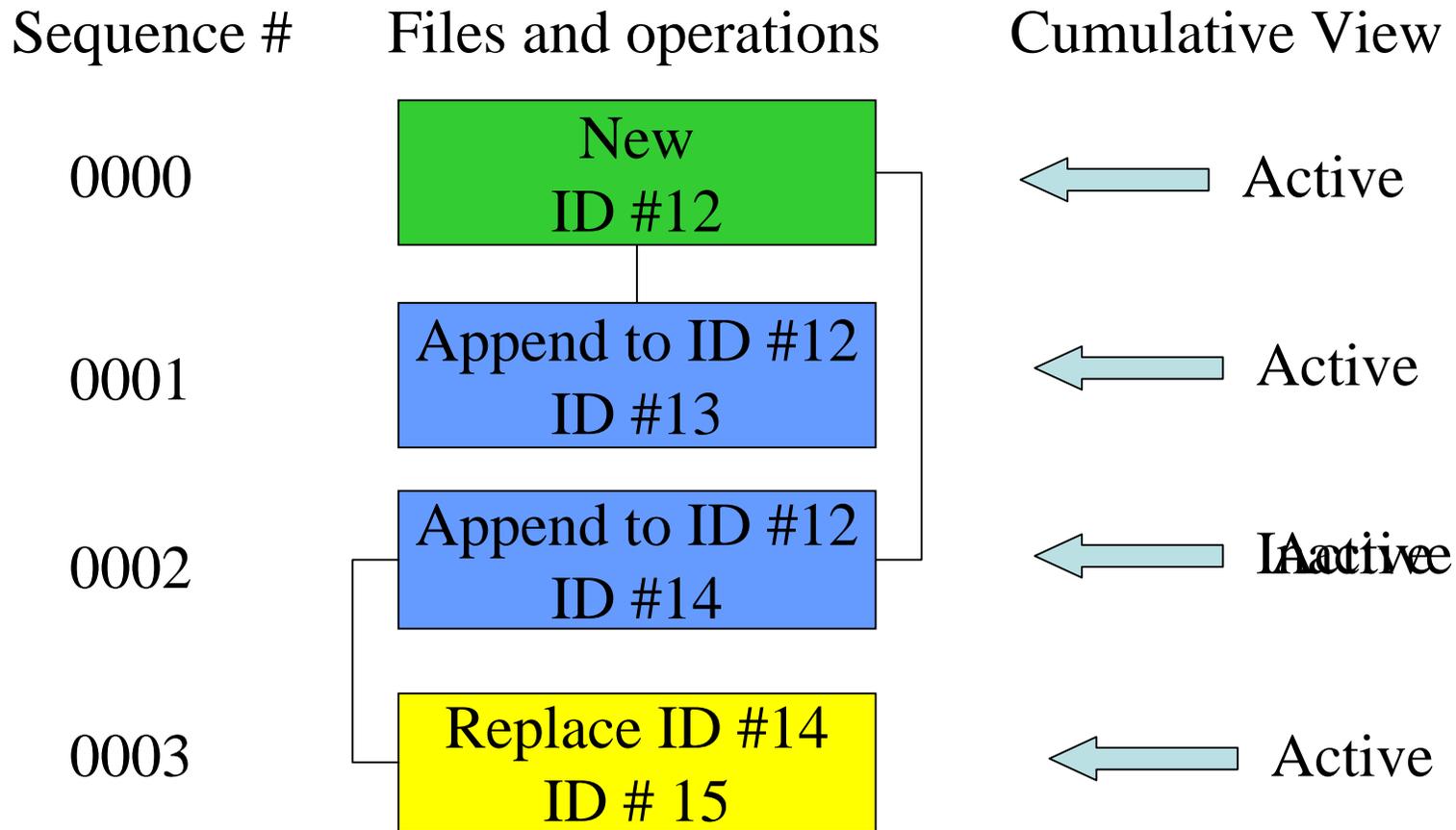
Document Life Cycle Scenario #4 Replace

Sequence #	Files and operations	Cumulative view

0000 — New ID #12 — Inactive ~~Active~~

0001 — Append to ID #12 ID #13 — Deleted ~~Active~~

0002 — Append to ID #12 ID #14 — Deleted ~~Active~~

0003 — Replace ID #12 ID # 15 — Active
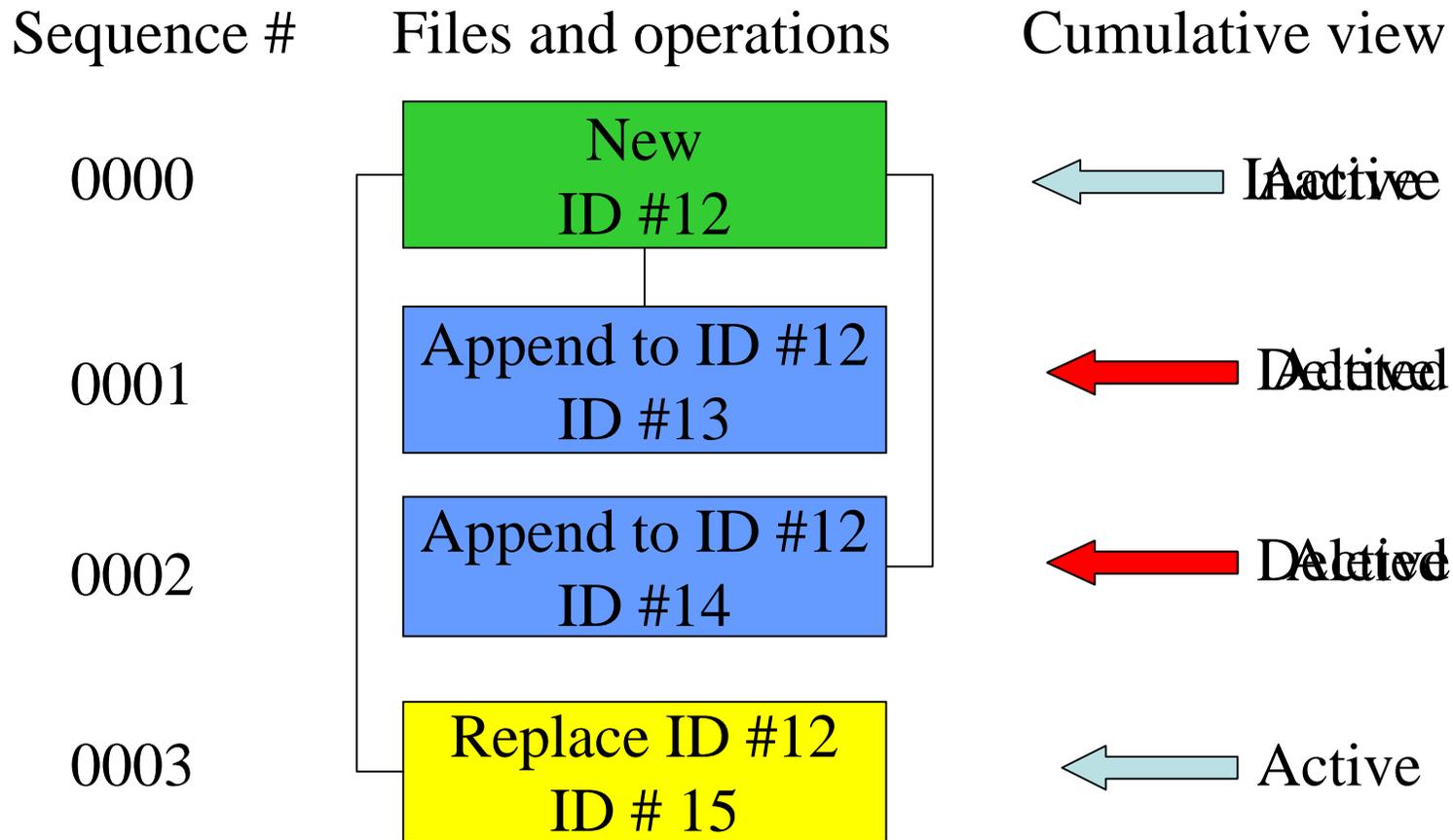
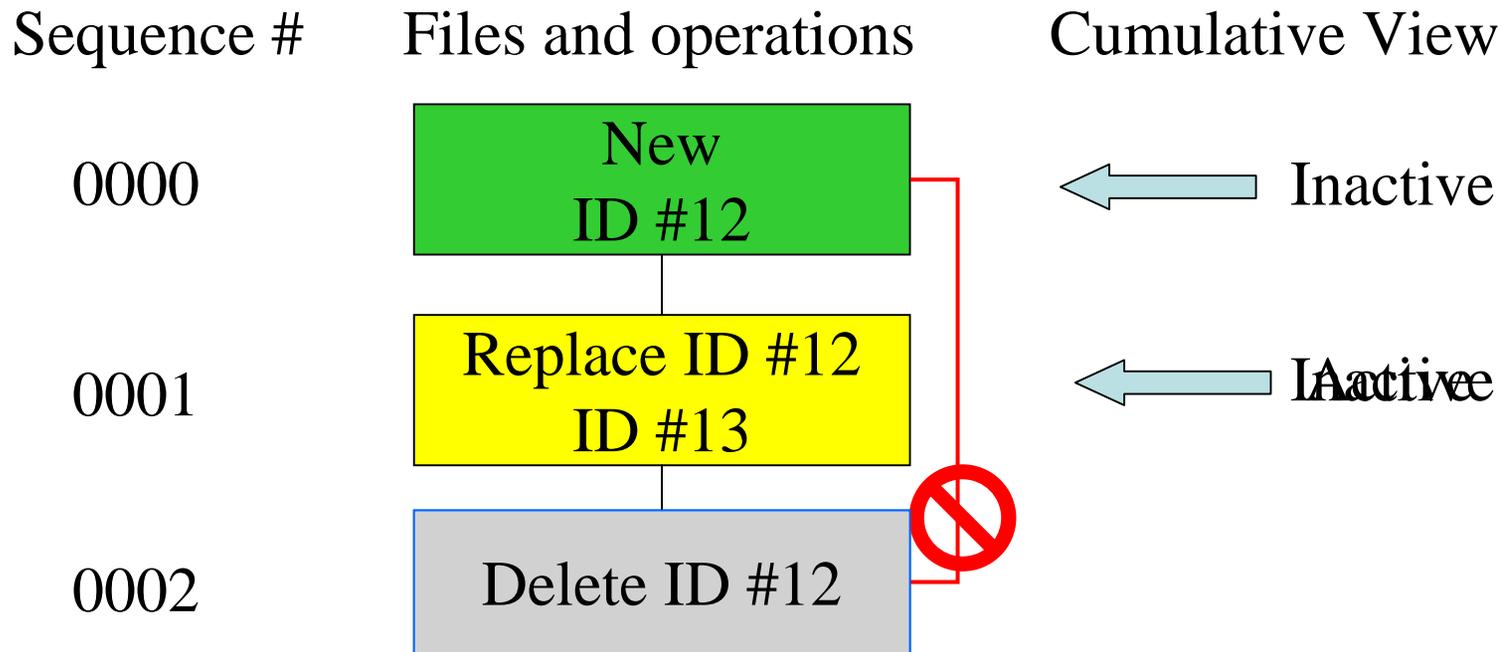**When replacing the original document any documents appended must be deleted**

Document Life Cycle Scenario #1 Delete
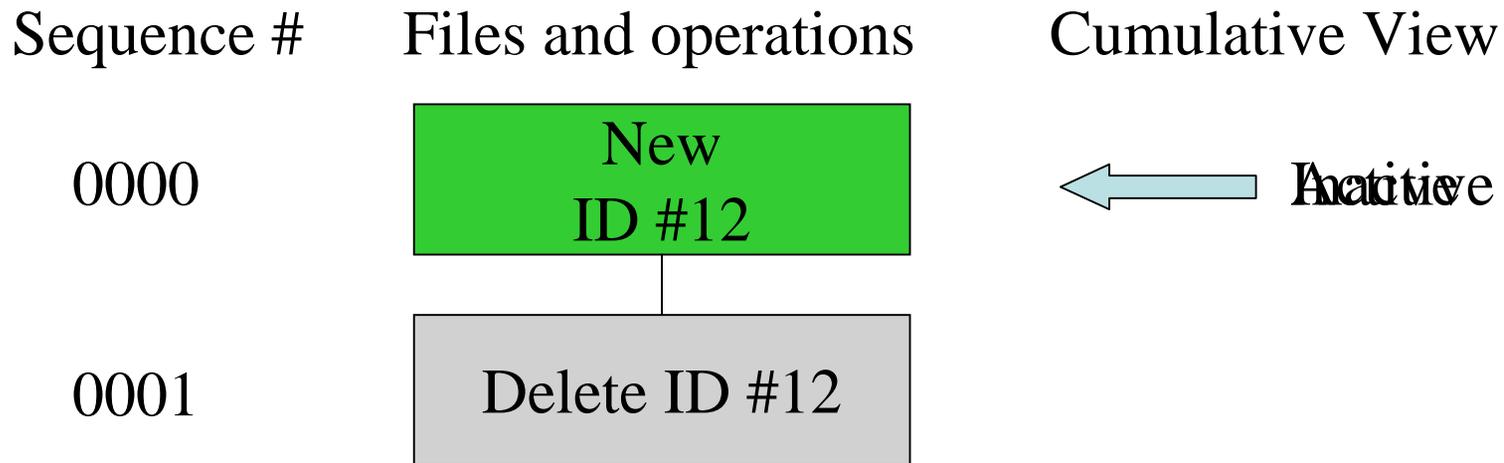
Sequence #	Files and operations	Cumulative View

0000

New
ID #12

Inactive

0001

Delete ID #12
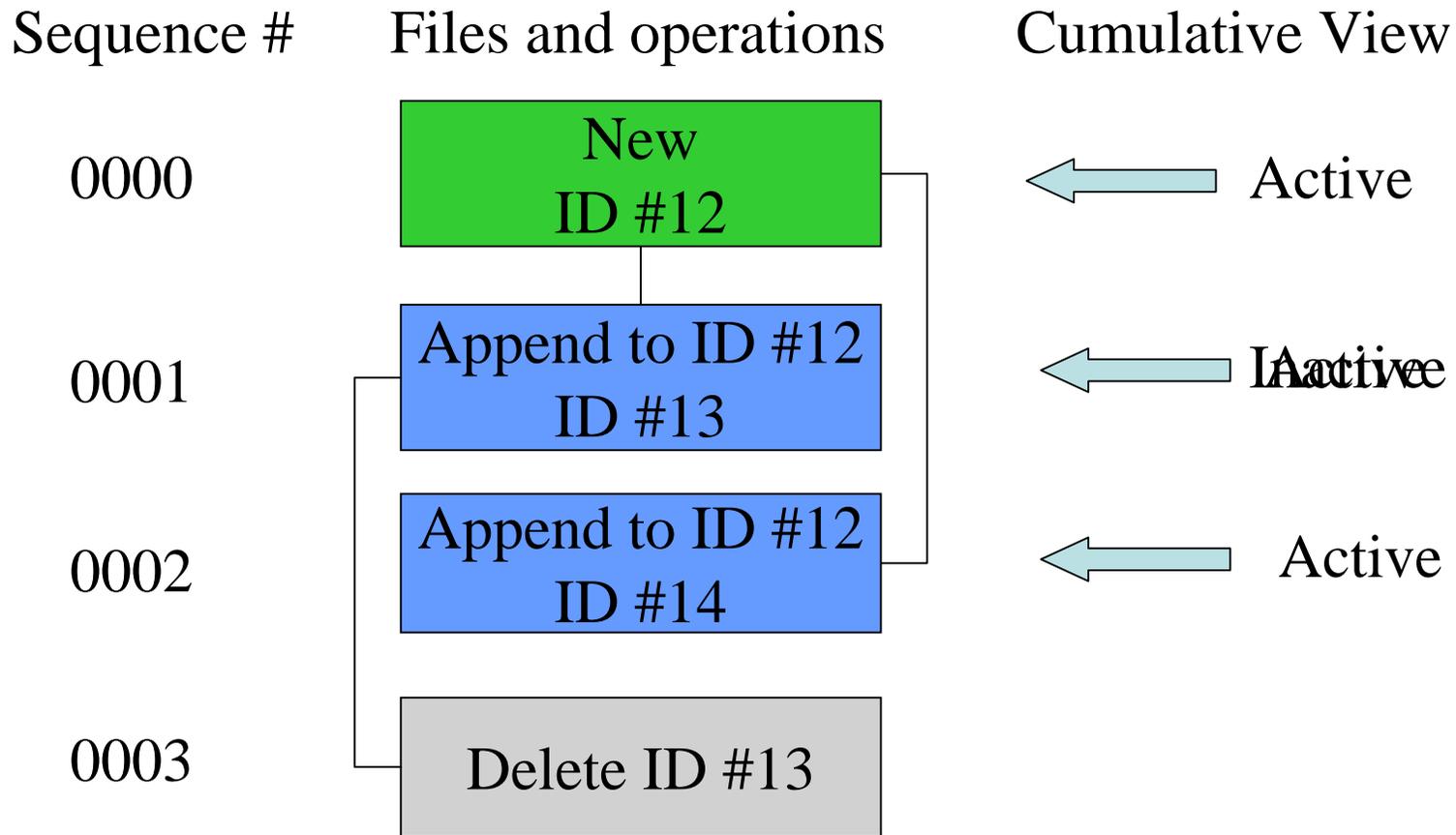
Document Life Cycle
Scenario #5 Delete

Sequence #	Files and operations	Cumulative view
0000	**New** ID #12	Inactive / Active
0001	Append to ID #12 ID #13	Deleted / Active
0002	Append to ID #12 ID #14	Deleted / Active
0003	Delete ID #12	
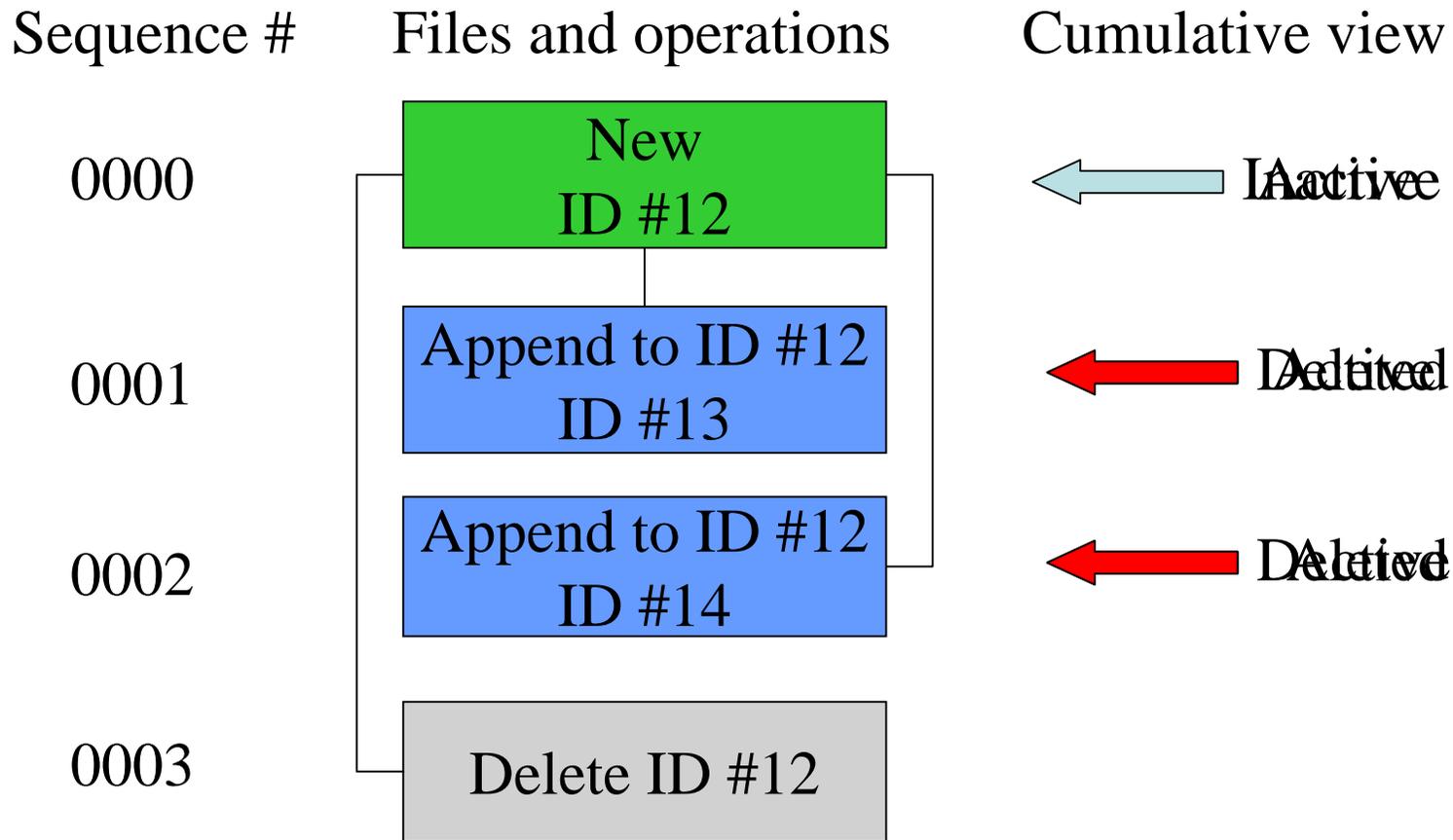
When deleting the original document any documents appended must be deleted

Document Life Cycle
Scenario Product Monograph (PM)

Sequence #	Files and operations			Cumulative view	
0000	NDS	PM	New	← Active	
0001	NDS / NON	PM	Replace	← Active	
0002	NDS / CFx	PM	Replace	← Active	
0003	NDS / Pristine	PM	Replace	← Active	**A**
0004	NC-1	PM	New	← Active	**P**
0005	NC-2	PM	New	← Active	**P**
0006	NC-2 / Pristine	PM	Replace	← Active	**A**
	Seq. 0003	PM	Delete		
0007	NC-1 / CFX	PM	Replace	← Active	**P**
0008	NC-1 / Pristine	PM	Replace	← Active	**A**
	Seq. 0006	PM	Delete		
0009	SNDS	PM	New	← Active	**P**
0010	SNDS / Pristine	PM	Replace	← Active	**A**
	Seq. 0008	PM	Delete		

Summary of Life Cycle Rules to Use for Operation Attribute (OA)

- All document life cycle start with OA [*New*]

- A document with OA [*Append*] should only be related to a document with the OA [*New*] or [*Replace*]

- A document with OA [*Replace*] will remove the document it replaced and delete any appended documents

- A document with OA [*Replace*] can be related to a document using OA [*New*], [*Append*] or [*Replace*]

- *OA* [*Delete*] will remove any appended documents related to the deleted document

- OA [*Delete*] will end any document life cycle

Other Refinements

- **Content**

  - Cover letter, Letter of Attestation

  - Labelling requirement for CD/DVD containing submissions in eCTD format

  - File formats, media, signatures

- **Editorial Changes**

  - Elimination of ambiguities

Key Messages

- **Read thoroughly the Guidance documents**

- **Request Technical pre-Submission Meeting**

- **File eCTD Sample**

- **QA your Submission in eCTD format**

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Questions?