
Implementation of Regulatory
Information Submission Standards
(IRISS) eCTD Tool Interoperability
Group (ETIG) eCTD Tool
Interoperability and Compliance Study
III (ETICS III)

Phase 1 Health Canada
Compliance Report

ETICS 3- May 2011

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Disclaimer

Tests were independently designed & conducted collaboratively with a diverse group of community stakeholders from agencies, vendors and industry against available validation criteria. The study design is without regard to currently available software tools or known functionality that may, intentionally or unintentionally, cause bias to a single tool. The analyses of results were conducted and the reports written by volunteers from the pharmaceutical industry and CROs. ETICS III has an expanded scope vs. ETICS I/II and while we have compared analyses, you should be aware that there are new tests and new tools being tested. These comparisons were completed to allow an understanding of any trends in interpretation and adherence to available validation criteria over time.

Tool vendors who participated should not use their comparative results in promotional materials or public statements. It is acceptable to inform your customers or make public statements of support for the ETICS project or to indicate that your company participated. The IRISS ETIG ETICS III project is not a contest. We appreciate your support and participation as we continue to improve and expand on the ideals that created ETICS. We further hope you find these results valuable to your organization for internal discussions on interpretation of validation criteria and planning of software releases that provide value to your customers. We have released the full set of data in the event you find it useful to benchmark your own product, and appreciate your consumption of these results exclusively for internal use only, in the spirit of which ETICS III is intended and out of respect for the continuation of future efforts serving the eCTD community.

About IRISS

Implementation of Regulatory Information Submission Standards (IRISS) is a global, non-profit professional organization, dedicated to the implementation and widespread successful adoption of electronic regulatory submission standards around the world.

IRISS aims to accelerate the adoption of electronic submission standards by making experience and expertise available to its membership through an operating model commonly known as crowdsourcing.

- Issues are broadcast to a wide community of domain experts and novice users
- Solutions and points to consider are offered through the membership community
- Novice users benefit from lessons of experienced early adopters
- Development organizations can benefit from listening to trends and issues in the community of users
- All member organizations benefit from a wider pool of talent than exists within their own organization

IRISS-forum operates as an independent, neutral body. It is free from regional or vendor solution bias, and allows experts and novices alike, regardless of organizational affiliation, to gather and discuss, clarify and address pressing issues relevant to the successful adoption of a paperless regulatory environment for submissions.

Background

ETICS III is a project of the IRISS eCTD Tools Interoperability Group (ETIG). ETIG was launched in October 2008. The group's main purpose is to discuss eCTD building and viewing tools and the interoperability aspects between them. Membership is comprised of global regulators, vendors and industry affiliates who have an interest in making the eCTD a more common format. The IRISS eCTD Tool Interoperability group is a forum for discussion and resolution of eCTD interoperability issues. Discussion amongst the membership is based on ideas and concepts and is not tool or vendor specific. The group's [Concept Paper](#) provides further details.

Increasingly, there is a need to exchange eCTDs between tools, and hence interoperability remains important. Interoperability is achieved when the eCTD message created by one tool and received by another tool meets the following criteria:

- EITHER the eCTD is loadable / readable without significant errors
- OR the receiving tool correctly identifies and describes the impact of errors but the eCTD is still transferred with information integrity intact.

The consistency of submission building, the adherence to ICH and regional specifications and the ability to detect non-compliance with these specifications are all important factors. In the case of an eCTD submission prepared for Health Canada (HC), a significant error is one which indicates; a loss of information integrity; failure to follow ICH eCTD Q&A Question 36 rules (compliance); indicates failure to follow the *Health Canada (HC) eCTD Validation Rules eCTD Validator - Profile HC-SC-2.0 (November 13, 2007)*, or key requirements listed in the *Guidance for Industry: Preparation of Drug Submissions in the Electronic Common Technical Document (eCTD) Format (November 4, 2009)* and *Creation of the Canadian Module 1 eCTD Backbone File (June 28, 2004)*. To judge the significance of an error, issue or information generated by an eCTD validation tool, the error message itself must be clear, unambiguous and detailed.

Introduction

The selection of the potential non-conformities to be tested during Phase 1 was led by the ETICS III multi-regional team and later scoped down by the Canadian team. Since most of the ICH eCTD Q&A Question 36 rules were tested by the EU and US ETICS Phase 1 teams, the Canadian team focused primarily on the ability of the tools to detect non-conformities with Health Canada eCTD rules. The team analyzed the HC validation rules and guidance documents mentioned above and created a list with issues relating to HC requirements to be tested in Phase 1 of the project. The prepared samples tested the ability of the eCTD tools to detect only the most common and serious error conditions.

Table 1 displays the number of validation categories (severity) and number of samples which challenged them.

The baseline submission “e123456”, used as a starting point for all samples, was considered by the ETICS team to be compliant with current eCTD specifications and therefore should not have reported any warnings or errors. This submission was validated using HC validating software, and found error free.

Testing Methodology

The team provided vendors with 49 samples, each consisting of three sequences. Each sample was prepared using the baseline submission “e123456” and, except one, contained at least one error from the above mentioned list. Not all validation rules included in the HC document were included in testing, as some of these rules refer to the internal HC system notifications. In addition, please note that some testing cases incorporated into samples may cover more than one validation rule, and that some rules are challenged with more than one sample.

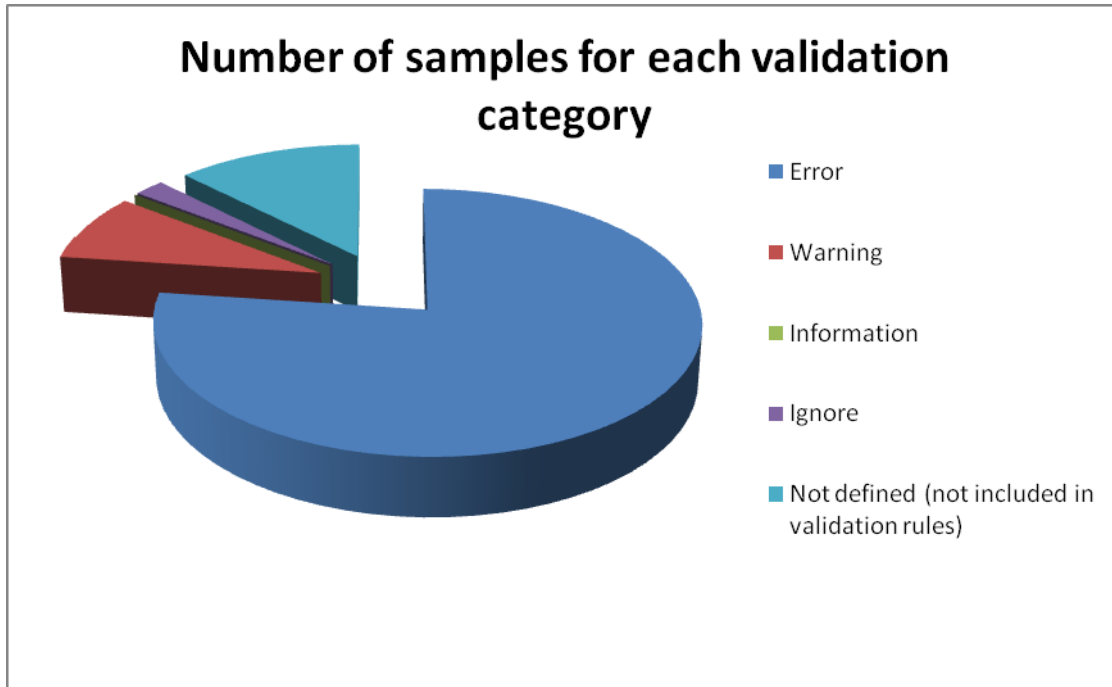
Table 3, Table 4, Table 5, Table 6, Table 7, Table 8, and Table 9 describe test cases grouped by the validation rule options. They also describe in detail the ways samples were modified to express individual errors. Participating tool vendors assessed these submissions and reported their findings. These findings are analysed in Results section.

Table 1: Number of Submissions for Each Validation Category (Severity)

Validation Category (Severity)	Number of Samples
Error	38
Warning	4
Information	0
Ignore	1
Not defined (not included in HC validation rules)	5
Total number of samples analyzed	48¹

¹ Please note that the team prepared 49 samples. One sample did not contain any errors.

Figure 1: Number of Samples for Each Validation Category (Severity)



The *Health Canada (HC) eCTD Validation Rules* document organizes validation rules into primary and secondary options. The primary options are those that affect any eCTD and consist of four categories: General, PDF Analysis, Referenced Files, XML Files. The secondary options are based on regional requirements and include: ICH, Canada Module 1. Table 2 summarizes the number of samples for each validation option.

Please note that categories of ICH Backbone - 3.00, STF - 2.0 were not included in the ETICS III testing, as although they are still included in the validation rules, are generally considered to be obsolete.

The category of STF - 2.2, was extensively tested by the US team, and was also excluded from Canadian samples.

Table 2: Number of Samples prepared for Each Validation Category (Severity)

	No. of samples	No. of samples with errors	No. of samples with warnings	No. of samples with ignore	No. of samples with Information
<i>Primary Options</i>					
General (Table 3)	1	1	-	-	-
PDF Analysis (Table 4)	10	9	-	1	-
Referenced Files (Table 5)	5	5	-	-	-
XML Analysis (Table 6)	1	1	-	-	-
<i>Secondary Options</i>					
CA Regional 1.0 (Table 7)	21	18	3	-	-
ICH Backbone 3.2 (Table 8)	5	4	1	-	-
<i>Not included in HC validation rules</i>					
Not defined	5	N/A	N/A	N/A	N/A
Total	48	38	4	1	-

The Primary Options

Table 3: General

Sample ID No.	HC rule ID No.	Severity	Tested HC rule	Modifications to the sample	Expected outcome
ca-015	5	error	Sequence Folder Requirements (...) Sequence number 0000 for initial sequence?	Sequence 0000. Modify ca-regional.xml from <sequence-number>0000</sequence-number> to <sequence-number>0003</sequence-number>, and modify sequence level folder from 0000 to 0003	Initial sequence should have sequence number 0000 (error)

Table 4: PDF Analysis

Sample ID	HC rule ID No.	Severity	Tested HC rule	Modifications to the sample	Expected outcome
ca-038	8	error	Bookmarks - Absolute (Rooted), broken Retrieves all broken non-relative bookmarks from PDF documents and prints the total count.	Sequence 0000. In qos.pdf create an absolute destination bookmark.	Absolute destination bookmark found in the document qos.pdf (error)
ca-039	8	error	Bookmarks - Absolute (Rooted), broken Retrieves all broken non-relative bookmarks from PDF documents and prints the total count.	Sequence 0000. In qos.pdf create a bookmark pointing to a page added to the end of the document. Then delete the page.	Broken bookmark found in the document qos.pdf (error)
ca-040	10	error	Bookmarks - Inactive Retrieves all inactive bookmarks from PDF documents and prints the total count.	Sequence 0000. Create a bookmark in qos.pdf. In the bookmark properties go to the Actions Tab and delete any action.	Inactive bookmark found in the document qos.pdf (error)
ca-041	14	error	Bookmarks - Intra Application, broken Retrieves all broken intra-application hyperlinks from PDF documents and prints the total count.	Sequence 0000. In qos.pdf create an absolute external bookmark pointing to a file on the desktop.	Absolute destination bookmark found in the document qos.pdf (error)

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Sample ID	HC rule ID No.	Severity	Tested HC rule	Modifications to the sample	Expected outcome
ca-042	19	error	Hyperlinks - Absolute (Rooted), broken Retrieves all broken non-relative hyperlinks from PDF documents and prints the total count.	Sequence 0000. In qos.pdf create an absolute destination hyperlink.	Absolute destination hyperlink found in the document qos.pdf (error)
ca-044	21	error	Hyperlinks - Inactive Retrieves all inactive hyperlinks from PDF documents and prints the total count.	Sequence 0000. In qos.pdf create a hyperlink. In the hyperlink properties go to the Actions Tab and delete any action.	Inactive hyperlink found in the document qos.pdf (error)
ca-043	23	error	Hyperlinks - Inter Application, broken Retrieves all broken inter-application hyperlinks from PDF documents and prints the total count.	Sequence 0000. Create a hyperlink pointing to a page added to the end of the document. Then delete the page.	Broken hyperlink found in the document qos.pdf (error)
ca-045	24	error	Hyperlinks - Intra Application Retrieves all intra-application hyperlinks from PDF documents and prints the total count. (...)	Sequence 0000. In qos.pdf create an external hyperlink pointing to a file on the desktop.	Intra application link found in qos.pdf file (error)
ca-046	29	ignore	PDF Optimization Any PDF documents that are not optimized (not linearized)?	Sequence 0000. Make a change in a qos.pdf document (i.e. delete a bookmark) and save. Make sure that the document is not optimized.	Document qos.pdf is not optimized (message)
ca-048	30	error	PDF Protection Any PDF documents with a password protection set?	Sequence 0000. Password-protect qos.pdf. In "Document properties" window select "Security" tab and in "Security method" select Password security. Apply password.	Document qos.pdf is password protected (error)

Table 5: Referenced Files

Sample ID	HC rule No.	Severity	Tested HC rule	Modifications to the sample	Expected outcome
ca-028	34	error	Life Cycle Management Semantics (...) The eCTDValidator checks that all files referenced in the backbone exist.	Sequence 0000. Delete the 0000-ca-m131-pm.pdf document from the dossier.	File 0000-ca-m131-pm.pdf listed in an index does not exist (error)
ca-036	34	error	Life Cycle Management Semantics (...) The eCTDValidator checks modified files in LCM: leaf in previous sequence must exist. It also verifies that when the attribute "modified-file" has been used for a leaf document then the referenced document exists in the previous submission. (...)	Sequence 0001. Change the leaf ID for 0001\m2\22-intro. Change <m2-2-introduction> to the following: <m2-2-introduction> <leaf xmlns:xlink="http://www.w3c.org/1999/xlink" ID="a021" application-version="PDF 1.4" operation="replace" font-library="TimesNewRoman" xml:lang="en" checksum="1e746410e8e4b61098cdd4f0e0bf880d" checksum-type="md5" xlink:href="m2/22-intro/introduction.pdf" modified-file="../0000/index.xml#a0b09"> <title>CTD Introduction</title></leaf></m2-2-introduction>	No referenced file file="../0000/index.xml#a0b09" with ID a0b09 exists (error)
ca-019	36	error	Naming Syntax Checks the syntax all referenced file names (path length, illegal characters, etc.).	Sequence 0002. Modify href in index.xml in <m5-3-5-1-study-reports-of-controlled-clinical-studies-pertinent-to-the-claimed-indication> xlink:href value from xlink:href="m5/53-clin-stud-rep/535-rep-effic-safety-stud/confusion/5351-stud-rep-contr/etics-1/report-rev.pdf" to xlink:href="m5/53-clin-stud-rep/535-rep-effic-safety-stud/common-and-severe-neuropsychiatric-syndrome-with-core-features-of-acute-onset-and-fluctuating-course-and-attentional-deficits/5351-stud-rep-contr/study-report-etics-1/report-rev.pdf". Modify folder names accordingly.	Pathway exceeds allowed length limit message (error)

Sample ID	HC rule No.	Severity	Tested HC rule	Modifications to the sample	Expected outcome
ca-020	36	error	Naming Syntax Checks the syntax all referenced file names (path length, illegal characters, etc.).	Sequence 0000. Modify href in ca-regional.xml from <m1-2-1-drug-submission-application> from xlink:href="0000-ca-m121-hc-sc-3011-en.pdf" to xlink:href="0000-ca m121-hc-sc-3011-en.pdf"	Illegal character in file name found message (error)
ca-029	38	error	Unreferenced Files Searches for files not referenced in an index file (ICH, Regional or STF).	Sequence 0000. Add a file (test.pdf) under 0000\m1\ca	File test.pdf located in 0000\m1\ca is not referenced in an index file (error)

Table 6: XML Analysis

Sample ID	HC rule No.	Severity	Tested HC rule	Modifications to the sample	Expected outcome
ca-017	42	error	Validate against delivered DTD Performs XML validation for ICH Backbone and Regional backbones. Uses the DTD or Schema given in the application folder (util/dtd).	Sequence 0000. Modify ca-regional.xml from <!DOCTYPE hcsc:ectd SYSTEM "../util/dtd/ca-regional-1-0.dtd"> to <!DOCTYPE hcsc:ectd SYSTEM "../util/dtd/ca-regional-1-1.dtd">	No DTD ca-regional-1-1.dtd found message (error)

The Secondary Options

Table 7: CA Regional 1.0

Sample ID	HC rule No.	Severity	Tested HC rule	Modifications to the sample	Expected outcome
ca-035	47	error	Attribute Check-sum Type The checksum-type attribute must have the value md5 or MD5.	Sequence 0000. Change the checksum-type attribute value for a leaf in Module 1 from MD5 to SHA1. <m1-administrative-information-and-prescribing-information> <leaf ID="a003" operation="new" checksum="28f43814d7579fab847c66890816ca25" checksum-type="SHA1" xlink:href="0000-ca-m1-cover-letter.pdf" xlink:type="simple">	Wrong checksum type used for the file 0000-ca-m1-cover-letter.pdf (error)
ca-006	48	error	Attribute Submission Type Checks if the submission-type attribute is present.	Sequence 0001. Modify ca-regional.xml from <ectd-submission-info submission-type="NDS"> to <ectd-submission-info submission-type="">	Invalid submission type (error)
ca-007	48	error	Attribute Submission Type Checks if the submission-type attribute is present.	Sequence 0000. Modify ca-regional.xml from <ectd-submission-info submission-type="NDS"> to <ectd-submission-info submission-type="NDA">	Invalid submission type (error)
ca-032	50	warning	Element 3011 form = {en/fr} Checks that the 3011 form is named hc-sc-3011-en.pdf in the English version, or hc-sc-3011-fr.pdf in the French version.	Sequence 0000. Change the filename to hc-sc-3011.pdf	Wrong file name hc-sc-3011.pdf present (warning)
ca-001	51	warning	Element applicant Checks if the attribute value is present.	Sequence 0001. Modify ca-regional.xml from <applicant>ETICS III Canada</applicant> to <applicant></applicant>	Missing applicant value (warning)

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Sample ID	HC rule No.	Severity	Tested HC rule	Modifications to the sample	Expected outcome
ca-034	52	error	Element must have leafs Checks for elements not having any leaf child nodes. This only affects elements with a name that starts with 'm'.	Sequence 0000. Modify ca-regional.xml <m1-3-1-product-monograph> section to the following <m1-3-1-product-monograph> <annotated-pm> <leaf ID="a006" operation="new" checksum="aee1d33c916243404ac74c4c0f47f6e6" checksum-type="MD5" xlink:href="0000-ca-m131-annotated-pm.pdf" xlink:type="simple"> <title>Annotated Product Monograph</title> </leaf> </annotated-pm>	Element <m1-3-1-product-monograph>, expected leaf element not present (error)
ca-002	53	warning	Element product-name Checks if the attribute value is present.	Sequence 0000. Modify ca-regional.xml from <product-name>eticsamycin</product-name> to <product-name></product-name>	Missing product name value (warning)
ca-014	56	error	Element sequence- number The value of the sequence-number element must match the sequence folder name.	Sequence 0001. Modify ca-regional.xml from <sequence-number>0001</sequence-number> to <sequence-number>0002</sequence-number>. The sequence level folder should stay named 0001	Sequence number value does not match the sequence folder name (error)
ca-012	57	error	Element sequence-number format The value of the sequence-number element must consist of 4 digits.	Sequence 0002. Modify ca-regional.xml from <sequence-number>0002</sequence-number> to <sequence-number>002</sequence-number>	Wrong sequence number format (error)
ca-013	57	error	Element sequence-number format The value of the sequence-number element must consist of 4 digits.	Sequence 0002. Modify ca-regional.xml from <sequence-number>0002</sequence-number> to <sequence-number>002a</sequence-number>	Wrong sequence number format (error)
ca-003	58	error	Element submission-date The value of the submission-date element must be given in format YYYY-MM-DD	Sequence 0002. Modify ca-regional.xml from <submission-date>2010-04-17</submission-date> to <submission-date></submission-date>	Missing submission date value (error)

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Sample ID	HC rule No.	Severity	Tested HC rule	Modifications to the sample	Expected outcome
ca-004	58	error	Element submission-date The value of the submission-date element must be given in format YYYY-MM-DD	Sequence 0000. Modify ca-regional.xml from <submission-date>2010-04-15</submission-date> to <submission-date>20100415</submission-date>	Wrong submission date format (error)
ca-005	58	error	Element submission-date The value of the submission-date element must be given in format YYYY-MM-DD	Sequence 0000. Modify ca-regional.xml from <submission-date>2010-04-15</submission-date> to <submission-date>2010-15-04</submission-date>	Wrong submission date format (error)
ca-008	59	error	Element submission-identifier format The value of the application-identifier element must start with an e, followed by 6 digits.	Sequence 0000. Modify ca-regional.xml from <submission-identifier>e123456</submission-identifier> to <submission-identifier>123456</submission-identifier>	Wrong submission identifier format (error)
ca-009	59	error	Element submission-identifier format The value of the application-identifier element must start with an e, followed by 6 digits.	Sequence 0000. Modify ca-regional.xml from <submission-identifier>e123456</submission-identifier> to <submission-identifier>e12345</submission-identifier>	Wrong submission identifier format (error)
ca-010	59	error	Element submission-identifier format The value of the application-identifier element must start with an e, followed by 6 digits.	Sequence 0000. Modify ca-regional.xml from <submission-identifier>e123456</submission-identifier> to <submission-identifier>e12345o</submission-identifier>	Wrong submission identifier format (error)
ca-011	60	error	Element submission-identifier value The value of the application-identifier element must match the application folder name.	Sequence 0000. Modify ca-regional.xml from <submission-identifier>e123456</submission-identifier> to <submission-identifier>e123556</submission-identifier>. The root folder name should stay named e123456	Submission identifier value does not match the application folder name (error)
ca-021	60	error	Element submission-identifier value The value of the application-identifier element must match the application folder name.	All sequences. Place all three sequences in folder called "nds"	Submission identifier value does not match the application folder name (error)

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Sample ID	HC rule No.	Severity	Tested HC rule	Modifications to the sample	Expected outcome
ca-024	61	error	Folder m1\ca exists The folder m1\ca must exist.	Sequence 0000. Delete folder ca	Folder m1\ca does not exist (error)
ca-025	63	error	Module 1 (regional xml file) exists The regional backbone ca-regional.xml file must exist in folder m1\ca.	Sequence 0002. Move ca-regional.xml file to m1 folder.	Regional backbone ca-regional.xml does not exist in m1\ca folder (error)
ca-026	63	error	Module 1 (regional xml file) exists The regional backbone ca-regional.xml file must exist in folder m1\ca.	Sequence 0001. Modify ca-regional.xml file name to regional.xml	Regional backbone ca-regional.xml does not exist in m1\ca folder (error)

Table 8: ICH Backbone - 3.2

Sample ID	HC rule No.	Severity	Tested HC rule	Modifications to the sample	Expected outcome
ca-033	94	error	Element must have leafs Checks for elements not having any leaf child nodes. This only affects elements with a name that starts with 'm'.	Sequence 0002. In index.xml include the following: <m3-quality> <m3-2-body-of-data> </m3-2-body-of-data></m3-quality>	Element </m3-2-body-of-data> has no leaf child node (error)
ca-018	95	error	File index.xml exists The index.xml file must be present	Sequence 0001. Delete index.xml file	No index.xml found message (error)
ca-022	102	error	Folder util exists The util folder must be present	Sequence 0000. Delete folder util	Folder util does not exists (error)
ca-027	104	error	m1-administrative element must exist The element m1-administrative-information-and-prescribing information must be present.	Sequence 0002. Remove opening and closing tag <m1-administrative-information-and-prescribing-information> from ca-regional.xml	m1-administrative element does not exist (error)
ca-016	109	warning	Regional backbone(s) referenced operations Regional backbone(s) referenced (ca-regional.xml) should have 'new' operation attribute.	Sequence 0002. Modify index.xml from <leaf xmlns:xlink="http://www.w3c.org/1999/xlink" ID="a026" operation="new" checksum="2a1d405221e15556593cab62a2322262" checksum-type="md5" xlink:href="m1/ca/ca-regional.xml"> to <leaf xmlns:xlink="http://www.w3c.org/1999/xlink" ID="a026" operation="replace" checksum="2a1d405221e15556593cab62a2322262" checksum-type="md5" xlink:href="m1/ca/ca-regional.xml" modified-file="../0001/index.xml#a018">	Regional backbone referenced (ca-regional.xml) should have 'new' operation attribute (warning)

Requirements Not Included in the Validation Criteria Document but Specified in the eCTD Guidance.

The ETICS team created submissions which were technically valid but contained real world “issues” which have or could cause review or lifecycle integrity issues.

Table 9: Rules not Included in HC Validation Rules, but Listed in the eCTD Guidelines

Sample ID	HC rule No.	Tested issue	Modifications to the sample	Expected outcome
ca-030	N/A	Item tested: no subfolders created in ca regional folder	Sequence 0000. Create a 'test' subfolder under 0000\m1\ca and place a 'test.pdf' document underneath. Modify relevant href in ca-regional.xml	No subfolders should be included in m1\ca folder. Folder 'test' found (message)
ca-031	N/A	Item tested: System is able to accept dataset file formats (*.dat and *.inf)	Sequence 0000. Add two files 0000-ca-m128-etics-tab-et104-pk.dat and 0000-ca-m128-etics-tab-et104-pk.inf to "m1/ca" folder. Modify index accordingly	No error/warning message referring wrong file extension generated
ca-037	N/A	Item tested: Consecutive sequences should have consecutive sequence number	Change number for sequence 0002 to 0006. Modify folder name and ca-regional.xml.	Sequence number should be consecutive (or similar message)
ca-047	N/A	Item tested: PDF documents should be in Adobe Acrobat, version 5.0, 6.0, or 7.0	Sequence 0000. Save qos.pdf to version of PDF lower than 5.0 by opening a PDF file and going to file/reduce file size and select under "Make compatible with": "Acrobat 4.0 and later".	Document qos.pdf is in not allowed PDF version.
ca-049	N/A	Item tested: MS Word files with restricted access permission	Sequence 0000. Password-protect the file 0000-ca-m131-nonannotated-pm.doc by opening a Word file and going to tools/security and adding a password.	Document 0000-ca-m131-nonannotated-pm.doc is password protected (error)

(1) Not applicable

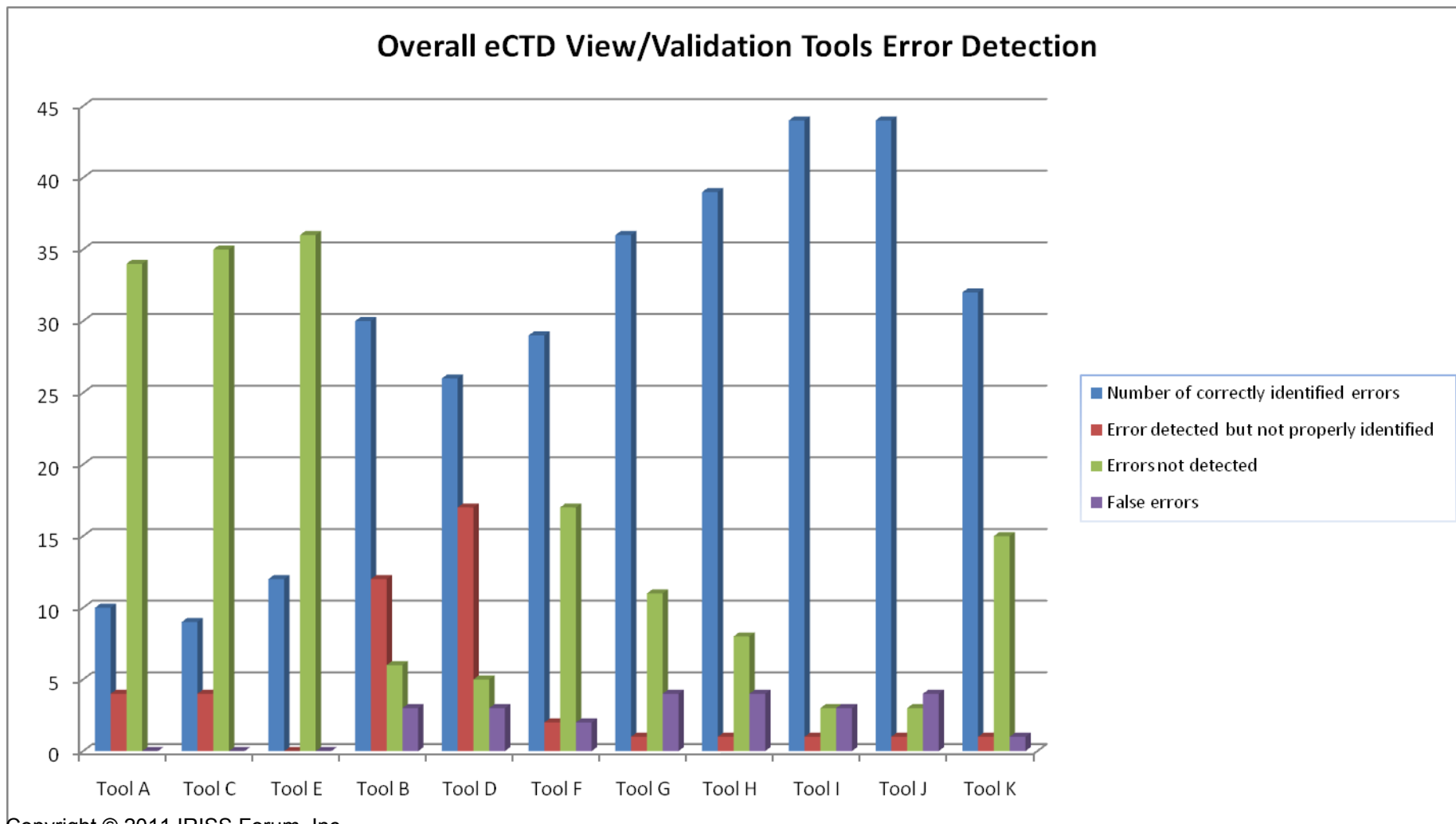
Results

The results provided by participants were reviewed by the ETICS team. These results are summarized in the following table and presented in Figure 2 and **Error! Reference source not found..**

Table 10: Summary of Overall Issue Detection Results

Tool	Tool A	Tool C	Tool E	Tool B	Tool D	Tool F	Tool G	Tool H	Tool I	Tool J	Tool K
Number of correctly identified issues	10	9	12	30	26	29	36	39	44	44	32
Issues detected but not properly identified	4	4	0	12	17	2	1	1	1	1	1
Issues not detected	34	35	36	6	5	17	11	8	3	3	15
False errors	0	0	0	3	3	2	4	4	3	4	1

Figure 2: Overall Issue Detection Grouped by Severity



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The analysis of the results indicated that the tools used in testing represent two different groups of the software. The tools in the first group with low detection scores seem to be dedicated to the eCTD submission viewing. The percentage of issue detection for tools in this group is below 50%. The second group with detection scores above 60% are viewers/validators.

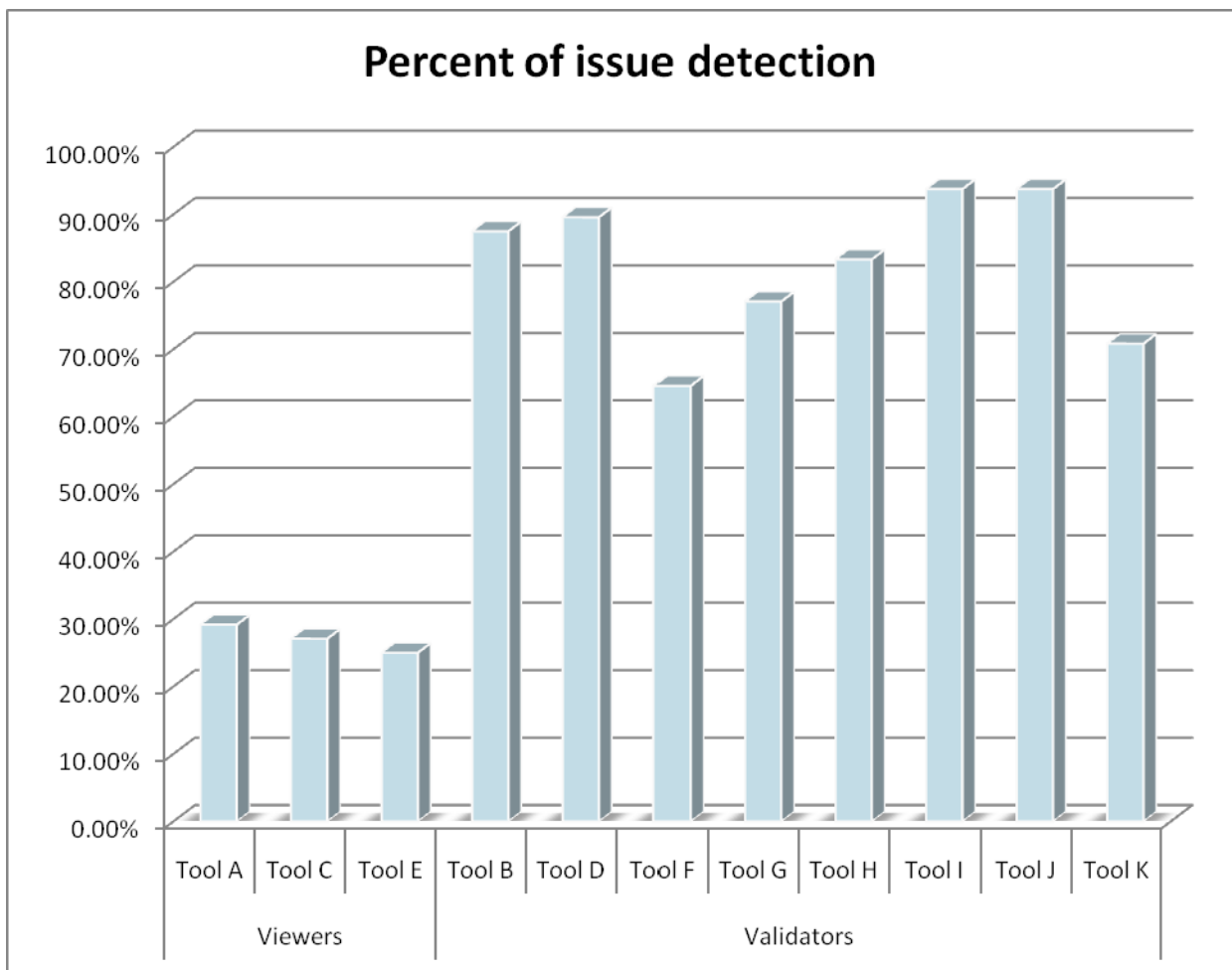
Table 11: Percentage of Error/Warning Detection – Viewer Tools

Tool A	Tool C	Tool E
29.17%	27.08%	25.00%

Table 12: Percentage of Error/Warning Detection – Viewer/Validator Tools

Tool B	Tool D	Tool F	Tool G	Tool H	Tool I	Tool J	Tool K
87.50%	89.58%	64.58%	77.08%	83.33%	93.75%	93.75%	70.83%

Figure 3: Percentage of Error/Warning Detection

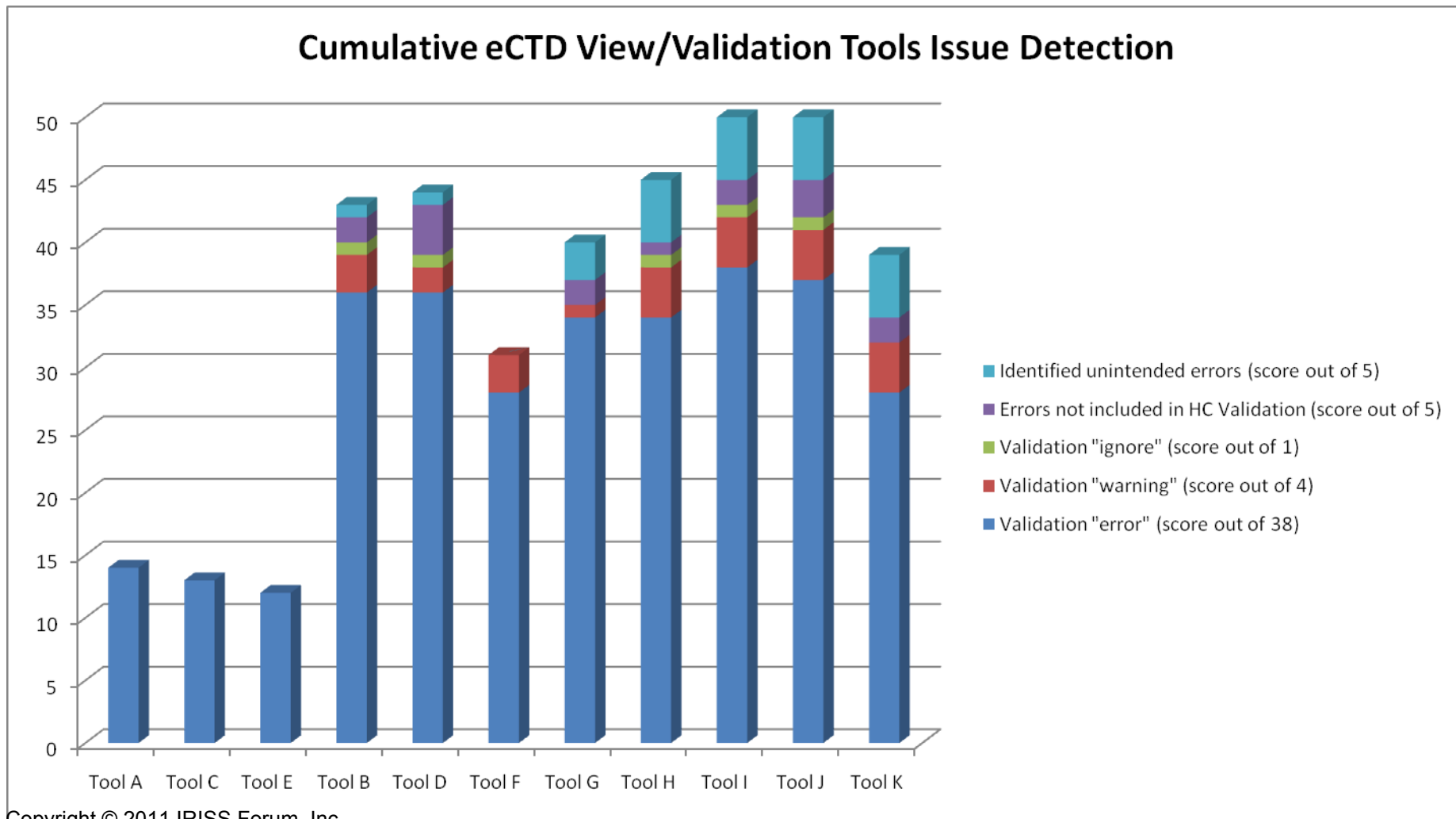


The results of testing were additionally analyzed with inclusion of the tools ability to detect identified unintended errors introduced to the samples during sample preparations, and also from the perspective of detection of issues relating to the PDF file format (HC Rules 7 to 31). The results are provided in the table below and in Figure 5 and Figure 6.

Table 13: Errors Organized by Health Canada Validation Rules Severity Criteria

HC Severity criteria and other error types	Viewer tools			Viewer/Validator tools							
	Tool A	Tool C	Tool E	Tool B	Tool D	Tool F	Tool G	Tool H	Tool I	Tool J	Tool K
Validation "error" (score out of 38)	14	13	12	36	36	28	34	34	38	37	28
Validation "warning" (score out of 4)	0	0	0	3	2	3	1	4	4	4	4
Validation "ignore" (score out of 1)	0	0	0	1	1	0	0	1	1	1	0
Errors not included in HC Validation (score out of 5)	0	0	0	2	4	0	2	1	2	3	2
Identified unintended errors (score out of 5)	<i>0</i>	<i>0</i>	<i>0</i>	<i>1</i>	<i>1</i>	<i>0</i>	<i>3</i>	<i>5</i>	<i>5</i>	<i>5</i>	<i>5</i>
PDF properties errors/warnings (score out of 11)	<i>0</i>	<i>1</i>	<i>0</i>	<i>10</i>	<i>11</i>	<i>0</i>	<i>9</i>	<i>7</i>	<i>11</i>	<i>10</i>	<i>0</i>

Figure 4: Cumulative eCTD View/Validation Tools Issue Detection



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Figure 5: Detection of PDF Related Errors (HC Rules 7 to 31)

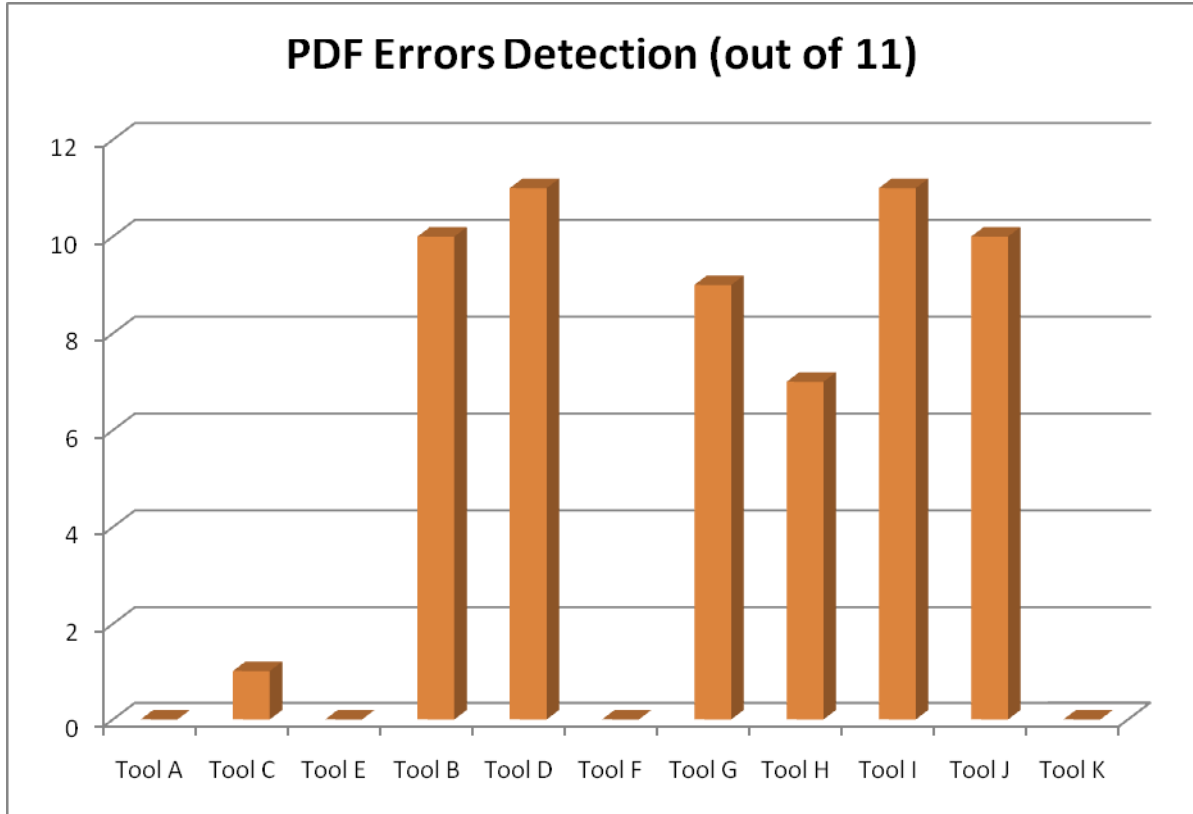
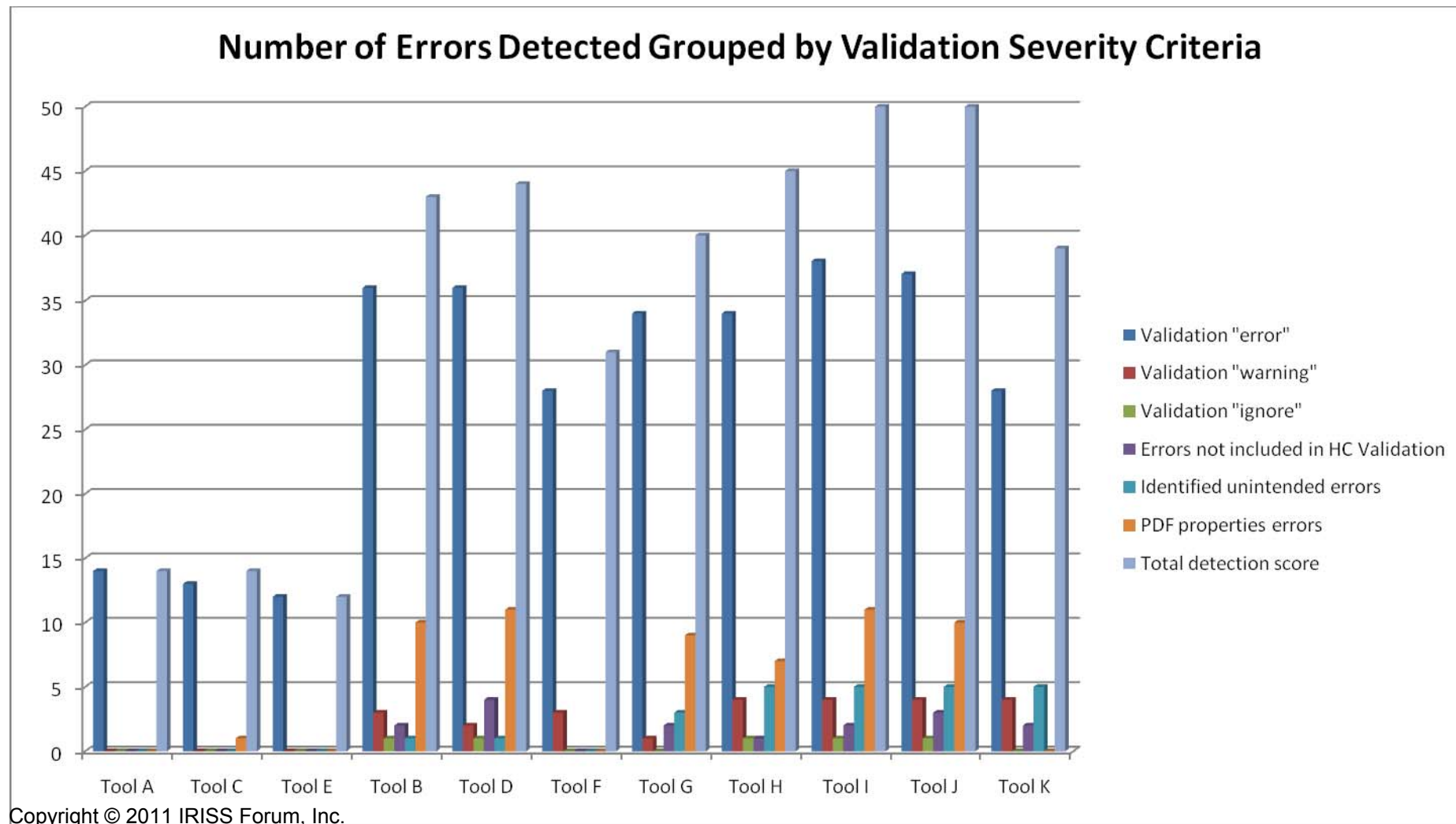


Figure 6: Results Grouped by Severity Criteria – Including Unintended Errors



Since some tools reported issues in an ambiguous way, an additional scoring scale was applied to the results to distinguish between clear and unclear issue reporting.

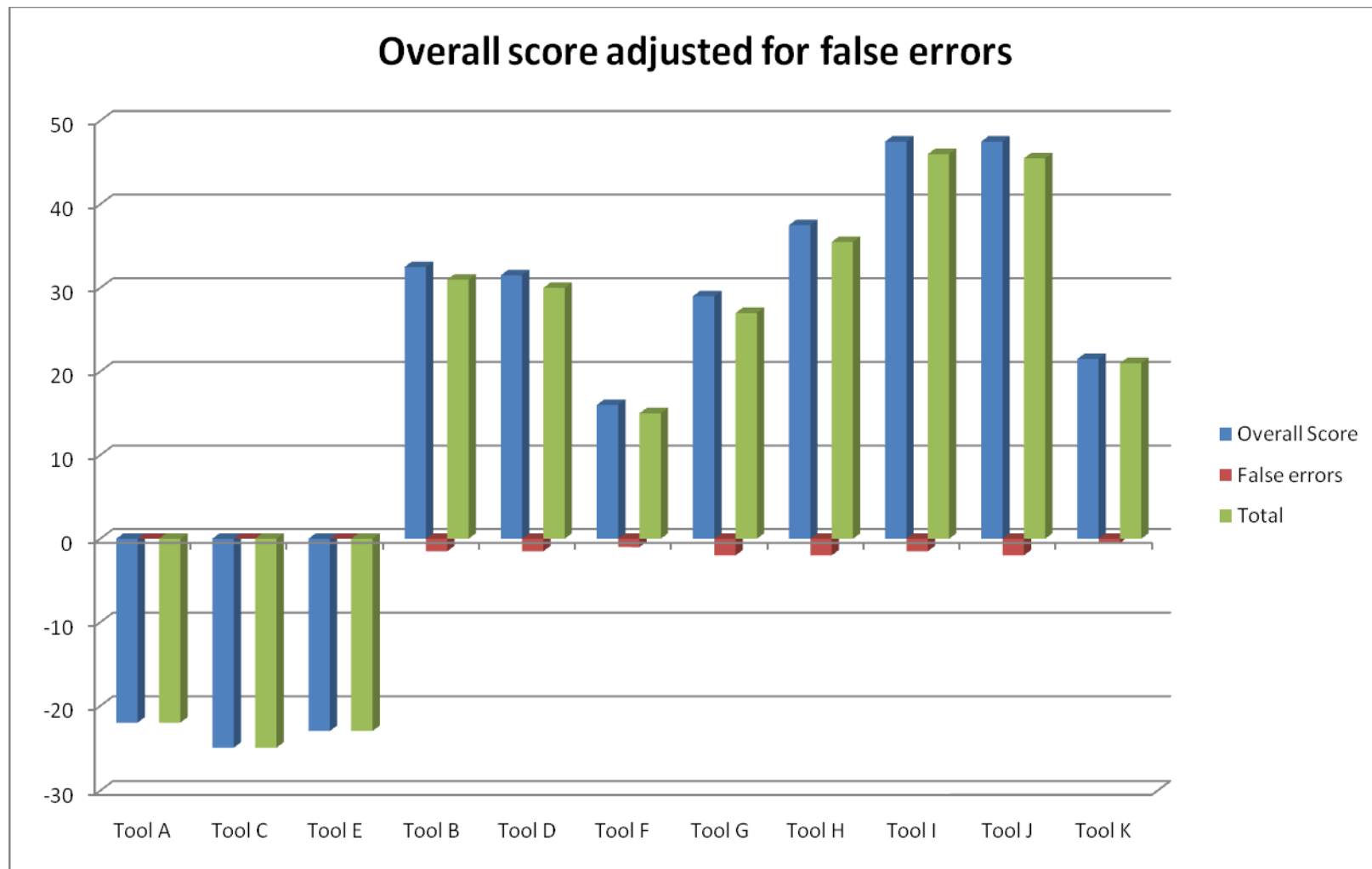
Table 14: Results Scoring Scale

Outcome	Score
Positive: tested error + any other unintentional error identified	2
Positive: tested error identified	1
Partial of unclear result: error detected but not properly defined	0.5
False error	-0.5
Negative: test error not detected	-1

Table 15: Overall Error Detection Score and Scores Adjusted for False Errors

	Viewer tools			Viewer/Validator tools							
	Tool A	Tool C	Tool E	Tool B	Tool D	Tool F	Tool G	Tool H	Tool I	Tool J	Tool K
Overall error detection score	-22	-25	-23	32.5	31.5	16	29	37.5	47.5	47.5	21.5
False errors	0	0	0	-1.5	-1.5	-1	-1	-2	-1.5	-2	-0.5
Overall score adjusted for false errors	-22	-25	-23	31	30	15	28	35.5	46	45.5	21

Figure 7: Overall Detection Score Adjusted for False Errors



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Table 16: Cumulative Results of ETICS 3 Phase 1 Testing

Sample No.	Viewer tools			Viewer/Validator tools								Tested rule
	A	C	E	B	D	F	G	H	I	J	K	
ca-001	-1	-1	-1	0.5	0.5	2	-1	2	2	2	2	The value of the applicant element must be present
ca-002	-1	-1	-1	0.5	0.5	1	-1	1	1	1	1	The value of the product-name element must be present
ca-003	1	-1	1	0.5	0.5	0.5	1	1	0.5	1	1	The value of the submission-date element must be present
ca-004	-1	-1	-1	0.5	0.5	1	1	1	1	1	1	The value of the submission-date element must be given in format YYYY-MM-DD
ca-005	-1	-1	-1	0.5	0.5	1	1	1	1	1	1	The value of the submission-date element must be given in format YYYY-MM-DD
ca-006	1	-1	1	0.5	0.5	1	1	1	1	1	1	submission-type attribute is present
ca-007	1	-1	1	1	0.5	1	1	1	1	1	1	submission-type attribute as per list
ca-008	-1	1	-1	1	0.5	1	1	1	1	1	1	The value of the application-identifier element must start with an e, followed by 6 digits
ca-009	-1	0.5	-1	2	0.5	1	2	2	2	2	2	The value of the application-identifier element must start with an e, followed by 6 digits
ca-010	-1	1	-1	1	0.5	1	1	1	1	1	1	The value of the application-identifier element must start with an e, followed by 6 digits
ca-011	-1	0.5	-1	1	0.5	1	1	1	1	1	1	The value of the application-identifier element must match the application folder name.
ca-012	-1	1	-1	1	1	1	1	1	1	1	1	The value of the sequence-number element must be in a format "0000"
ca-013	-1	1	-1	1	1	1	1	1	1	1	1	The value of the sequence-number element must be in a format "0000"
ca-014	-1	1	1	0.5	1	1	1	1	1	1	1	The value of the sequence-number element must match the sequence folder name
ca-015	1	1	-1	1	1	0.5	0.5	1	1	0.5	0.5	Initial sequence must start with sequence-number "0000"
ca-016	-1	-1	-1	1	-1	1	-1	1	1	1	1	Regional backbone(s) referenced (ca-regional.xml) should have 'new' operation attribute

Implementation of Regulatory Information Submission Standards (IRISS) eCTD Tool Interoperability Group (ETIG) eCTD Tool Interoperability and Compliance Study III (ETICS III)

Phase 1 Health Canada Compliance Report

Sample No.	Viewer tools			Viewer/Validator tools								Tested rule	
	A	C	E	B	D	F	G	H	I	J	K		
ca-017	1	-1	1	1	1	1	1	1	1	1	1	1	ca-regional.xml DTD version disagreement
ca-018	1	0.5	1	2	2	2	-1	2	2	1	-1	-1	The index.xml file must be present
ca-019	-1	-1	-1	-1	1	-1	-1	1	1	1	1	1	Path length including file name and extension does not exceed 230 characters.
ca-020	0.5	0.5	1	1	0.5	1	1	1	1	1	1	1	No use of illegal characters in path
ca-021	-1	-1	1	1	0.5	1	1	1	1	1	1	1	Missing top level folder
ca-022	1	-1	1	0.5	0.5	1	1	1	1	1	1	1	The util folder must be present
ca-024	0.5	-1	1	0.5	1	1	2	2	2	2	2	2	The folder m1\ca must exist.
ca-025	0.5	-1	-1	0.5	1	1	1	1	1	1	1	1	The regional backbone ca-regional.xml file must exist in folder m1\ca.
ca-026	-1	-1	-1	0.5	1	1	1.5	2	2	2	2	2	The regional backbone file name must be ca-regional.xml
ca-027	1	-1	1	0.5	0.5	1	1	1	1	1	1	1	The element m1-administrative-information-and-prescribing information must be present.
ca-028	0.5	1	-1	1	1	1	1	1	1	1	1	1	All referenced files in the ca-regional.xml exist
ca-029	-1	-1	-1	1	-1	1	-1	1	1	1	1	1	Unreferenced files in the ca-regional.xml
ca-030	-1	-1	-1	-1	-1	-1	-1	-1	-1	1	-1	-1	No subfolders created in ca regional folder
ca-031	-1	-1	-1	1	1	-1	1	-1	1	1	1	-1	System is able to accept dataset file formats (*.dat and *.inf)
ca-032	-1	-1	-1	-1	-1	-1	1	1	1	1	1	1	Incorrect naming of the 3011 form
ca-033	-1	-1	-1	1	1	1	1	1	1	1	1	1	Checks for elements not having any leaf child nodes. This only affects elements with a name that starts with 'm'.
ca-034	1	-1	1	1	0.5	1	1	1	1	2	2	2	For node extensions, the title child must be present (value must be present).
ca-035	-1	-1	-1	-1	-1	1	1	1	1	1	1	1	The checksum-type attribute must have the value md5 or MD5.
ca-036	1	-1	-1	1	0.5	1	1	1	1	1	1	1	Life cycle management of the document: invalid file reference or no previous ID found
ca-037	-1	-1	-1	-1	1	-1	-1	-1	-1	-1	-1	-1	Consecutive sequences should have consecutive sequence number

Sample No.	Viewer tools			Viewer/Validator tools								Tested rule
	A	C	E	B	D	F	G	H	I	J	K	
ca-038	-1	-1	-1	1	1	-1	1	-1	1	1	-1	Presence of non-relative bookmarks
ca-039	-1	-1	-1	1	1	-1	1	-1	1	1	-1	Presence of broken bookmark
ca-040	-1	-1	-1	1	1	-1	-1	1	1	1	-1	Presence of inactive bookmark
ca-041	-1	-1	-1	1	1	-1	1	1	1	1	-1	External bookmark - pointing to the folder or destination that does not exist in the folder structure on the CD/DVD.
ca-042	-1	-1	-1	1	1	-1	1	1	1	1	-1	Presence of non-relative hyperlinks
ca-043	-1	-1	-1	1	1	-1	1	0.5	1	1	-1	Presence of broken hyperlink
ca-044	-1	-1	-1	1	1	-1	1	-1	1	-1	-1	Presence of inactive hyperlink
ca-045	-1	1	-1	1	1	-1	1	1	1	1	-1	External links - pointing to the folder or destination that does not exist in the folder structure on the CD/DVD.
ca-046	-1	-1	-1	1	1	-1	-1	1	1	1	-1	PDF documents should be optimized
ca-047	-1	-1	-1	1	1	-1	1	1	1	1	-1	PDF documents should be in Adobe Acrobat, version 5.0, 6.0, or 7.0
ca-048	-1	-1	-1	1	1	-1	1	-1	1	1	-1	PDF files should not be password protected
ca-049	-1	1	-1	-1	1	-1	-1	-1	-1	-1	-1	MS Word files with restricted access permission

Table 17: Colour Codes Used in Test Results Tabulation

HC Validation "error"
HC Validation "warning"
HC Validation "ignore"
Not included in HC Validation

Positive	1=tested error identified
Partial of unclear result	0.5=error detected but not properly defined
False error	-0.5
Negative	-1=test error not detected

Conclusions

The analysis of the results indicated that there is a significant difference in the level of error/warning detection between tools. These results point out that there are two groups of tools with each having different functionality goals. Tools A, C and E appear to be eCTD viewers. These tools had a low error detection score with 29.17%, 27.08%, and 25.00%, respectively (see Table 11), and almost no ability to detect PDF related issues (see Table 13, Figure 5). The remaining tools had significantly higher error detection scores. However, tools G, H, I and K had limited or no ability to detect PDF related issues

Contact Details

Following your review of this report, if you wish to further discuss your individual results or would like to discuss the IRISS ETIG ETICS 3 CN Phase 1 in general, please request a meeting with the CN regional lead using the details below.

Email: etics-ca@iriss-forum.org