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e-Review

Modernizing Canada's E-Regulatory System

Irena Pastorekova
Office of Submissions and Intellectual Property
Therapeutic Products Directorate

Outline

- Guidance Documents and Planned Revisions
- Areas of Deficiency or Insufficient Information in eCTD Format
- Validation Rules
- Update on How the Health Canada eCTD Viewing Tool is Used
  - ✓ Submission Management
  - ✓ Regulatory Information Management (RIM)
  - ✓ Electronic Workflow Management

Guidance Documents for Submissions in eCTD Format

- Creation of the Canadian Module 1 Backbone
  - ✓ Final version posted – September 2012
  - ✓ Revision to Table 4 planned for late 2014/early 2015
    - To be posted for comment period
- Canadian Module 1 Schema version 2.2
  - ✓ Final version 2.2 posted – July 2012
  - ✓ The old module 1 dtd 1.0 is no longer accepted
- Preparation of Drug Regulatory Activities in eCTD format
  - ✓ Structure and Content of the RAs and RTs in eCTD format
  - ✓ Life Cycle Management
  - ✓ Filing Process for Regulatory Transactions in eCTD format
- Preparation of Drug Regulatory Activities in CTD format
  - ✓ Structure of the Canadian module 1 and module 2-5
  - ✓ Examples of document placement in every section of module 1

Guidance Documents for Submissions in eCTD Format con't

- Notice – Validation Rules for Regulatory Transactions in eCTD format
  - ✓ Validation Rules implemented – August 2013
  - ✓ eCTD Validator - Profile HC-SC-3.0
  - ✓ Revision Planned for late 2014/early 2015
- Various Other Notices
  - ✓ Notice: Post NOC Changes: Level III changes
  - ✓ Notice: Instructions for Submitting Drug Notification Forms (DNFs)
  - ✓ Notice: Adoption of the ICH Guidance on PBRER
  - ✓ Notice: Pilot Project for the Implementation of DSUR

  <u>Will be consolidated in the final eCTD Guidance</u>

Pre-Submission Meeting Information

- The following Regulatory Activity Types should be used: MPNDS, MPSNDS, MPNC
- HC strongly recommends that Pre-Submission meeting information should be provided in eCTD format
- If you intend to submit the Pre-Submission Meeting Package in eCTD format the Request must be provided in eCTD format
- The whole Regulatory Activity could have the following transactions:
  - ✓ 0000 – Pre-Submission Meeting Request
  - ✓ 0001 – Pre-Submission Meeting Package
  - ✓ 0002 – Meeting Slides
  - ✓ 0003 – Priority Review Package (PRNDS)
  - ✓ 0004 – Draft Meeting Minutes
  - ✓ 0005 – Final Meeting Minutes
  - ✓ 0006 – NDS …….

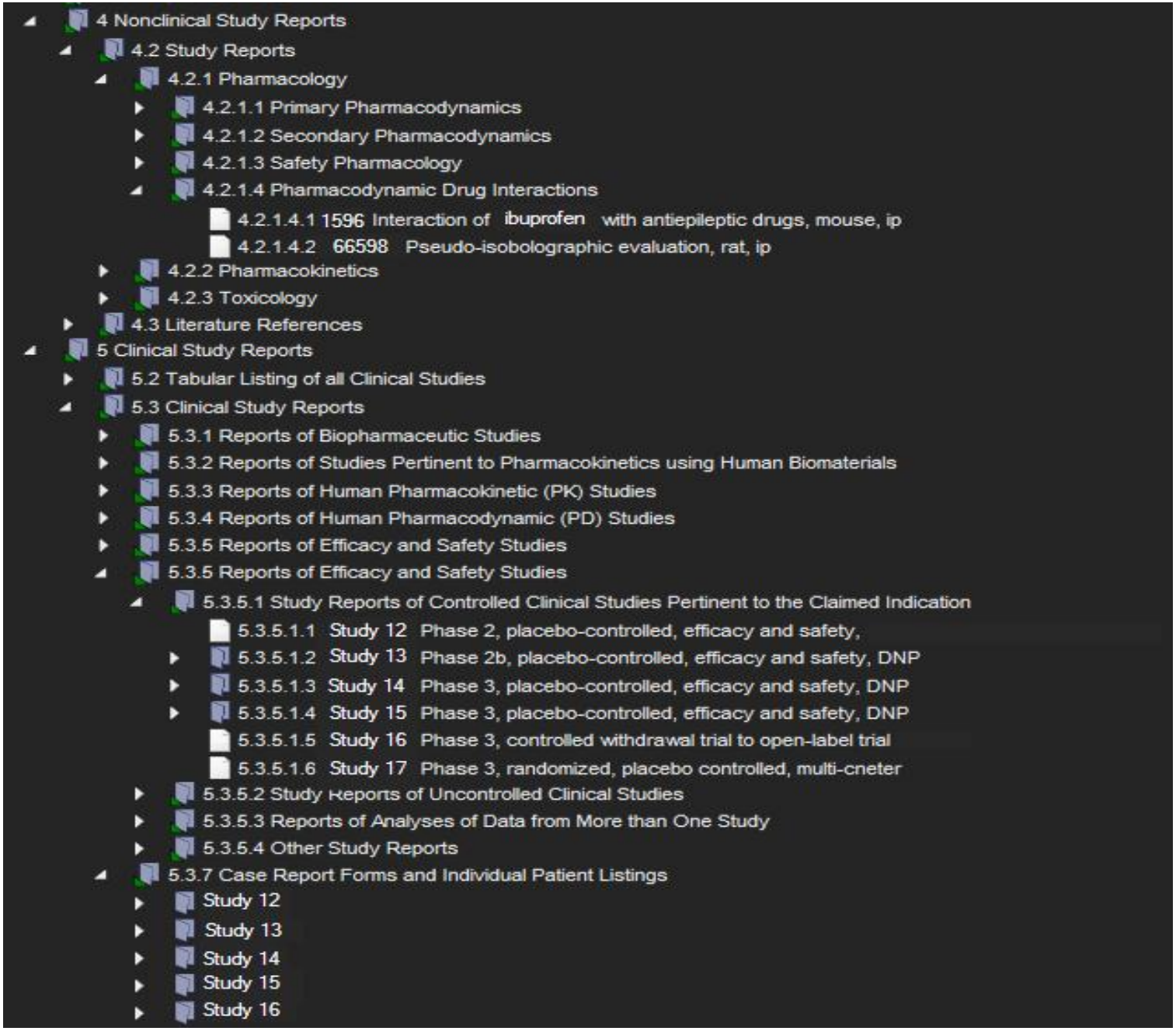
Post-NOC Pharmacovigilance Data

- The following Regulatory Activity types should be used: PSUR-PV, RMP-PV, UD-PV
- Even though MHPD might issue a single request, the requested information should be provided as separate Regulatory Activities:
  - ✓ PSUR-PV - as a separate eCTD sequence using the corresponding sequence description - For Period of Mmm. dd, yyyy to Mmm. dd, yyyy
  - ✓ RMP-PV – as a separate eCTD sequence using the corresponding sequence description - RMP version <number> dated Mmm. dd, yyyy
  - ✓ UD-PV – as a separate eCTD sequence using the corresponding sequence description - e.g Response to MHPD Requests dated Mmm. dd, yyyy, Risk communication document…..
- For PBRER use PSUR-PV as the Regulatory Activity type in the module 1 schema

Study Tagging Files and Node Extensions

- Health Canada accepts data organized using Study Tagging Files and Node extensions in module 4 and 5
- Study Tagging Files
  - ✓ Data has to be organized according to the ICH eCTD Specification v2.6.1
  - ✓ If STFs are used in module 4 and 5 then the CRFs should be built in the related STF and not submitted separately in 5.3.7
- Node extensions
  - ✓ If the **Study report** is broken into multiple pdf files
  - ✓ For **Case Report Forms** it is recommended to first organize them by study name then by site (CRFs have to be filed under *m5-3-7-case-reports-forms-and-individual-patient-listinigs* heading)
  - ✓ In Module 1 it can be used to organize data under *m1-2-7-International-Information* heading (to provide to HC a copy of information exchanged with EMA or FDA)

    Node extension should not be used under any other nodes in module 1
  - ✓ A consistent approach should be used when creating node extensions


4 Nonclinical Study Reports
4.2 Study Reports
4.2.1 Pharmacology
4.2.1.1 Primary Pharmacodynamics
4.2.1.2 Secondary Pharmacodynamics
4.2.1.3 Safety Pharmacology
4.2.1.4 Pharmacodynamic Drug Interactions
4.2.1.4.1 1596 Interaction of ibuprofen with antiepileptic drugs, mouse, ip
4.2.1.4.2 66598 Pseudo-isobolographic evaluation, rat, ip
4.2.2 Pharmacokinetics
4.2.3 Toxicology
4.3 Literature References
5 Clinical Study Reports
5.2 Tabular Listing of all Clinical Studies
5.3 Clinical Study Reports
5.3.1 Reports of Biopharmaceutic Studies
5.3.2 Reports of Studies Pertinent to Pharmacokinetics using Human Biomaterials
5.3.3 Reports of Human Pharmacokinetic (PK) Studies
5.3.4 Reports of Human Pharmacodynamic (PD) Studies
5.3.5 Reports of Efficacy and Safety Studies
5.3.5 Reports of Efficacy and Safety Studies
5.3.5.1 Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication
5.3.5.1.1 Study 12 Phase 2, placebo-controlled, efficacy and safety,
5.3.5.1.2 Study 13 Phase 2b, placebo-controlled, efficacy and safety, DNP
5.3.5.1.3 Study 14 Phase 3, placebo-controlled, efficacy and safety, DNP
5.3.5.1.4 Study 15 Phase 3, placebo-controlled, efficacy and safety, DNP
5.3.5.1.5 Study 16 Phase 3, controlled withdrawal trial to open-label trial
5.3.5.1.6 Study 17 Phase 3, randomized, placebo controlled, multi-cneter
5.3.5.2 Study Reports of Uncontrolled Clinical Studies
5.3.5.3 Reports of Analyses of Data from More than One Study
5.3.5.4 Other Study Reports
5.3.7 Case Report Forms and Individual Patient Listings
Study 12
Study 13
Study 14
Study 15
Study 16

Questions from Sponsors and eCTD requirements

- Use of Operation Attributes “new”, “replace”, “append”
  - ✓ Refer to section 4.3.4 general rules and 4.3.5 for specific examples
    - The use of an operation attribute depends on how the content of the document is managed
    - “Replace” – to be used when the additional information and the previously submitted information are provided as a consolidated document.
    - “Append” – when the additional information submitted is used to build upon previously submitted information, without resubmitting it.
    - Cover letter requirements – the operation attribute should be always “new”. “Replace” should be used when correcting an error in the letter
    - Submission Application Form (3011) – “new” should be used when provided with a new (initial) RA. “Replace” should be used when correcting an error in a 3011
    - Life Cycle Management Table - 0000 “new”, all other sequence numbers “replace”

Questions from Sponsors and eCTD requirements

- ✓ For the documents (such as: Risk Management Plan, CIPD…) that have changed location continue the life cycle using “replace” operation attribute
- ✓ ”Append” should not be used in module 1 - sections 1.0 to 1.5

  for the documents such as: Cover letter, Life Cycle Management Table, Post NOC change (Level III form)…
- ✓ How to provide corrections to Pristine Product Monograph
  - When correcting typos in the Pristine PM, “replace” should be used
  - If applicable the request from HC should be included in 1.0.3
  - The next version of the eCTD Guidance will include a complete revision of the operation attribute for the Product Monograph
- ✓ Second Language Product Monograph
  - For eCTD dossier always provide the second language PM as a sequence in eCTD format
  - When combining Pristine PM and Second Language PM, ensure that the cover letter indicates that both PMs are included

Questions from Sponsors and eCTD requirements

- Cross Referencing
  - ✓ Internal discussion to be held to confirm a consistent approach and provide examples. Outcome will be discussed in the next version of the eCTD Guidance document
    - File Reuse - could be used when cross referencing a full section from a previous sequence (e.g 3.2.S)
    - Hyperlink - could be used when cross referencing a single document from a previous sequence
    - Is the section or document that is cross referenced approved?
    - Which operation attributes to use when applying file reuse: “new” or “replace”
    - Parallel submission
  - ✓ For the time being, a case-by-case approach should be discussed with Health Canada

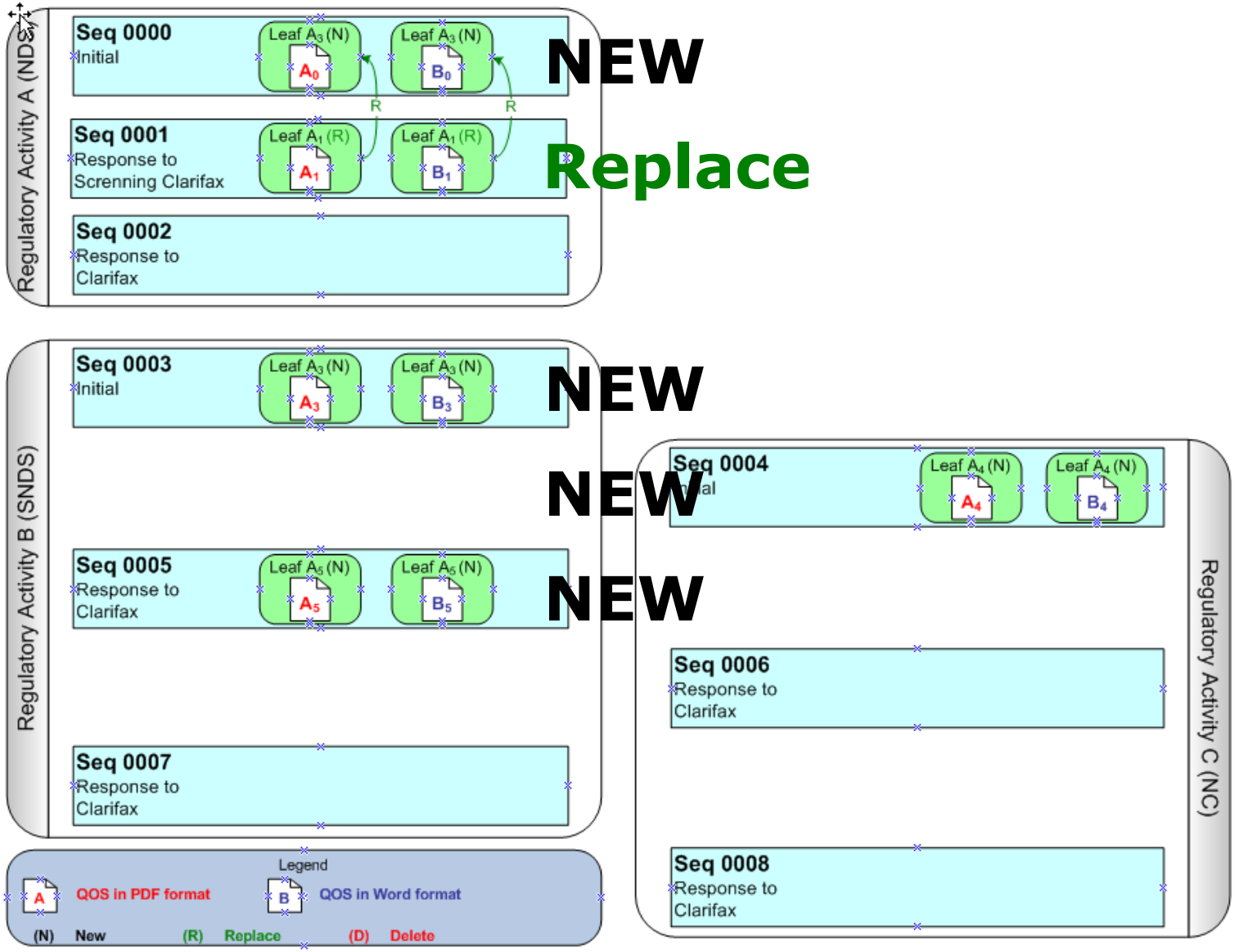
Questions from Sponsors and eCTD requirements

- How to handle multi-product submissions
  - ✓ Long term solution - eCTD version 4
  - ✓ For the time being, a case-by-case approach should be discussed with Health Canada
- Withdrawals
  - ✓ Internal discussion to be held to confirm a consistent approach and provide examples. Outcome will be discussed in the next version of the eCTD Guidance document
    - At what stage is the submission being cancelled/withdrawn
    - Is the submission being refiled at later time
    - Is the submission being refiled as a different submission type
  - ✓ For the time being, a case-by-case approach should be discussed with Health Canada

Questions from Sponsors and eCTD requirements

- Cover Letter Requirements as outlined in the eCTD Guidance
  - ✓ Most common deficiencies:
    - Dossier Identifier
    - Control number (if known)
    - Reason for filing
    - Regulatory Transactions that contain HC-SC3011 should include a table structured as recommended in the eCTD Guidance
    - Response to requests for clarification should clearly state the name of the requester
- Mailing Requirements
  - ✓ The printed cover letter should be provided with the media (CD, DVD, USB….)
  - ✓ Of course the preferred method of communication is the Gateway (CESG)

Lifecycle Management of the QOS



Element Attributes

- Element Attributes in module 2, module 3, and module 5 as per ICH eCTD Specification V 3.2.2 dated 16-July-2008

Table 6-9

Element	Attribute	Description/Instructions	Example
<m2-7-3-summary-of-clinical-efficacy>	indication	Name of the indication	Pain
<m5-3-5-reports-of-efficacy-and-safety-studies>	indication	Name of the indication.	Pain

Table 6-10

Element	Attribute	Description/Instructions	Example
<m3-2-s-drug-substance>	substance	Name of one of the drug substances	Acetaminophen
	manufacturer	Name of the manufacturer of the drug substance	My Supplier

Table 6-11

Element	Attribute	Description/Instructions	Example
<m3-2-p-drug-product>	product-name	Name of one of the drug products	Wonder drug
	dosageform	Dosage form	Capsule
	manufacturer	Manufacturer of the drug product	Company A

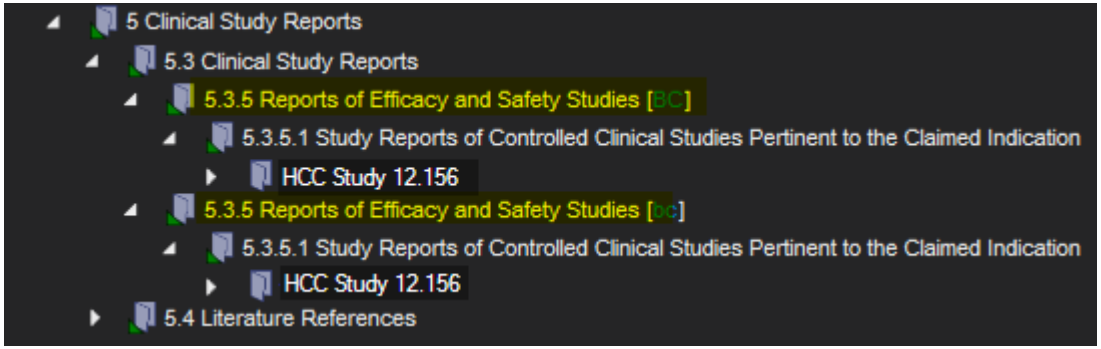
Element Attributes con't

- ✓ There is currently no standard terminology list for element attributes. Applicants should choose these attributes carefully as they can not be easily changed during the life cycle of the application
- ✓ The attributes are case sensitive: [Nausea] [nausea]
- ✓ Should not be changed when the company undergone company name change
- ✓ Typographical mistakes should not be corrected
- ✓ The attributes should be left as they have been written in the sequence of the original submission
  - Most likely sequence 0000 or a sequence higher if sequence 0000 was a pre-submission meeting
- ✓ Any slight modification to these attributes creates a duplicate node

Element Attributes (con't) Consequences

- Data for one study are found under more than one node

Example 1



- Data for one dosage form are found under more than one node

Example 2

Important message

“Once a sponsor files a regulatory activity in eCTD format, all additional information and subsequent regulatory activities for the same dossier should be filed in eCTD format. Sponsors should not revert to paper-based CTD format.”

- As stated in the current Draft Guidance Document: Preparation of Drug Regulatory Activities in eCTD format: All information related to a submission exchange with Health Canada must be provided as a sequence in eCTD format. Including:
  - ✓ Second language Product Monograph
  - ✓ Pristine Product Monograph
  - ✓ Response to e-mail clarification
  - ✓ Response to telephone request
  - ✓ Market notification (DNF and final labelling materials)
  - ✓ Correspondence with OPML
  - ✓ etc.

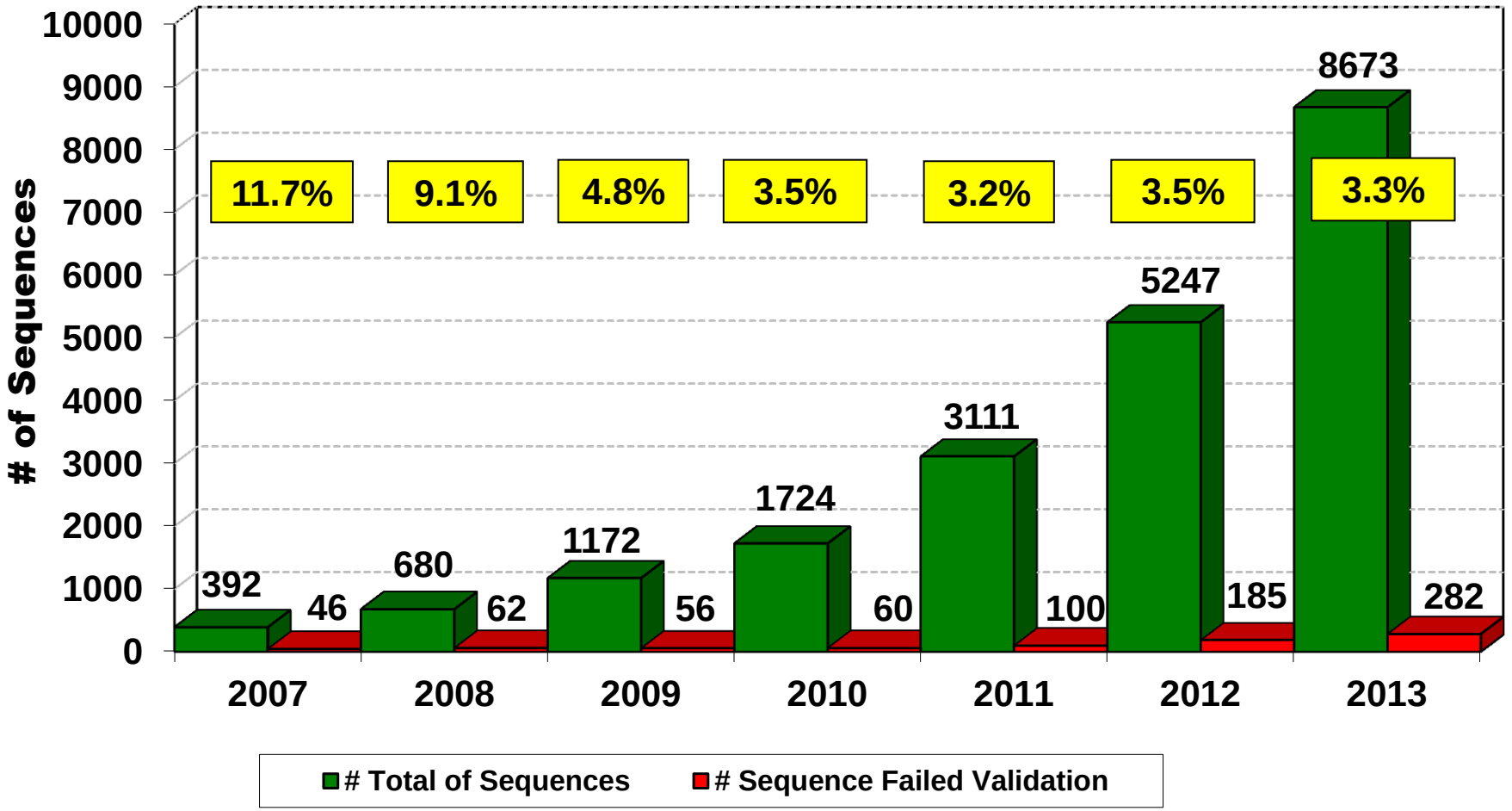
Validation rules and profile

Revision to Validation Rules for Regulatory Transactions in eCTD format planned for late 2014/early 2015

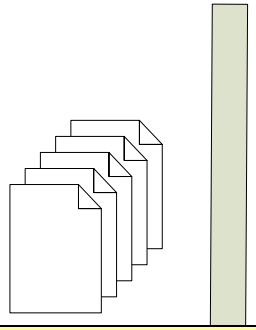
- Rules to be revised:
  - ✓ HREFs to target outside sequence
  - ✓ File Reuse
  - ✓ PDF protection: Owner password (eForms)
  - ✓ Replace or append should not provide identical content
- Common validation errors and warnings
  - ✓ Broken bookmarks and hyperlinks
  - ✓ Life Cycle Management Semantics
  - ✓ Unreferenced files, md-5 cheksum related errors
- In most cases those validation errors are caused by faulty burning process of data onto CD (media)
  - ✓ The eCTD sequence should be validated **after** burning the CD (media)

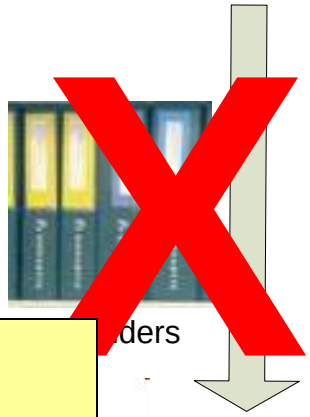
Sequences that Failed eCTD Validation

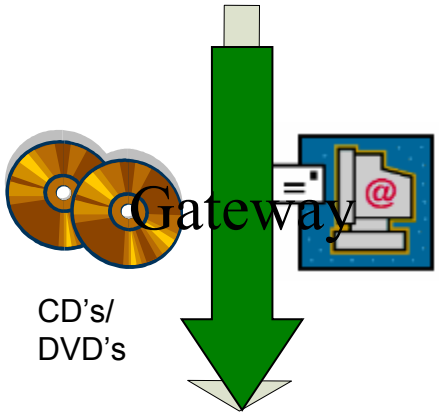
as of December 2013



Regulatory Data from Sponsors







Regulatory Information Generated by Health Canada

- **Administrative letters**
  - Acknowledgement
  - Acceptance
- **Clarification Requests** (clarifax)
- **Regulatory Notices**
  - SDN, NSN, NON, NOD, NOC
- **Regulatory Letters**
  - Refusal
  - Withdrawal
  - No Objection
- **Licences**
- **Review Reports**

Etc.

25,000 volumes

uction of Boxes received since 2005

(8465 → 1441) 83%

D (846 → 38) 95%

Off Site Storage

Viewing Tool

Regulatory Information Management (RIM) Project

Submission Management

Submissions that have been uploaded and managed in the Health Canada eCTD viewing tool:

- All submissions in eCTD format since 2006
- (CDs/DVDs) (electronic portion) received with paper-based submissions
  - ✓ Human Pharmaceutical and Biologic since May 2007
  - ✓ Pharmacovigilance since May 2009
  - ✓ Clinical Trial Applications since July 2008
  - ✓ Medical Device since July 2009
  - ✓ Veterinary Drugs since October 2011

Regulatory Information Management (RIM)

The RIM functionality of the eCTD viewing tool was implemented in the spring of 2012 for submission related documents generated by HPFB

Type of RIM Documents

- Regulatory Information Generated by Health Canada
- Templates used in the review process
- Foreign Information received directly from other regulators

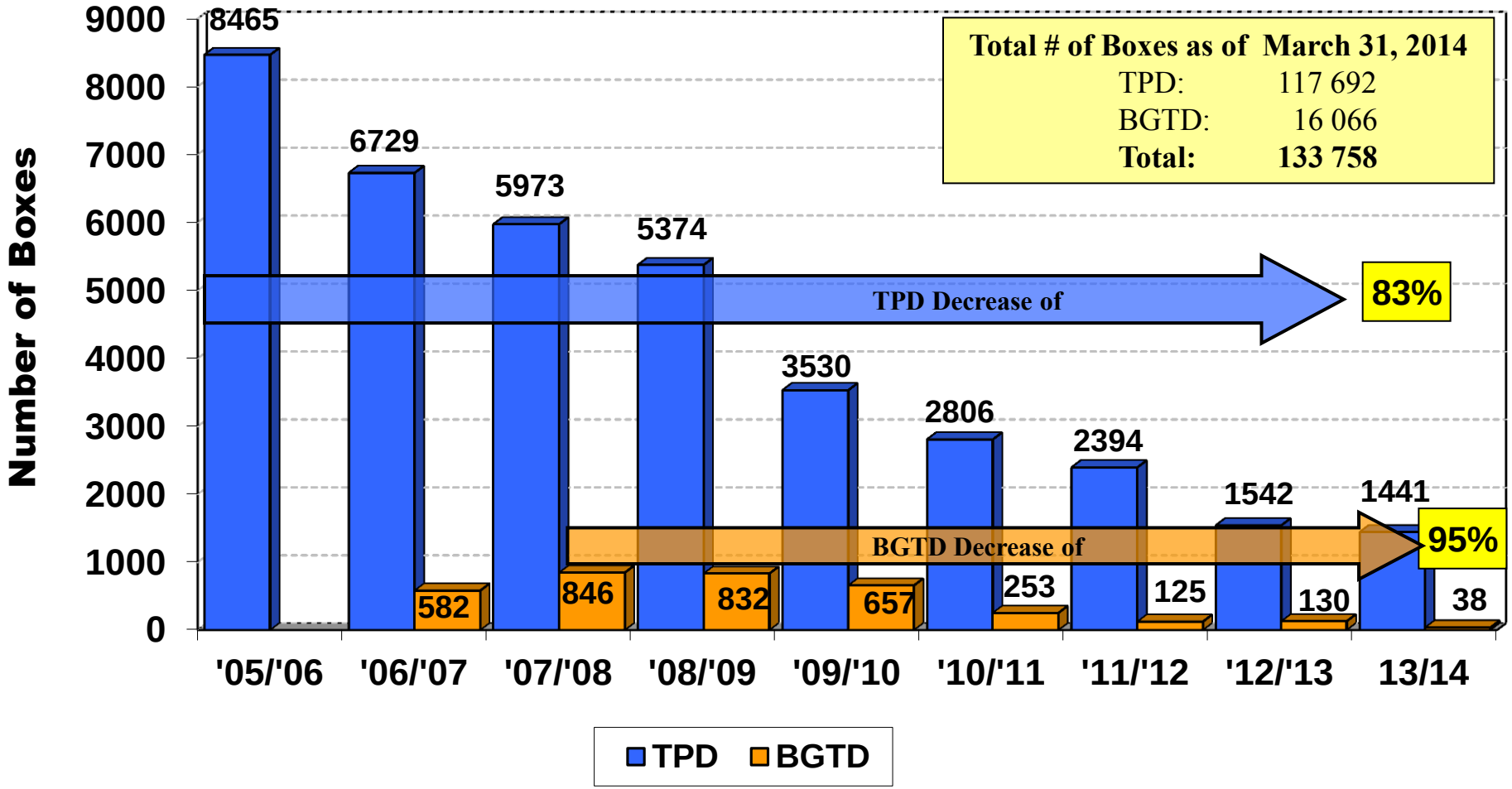
This new process provides many benefits:

- ✓ easy access of all documents
- ✓ complete life cycle management of information in one system
- ✓ eliminates printing and filing in paper-based Central Registry files;
- ✓ eliminates used of share drive for storage of transitory electronic copies of information

Electronic Workflow Management

- Implemented for the Notice Approval Process
  - ✓ Piloted for generic drugs July 2012-March 2013
  - ✓ As of April 1, 2013, in use for all pharmaceutical (including Administrative Submissions)
  - ✓ To follow: Biologic, Veterinary Drug, and Medical Device
  - ✓ Next Step: e-Signature and publishing e-Notice/e-Letter
- Implemented for the Medical Device Special Access Program since May 2013
- Will be implemented for Clinical Trial Notification and Site Information in June 2014
- Investigating as a replacement of the Review Folders (targeted for Summer 2014)

Number of Boxes of Submissions Received
per fiscal year between April 2005 and March 2014
Paper Reduction



Questions?

ereview@hc-sc.gc.ca