

PKMP
Software Verification and Validation Test Report (SVVR)

Prepared for:

APL

Eden Prairie

Minnesota 55347, USA

Prepared by:

Santosh Sonbarse

APL

APL Proprietary

To be used only as permitted by Non-Disclosure Agreement, dated June 2014

REVISION HISTORY

Revision	Description	Incorporated	
		Date	Change Authority
01	Initial Issue	Jul 30, 2018	Eng.
02	Updates after peer review	Sep 3, 2018	Eng.
03	Further Updates after peer reviews	Sep 15, 25 2018	Eng.
04	Added Analysis of Failed cases	Oct 14, 2018	Eng.
05	Updated after peer review	Nov 24, 2018	Eng.
06	Added examples of validation process	Aug 9, 2020	Eng

Eng.= Software Engineering Department

Table of Contents

1 SCOPE	1
1.1 ABSTRACT.....	1
1.2 Identification.....	1
1.3 PKMP Overview	1
1.3.1 System Definition	1
1.4 DOCUMENT OVERVIEW.....	2
2 Referenced Documents	3
2.1 Government (FDA) Documents	3
2.2 Non-Government Documents.....	3
3 Software Verification and validation Tesing Procedure	4
3.1 Brief Description of Testing Process:.....	4
3.1.1 : Testing team.....	4
3.1.2 : Test Plan Documents and Review	4
3.1.3 : Test Results and Issues Handling	4
3.1.4 : Test Iterations	4
3.1.5 : Test Engineers Role.....	4
3.1.6 Verification Testing:	5
3.1.7 Validation Testing:.....	5
3.2 Analysis of Testing Results.....	5
3.2.1 Iteration 1 Summary and Analysis.....	5
3.2.1.1 Version Tested	5
3.2.1.2 Modules Covered	5
3.2.1.3 Test Results Analysis.....	5
3.2.2 Iteration 2 Summary and Analysis.....	7
3.2.2.1 Version Tested	7
3.2.2.2 Modules Covered	7
3.2.2.3 Test Results Analysis.....	7
3.2.3 Iteration 3 Summary and Analysis.....	8
3.2.3.1 Version Tested	8
3.2.3.2 Modules Covered	9
3.2.3.3 Test Results Analysis.....	9
3.2.4 Iteration 4 Summary and Analysis.....	10
3.2.4.1 Version Tested	10
3.2.4.2 Modules Covered	10
3.2.4.3 Test Results Analysis.....	11
3.2.5 Examples of Validation Testing.....	12

4 Definitions, Abbreviations, and Acronyms.....	17
5 APPEXDIX.....	18
<i>5.1 Iteration -1 Results:</i>	<i>18</i>
<i>5.2 Iteration -2 Results:</i>	<i>18</i>
<i>5.3 Iteration-3 Results:</i>	<i>18</i>
<i>5.4 Iteration-4 Result:</i>	<i>18</i>

List of Figures

Figure 1. PKMP Top-Level Diagram..... 1
Figure 2. Iteration-1 Failed cases distribution 6
Figure 3. Iteration-2 Failed cases distribution 8
Figure 4. Iteration-3 Failed cases distribution 10
Figure 5. Iteration-4 Failed cases distribution 11

List of Tables

Table 1 Iteration 1 Results Summary 5
Table 2. Iteration 2 Results SummaryError! Bookmark not defined.
Table 3. Iteration 3 Results SummaryError! Bookmark not defined.
Table 4. Iteration 4 Results SummaryError! Bookmark not defined.

1 SCOPE

1.1 ABSTRACT

This document is a report compiled for the System Verification and Validation Testing for the PKMP application software. The process followed is described and related documents are referred. Analysis is performed of the results of the formal testing performed over four different iterations. Each new iteration tested new modules and changes that were made to resolve issues. The results from each iteration were documents in the excel reports. The issues or defects found were categorized into several level of severities ranging from blocked, Critical, Major, Medium, Minor, and Informational. The quality of PKMP software improved gradually over the iterations. At the end of 4th iteration there were only 34 defects – 29 minor and 5 major in severity.

After the end of 4th iteration and analysis of the test results, the test team has recommended that the PKMP application can be released for the production environment available to customers for their data analysis usage. The defects at the end of 4th iteration are entered in the defect tracking system for the development team to resolve and documented in our release notes for the version 1.03.8.

1.2 IDENTIFICATION

Pharmacokinetic modeling program (PKMP) is a data analysis software developed by APL to support drug discovery research and development evaluations. This Software Verification and Validation Test Report (SVVR) document describes the test procedures followed and the analysis of the verification and validation testing results for the PKMP software Application– a Computer Software Configuration Item (CSCI) developed by APL. This document refers to several other related documents produced towards requirements, design, and other documents for the product.

1.3 PKMP OVERVIEW

1.3.1 System Definition

A top-level view of the PKMP functionalities with its components are depicted in Figure 1.

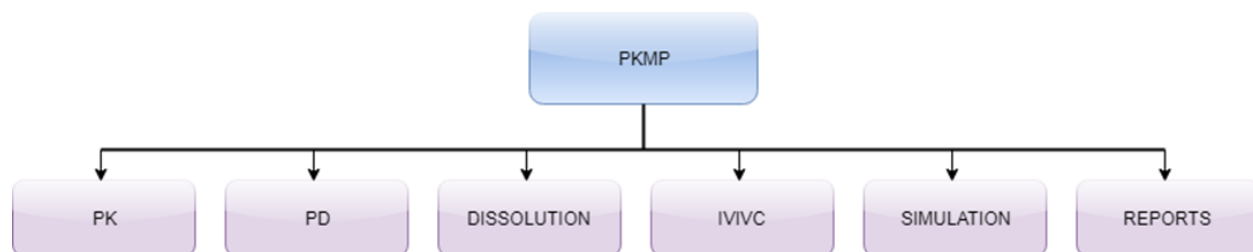


Figure 1. PKMP Top-Level Diagram

The major components of the PKMP are listed below:

- NCA-PK

- CA-PK
- PD
- Dissolution
- IVIVC
- Validations
- Simulations
- Reporting
- Global Settings

1.4 DOCUMENT OVERVIEW

This document is a report summarizing the verification and validation testing done before the release of the PKMP application. This document covers analysis of results to verify and validate the functional and non-functional requirements for the PKMP product. This document is organized in accordance with APL Systems and Services Development Process. This document is comprised of the following sections.

- Section 1 -Scope This section identifies and states the purpose of the software system and summarizes the purpose and contents of this document.
- Section 2 - Referenced Documents, lists the documents that contain information applicable to the contents of this document.
- Section 3 – Specifies the procedure and instructions followed towards the verification and validation of the PKMP software application. It also provides the analysis and summary of the results.
- Section 4 - Definitions, Abbreviations and Acronyms, contains general information that may aid in understanding this specification, including a list of acronyms and abbreviations used in this document.
- Section 5 – Appendices including the results from different test iterations.

2 REFERENCED DOCUMENTS

The following documents form a part of this specification to the extent specified herein. In the event of a conflict between the documents referenced herein and the contents of this specification, the following order of precedence will apply:

- Software Product Requirements for PKMP
- Software Design Document for PKMP
- Software Verification and Validation Testing Instructions
- Software Verification and Validation Test Plan and Results for PKMP – Iteration 1
- Software Verification and Validation Test Plan and Results for PKMP – Iteration 2
- Software Verification and Validation Test Plan and Results for PKMP – Iteration 3
- Software Verification and Validation Test Plan and Results for PKMP – Iteration 4

2.1 GOVERNMENT (FDA) DOCUMENTS

<https://www.fda.gov/downloads/medicaldevices/.../ucm085371.pdf>

2.2 NON-GOVERNMENT DOCUMENTS

- INCOSE Systems Engineering Handbook 4e 2015 07.

3 SOFTWARE VERIFICATION AND VALIDATION TESTING PROCEDURE

The detailed Software Verification and Validation Testing procedure followed for testing the PKMP program is described in the APL document - Software Verification and Validation Test Instruction Document. A summary of the methodology is described below.

3.1 BRIEF DESCRIPTION OF TESTING PROCESS:

3.1.1 : Testing team

Entire PKMP functionalities built in different modules and their submodules were tested by a team comprising of test engineers. This team was different from the development engineers. Testing effort was led by a system test lead along with test engineers working in collaboration to test different features.

3.1.2 : Test Plan Documents and Review

Before the beginning of the testing, verification and validation test plan documents covering test cases corresponding to different use cases and scenarios were created. These documents were then reviewed by a cross-functional team of test and development engineers, to ensure all the features provided by PKMP application were covered in the plan.

3.1.3 : Test Results and Issues Handling

During the time of testing, the tester worked closely with the developers, communicating any issue and working through the resolution of the issue. The results of the testing were documented by updating the pass/fail status in the corresponding test plan document. Issues were also entered in a separate bug tracking system called Bugzilla to facilitate monitoring and tracking of the open issues across development and test teams.

3.1.4 : Test Iterations

The testing was performed in several iterations starting with the first iteration when most of the features and modules of the PKMP applications were ready for the verification and validation testing. More iterations of testing were performed as and when new modules and their features were available for testing. Strict discipline was observed to maintain the testing of same version number of the program for an iteration. In some cases, when iteration testing could not proceed because of critical issues, exceptions were made to allow the change of software and test with a new version number. Test iterations completed toward PKMP testing are described in more details in the sections below.

3.1.5 : Test Engineers Role

Test team ensured that all the subsequent changes made as part of new features or for bug fixes must successfully pass through the system verification and validation testing phase. All the defects found during the system testing must be addressed before the changes are moved into production. All changes must go through system testing before they are implemented into production.

3.1.6 Verification Testing:

As part of verification testing team verified that the PKMP application, and its features, performs as per the design documented in the Software Design Document(SDD) for PKMP. Team ensured that all the design section including functional and non-functional features were verified according to the expectation set in the SDD document.

3.1.7 Validation Testing:

As part of validation testing team verified that the PKMP application, and its features, performs as per the requirements documented in the Software Product Requirement (SPR) Document for PKMP. Team ensured that all the requirement sections including functional and non-functional requirements were validated according to the expectation set in the SPR document.

3.2 ANALYSIS OF TESTING RESULTS

This section describes in detail different iterations that were completed as part of the Software Verification and Validation testing of the PKMP application. As part of the testing performed during each iteration, the test plan document is updated with the pass/fail status for each test case. The test plan with test cases and updated results are documented by test engineers in MS excel files (See the references section). These files containing each iteration are also attached with this document. The results for these files are reviewed, analyzed and summarized in the sections below.

As of PKMP version 1.3.7, three iteration of system testing were completed.

3.2.1 Iteration 1 Summary and Analysis

3.2.1.1 Version Tested

PKMP version 1.02.01 – 1.02.07 were tested as part of this iteration.

3.2.1.2 Modules Covered

Following modules of PKMP were tested as part of the iteration.

- NCA-PK,
- CA-PK,
- PD,
- Dissolution,
- IVIVC,
- Validation

3.2.1.3 Test Results Analysis

Table 1. Iteration 1 Results Summary:

Table 1: Iteration 1 Results Summary

Module	Fail	Pass	(Not Tested)	Grand Total
Dissolution	1	37		38
Extravascular	65	63	37	165
IV Bolus	79	42	26	147
IV Infusion	86	17	36	139
IVIVC		12		12

Loo-Riegelman	23	1	97	121
Numerics			5	5
PD	3	101		104
PK		21		21
Superposition Analysis	2	5		7
Upload IVIVC File		1		1
Urine Analysis	9	8		17
Validations		27		27
Wagner Nelson	20	64	25	109
Grand Total	288	399	226	913

As part of iteration 1 913 test cases were developed for the PKMP modules in the test scope. Only 399 tests were passed, 288 failed and 226 could not be executed.

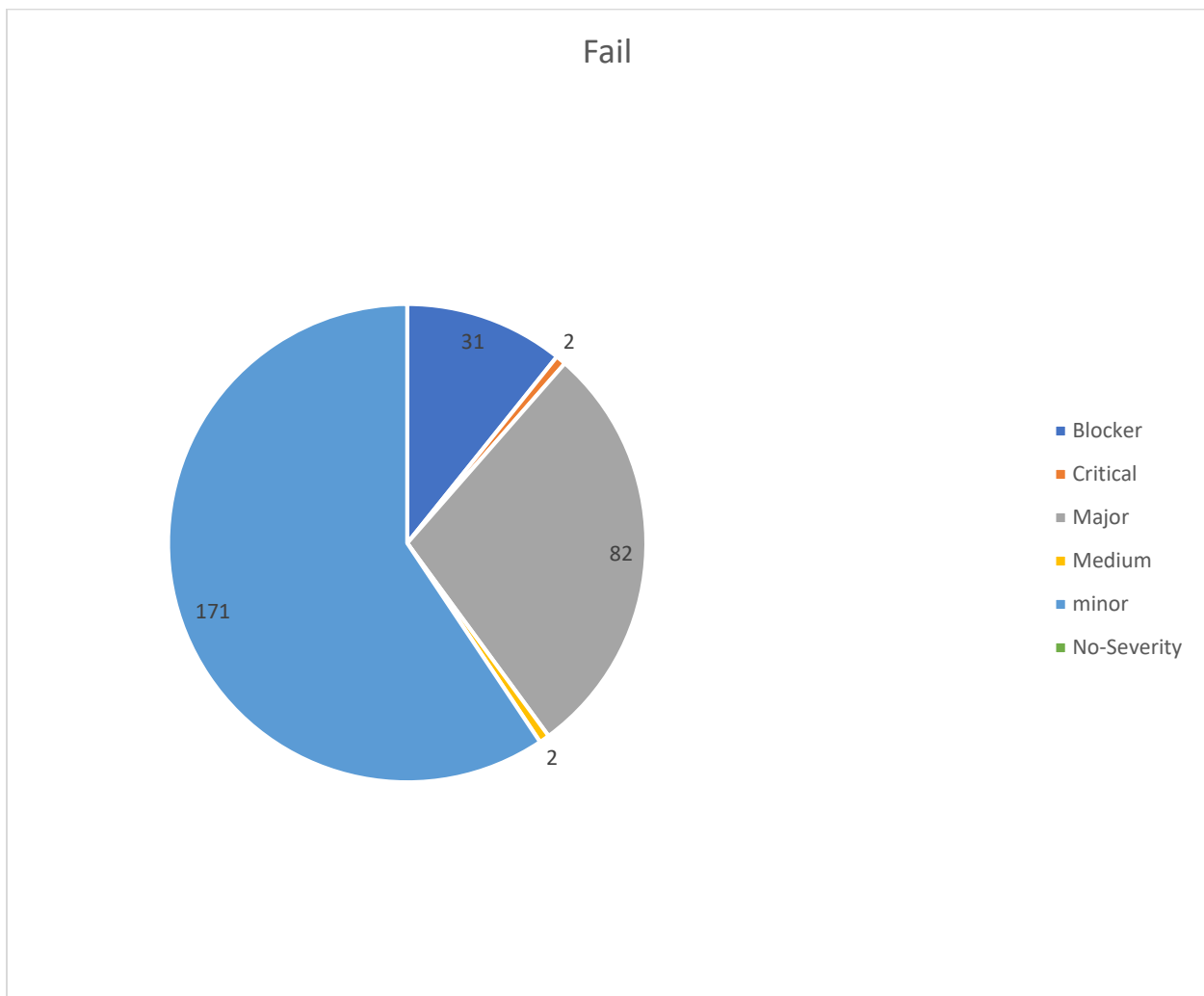


Figure 2. Iteration-1 Failed cases distribution

Out of the total failed cases their spread across different severities was analyzed. Refer to the pie chart in Figure 2. There were significant number of blockers – 31 cases that existed because of features that were not completed at the time.

Iteration 1 provided a good reflection on the status of the PKMP software. The feedback was provided to the developer to fix the issues found.

3.2.2 Iteration 2 Summary and Analysis

3.2.2.1 Version Tested

PKMP version 1.02.8- 1.03.3 was tested as part of the iteration.

3.2.2.2 Modules Covered

Following modules and features of PKMP were tested as part of the iteration.

- NCA-PK
- CA-PK
- PD
- Dissolution
- IVIVC
- Validations
- Simulations

3.2.2.3 Test Results Analysis

Table 2: Iteration 2 Test Results Summary:

Table 2: Iteration 2 Results Summary

Modules	Fail	Pass	(Undetermined)	Grand Total
Dissolution		38		38
Extravascular	75	94		169
IV Bolus	55	96		151
IV Infusion	67	76		143
IVIVC			12	12
Loo-Riegelman	49	64	20	133
Numerics		24	2	26
PD	3	77	24	104
PK			21	21
Superposition Analysis	2	5		7
Upload IVIVC File		1		1
Urine Analysis	6	11		17
Validations			27	27
Wagner Nelson	20	85	3	108
Grand Total	277	571	109	957

Iteration 2 of the PKMP verification and validation testing involved re-testing the tests cases developed during the iteration 1 again as well as testing of new features in several modules that were available before the iteration 2 testing began. One brand new module of Simulation was included as part of this iteration.

Out of total of 957 test cases, 571 test cases passed, 277 failed and 109 testcases were not able to determine or execute. The number of passed test cases % improved from the previous iteration. Feedback was provided to the development team on the test cases that did not pass iteration 2. Considering the number of failed test cases, testing team started planning for the iteration 3 test cases.

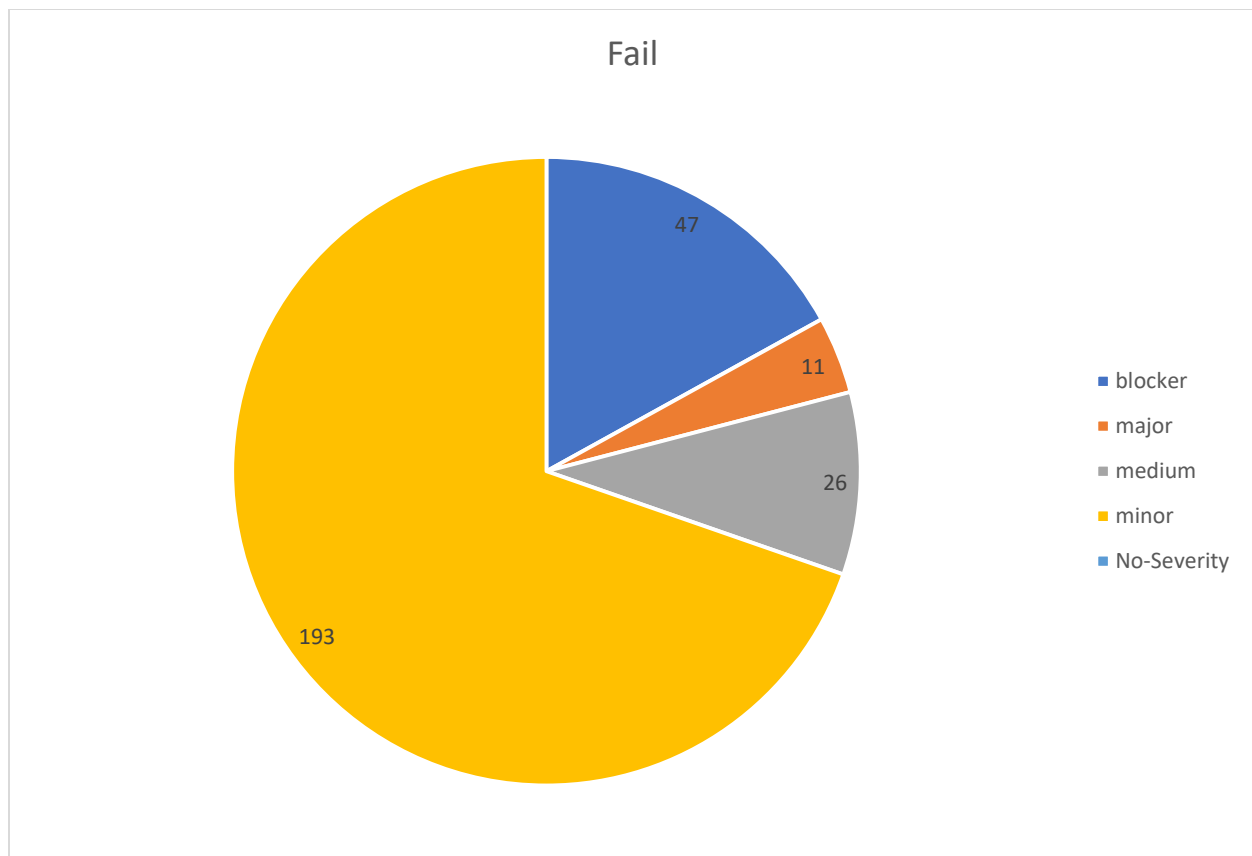


Figure 3. Iteration-2 Failed cases distribution

The pi-chart in Figure 3 shows the distribution of failed testcases across different severities. There were significant numbers of blockers existed during this iteration too.

Considering the number of failed test cases, testing team started planning for the iteration 3 test cases.

3.2.3 Iteration 3 Summary and Analysis

3.2.3.1 Version Tested

Version 1.03.6 and 1.03.7 were tested as part of the iteration

3.2.3.2 Modules Covered

Following PKMP modules were tested as part of this iteration

- NCA-PK
- CA-PK
- PD
- Dissolution
- IVIVC
- Validations
- Simulations
- Reporting
- Global Settings

3.2.3.3 Test Results Analysis

Table 3: Iteration 3 Test Results Summary:

Table 3: Iteration 3 Results Summary

Modules	Fail	Pass	Grand Total
BE		6	6
Extravascular	24	51	75
IV Bolus	36	19	55
IV Infusion	48	19	67
Loo-Riegelman		49	49
Superposition Analysis	1	1	2
Urine Analysis	3	3	6
Wagner Nelson	1	19	20
Grand Total	113	167	280

As part of iteration 3 only test cases that were failed in the previous two iterations were retested. Out of the total 280 test cases only 167 passed and 113 failed during this iteration.

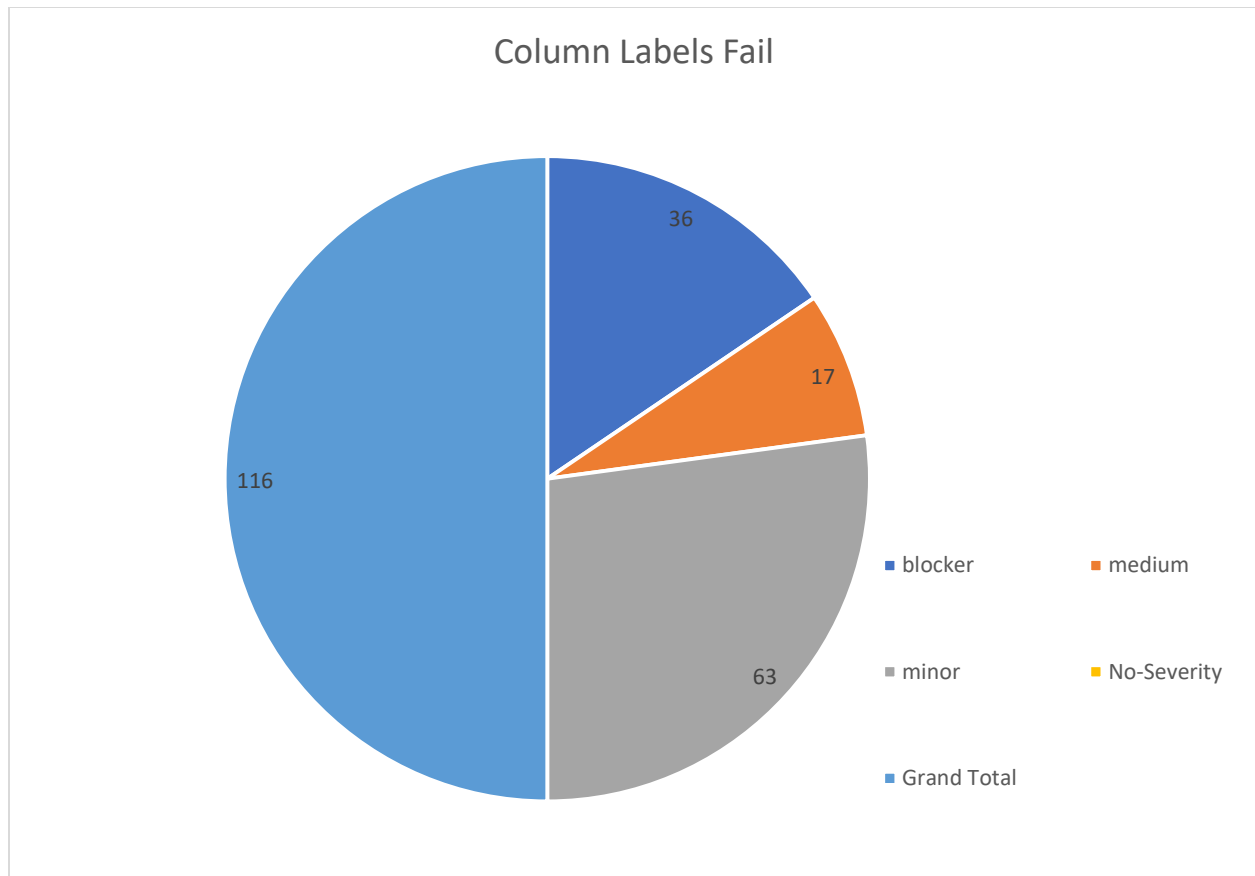


Figure 4. Iteration-3 Failed cases distribution

Feedback was provided to the development teams on the results of this iteration. Considering the amount of failed test cases still in large number, more development effort was needed from the team to resolve the open issues.

3.2.4 Iteration 4 Summary and Analysis

3.2.4.1 Version Tested

Version 1.03.5 tested as part of the iteration. This was a special iteration where only failed cases were tested. Also, test cases that were marked un-determined during the previous iteration were also reviewed with the development team and subject matter expert. Most of the cases were found to be passed. Some of those that needed retesting to verify the results with new set of data were included in this iteration.

3.2.4.2 Modules Covered

Following PKMP modules were tested as part of this iteration

- NCA-PK
- CA-PK
- PD
- Dissolution
- IVIVC

- Validations
- Simulations
- Reporting
- Global Settings

3.2.4.3 Test Results Analysis

Table 4: Iteration 4 Test Results Summary:

Table 4: Iteration 4 Results Summary

Modules	Fail	Pass	Grand Total
Extravascular	6	14	20
IV Bolus	9	26	35
IV Infusion	16	32	48
Loo-Riegelman		20	20
Numerics	1	2	3
Reports	1	2	3
Superposition Analysis		1	1
Urine Analysis		3	3
Wagner Nelson	1	3	4
Grand Total	34	103	137

Out of 137 test cases, most of the cases that were declared previously failed were found to have been passed (103 cases). There were still 34 cases that remained under the failed category. As part of this iteration the tests results were reviewed by the development team along with the subject matter expert.

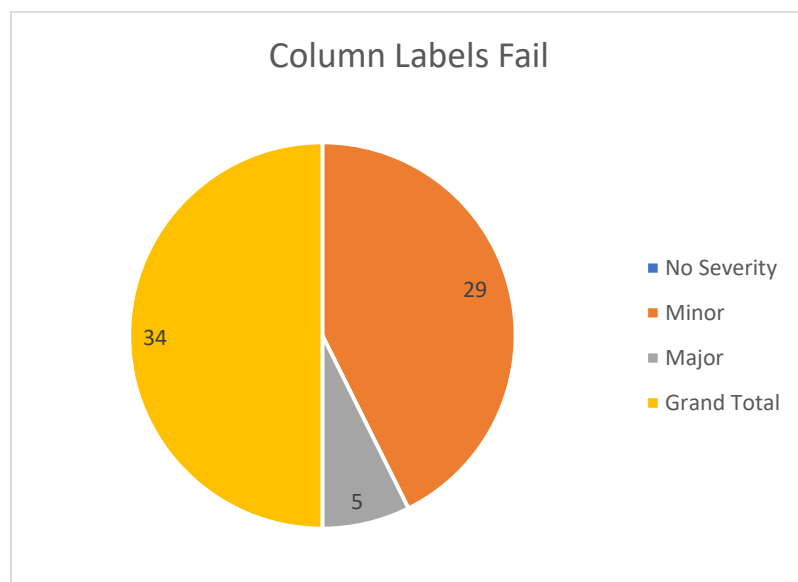


Figure 5. Iteration-4 Failed cases distribution

The pi-chart in Figure 5 above shows the distribution of the failed test cases. Out of 34 failed cases most of them were of severity minor (29 cases). There were five failed cases with major severity. The results were documented and shared with the application team to take further actions. Out of the 5 major issues 4 were related to the graphing display issue and one was related to report download issue.

3.2.5 Examples of Validation Testing

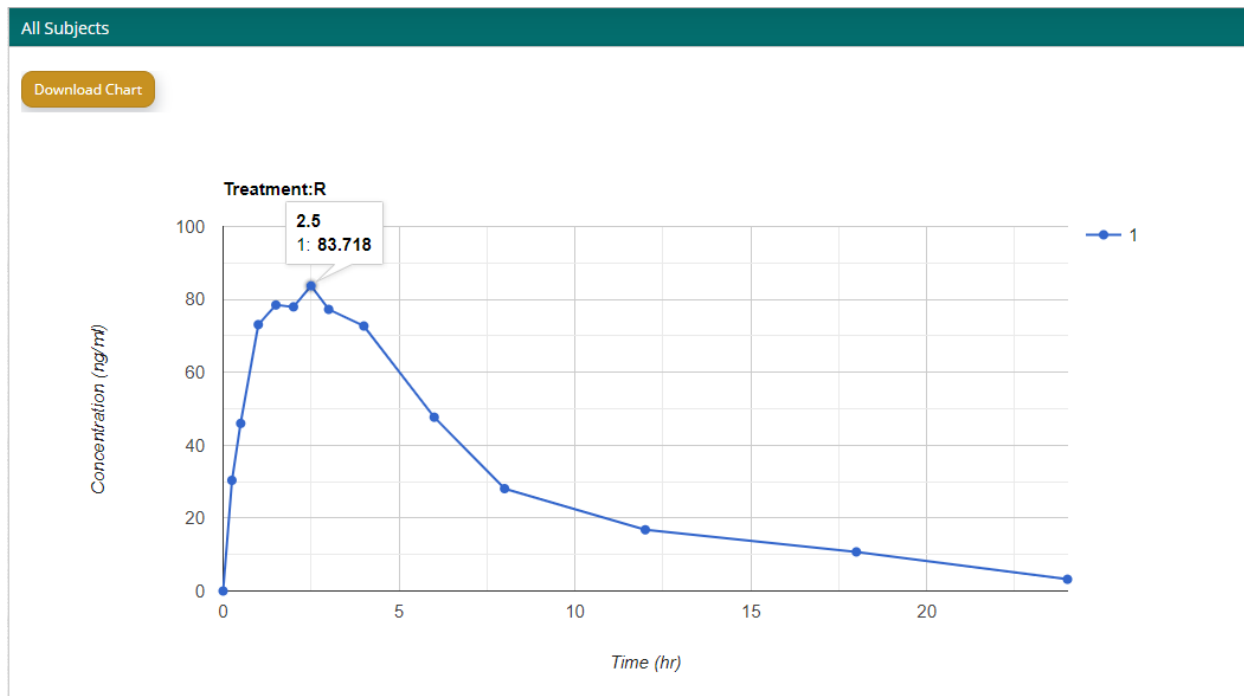
Example 1: Oral Data

Subject	Period	Treatment	Sequence	Dose(mg)	TIME (h)	CP (ng/mL)
1	1	R	RT	100	0.00	0.000
1	1	R	RT		0.25	30.357
1	1	R	RT		0.50	45.986
1	1	R	RT		1.00	73.083
1	1	R	RT		1.50	78.466
1	1	R	RT		2.00	77.961
1	1	R	RT		2.50	83.718
1	1	R	RT		3.00	77.260
1	1	R	RT		4.00	72.699
1	1	R	RT		6.00	47.675
1	1	R	RT		8.00	28.078
1	1	R	RT		12.00	16.791
1	1	R	RT		18.00	10.727
1	1	R	RT		24.00	3.2132

Data uploaded is shown below:

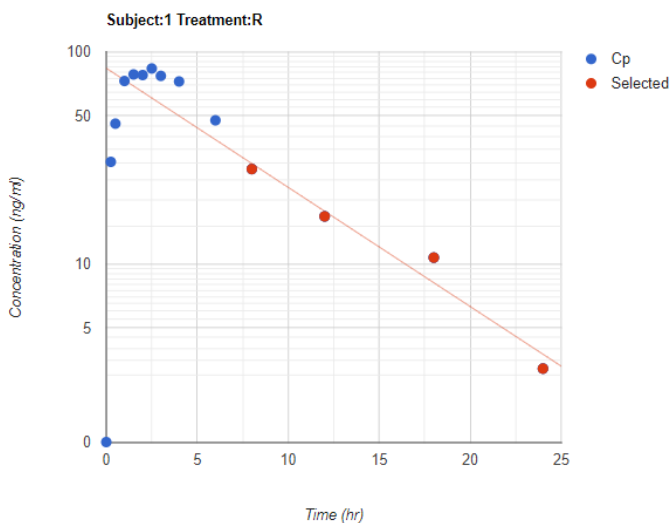
Subject	Period	Treatment	Sequence	Dose(mg)	TIME (h)	CP (ng/mL)
1	1	R	RT	100	0	0
1	1	R	RT		0.25	30.357
1	1	R	RT		0.5	45.986
1	1	R	RT		1	73.083
1	1	R	RT		1.5	78.466
1	1	R	RT		2	77.961
1	1	R	RT		2.5	83.718
1	1	R	RT		3	77.26
1	1	R	RT		4	72.699
1	1	R	RT		6	47.675
1	1	R	RT		8	28.078
1	1	R	RT		12	16.791
1	1	R	RT		18	10.727
1	1	R	RT		24	3.2132

Graph showing the value at 2.5 hour corresponding to CP value of 83.718.



PK parameter calculations and expected values are verified and validated manually by observation of output results to be correct for the input set of data. In this specific test case, the results were compared with Microsoft Excel program output.

KEL 0.129 SLOPE -0.129 INTERCEPT 83.99 RSQ 0.958 RSQ_ADJ 0.938 NO. OF POINTS 4



Subject	1	Units
Kel	0.129	1/hr
R ²	0.958	
T _{1/2}	5.353	hr
T _{max}	2.5	hr
C _{max}	83.718	ng/ml
T _{lag}	0.0	hr
C _{last} /C _{max}	0.038	
AUC 0-t	685.982	ng/ml*hr
AUC 0-inf	710.8	ng/ml*hr
AUC 0-t/0-inf	0.965	
AUC ALL	685.982	ng/ml*hr
AUMC 0-inf	5329.192	ng/ml*hr ²
MRT 0-t	6.62	hr
MRT 0-inf	7.497	hr
nVd/F	1.086	mg/(ng/ml)
nCl/F	0.14	mg/(ng/ml)/hr
Vd/F	1086657.4	mL
Cl/F	140686.4	mL/hr

Example 2: Fitting of data to IV bolus 1CBM model

Using the following parameters for IVbolus 1CBM model, data was fitted to 1CBM equation and concentration vs time data was generated as shown in the following table.

Bolus 1 CBM

ke	Number of Dose
<input type="text" value="0.5"/>	<input type="text" value="1"/>
Dose	Dose unit
<input type="text" value="100"/>	<input type="text" value="mg"/>
Vd	Vd unit
<input type="text" value="10"/>	<input type="text" value="L"/>
tau	tau unit
<input type="text" value="24"/>	<input type="text" value="hr"/>
Step Size	
<input type="text" value="0.25"/>	

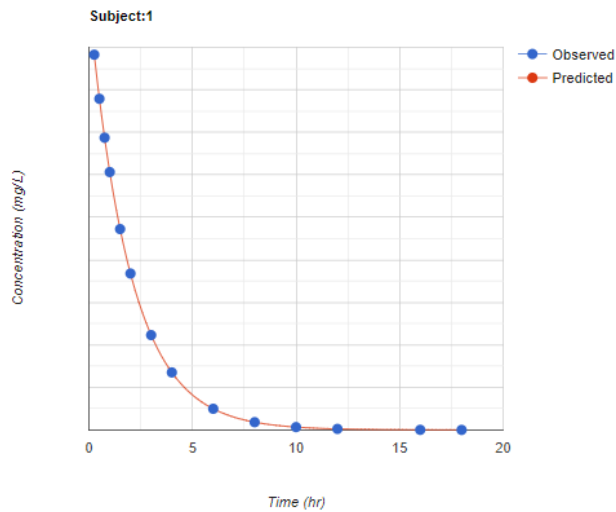
Simulated data

Subject	Time (hr)	Concentration (mg/L)
1	0.25	8.825
1	0.5	7.788
1	0.75	6.873
1	1	6.065
1	1.5	4.724
1	2	3.679
1	3	2.231
1	4	1.353
1	6	0.498
1	8	0.183
1	10	0.067
1	12	0.025
1	16	0.003
1	18	0.001

The above data was fitted to a 1CBM IVbolus model and the original parameters were obtained.

Parameter	Unit	Estimate	Standard Error	CV%
Subject	1			
C0	mg/L	10.0	0.956	9.562
k10	1/hr	0.5	0.094	18.843
t1/2	hr	1.386		
V	(mg)/(mg/L)	10.0		
CL	(mg)/(mg/L)/hr	5.0		
AUC 0-t	mg/L*hr	19.997		
AUC 0-inf	mg/L*hr	20.0		
AUMC	mg/L*hr ²	39.998		
MRT	hr	2.0		
Vss	(mg)/(mg/L)	10.0		
SS		0.0		
WSS		0.0		
R ²		1.0		
SE		0.0		
AIC		-187.464		
SC		-184.908		

Observed and predicted concentration-time plot is shown below.



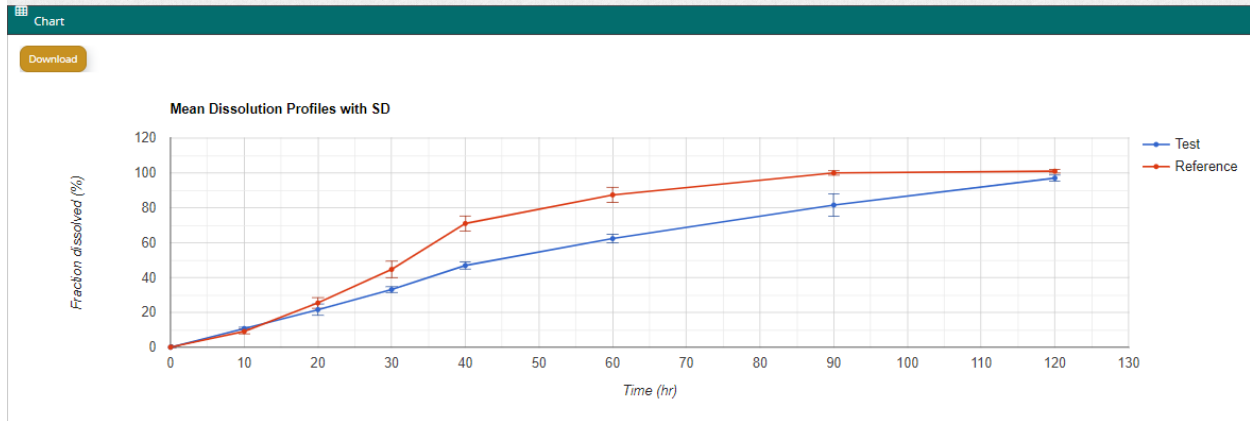
These results were verified to pass the test.

Example 3: Dissolution data analysis

Dissolution input													
Select Profile Comparison													
f1, Difference factor													
Batch	Time hr	t1 F(%)	t2 F(%)	t3 F(%)	t4 F(%)	t5 F(%)	t6 F(%)	t7 F(%)	t8 F(%)	t9 F(%)	t10 F(%)	t11 F(%)	t12 F(%)
Test	0	0	0	0	0	0	0	0	0	0	0	0	0
Test	10	10	10	10	10	11	11	12	12	11	10	11	11
Test	20	12	23	21	21	23	23	23	24	23	20	23	23
Test	30	32	34	30	32	34	34	34	35	34	30	34	34
Test	40	46	46	43	45	46	47	49	49	49	45	49	49
Test	60	60	63	68	59	63	61	64	62	63	59	63	63
Test	90	82	85	79	81	85	63	85	86	85	79	84	85
Test	120	99	97	95	96	98	97	98	98	97	93	98	99
Reference	0	0	0	0	0	0	0	0	0	0	0	0	0
Reference	10	9	7	10	6	10	8	9	10	10	10	10	10
Reference	20	26	22	28	18	25	23	26	26	28	28	28	27
Reference	30	46	41	49	33	43	41	44	45	49	48	49	48
Reference	40	69	66	75	69	69	66	70	66	75	74	74	79
Reference	60	91	87	93	80	88	86	89	87	82	91	93	82
Reference	90	102	100	100	99	98	101	100	99	99	99	102	101
Reference	120	103	101	101	101	99	102	101	101	100	100	102	101

The following results are confirmed using the Excel calculations.

Overall Statistics		
	Mean_R vs Individual_T	Mean_Test vs Mean_Reference
	Mean <input type="checkbox"/>	SE <input type="checkbox"/>
f1	25.244	0.933
Is f1 ∈ [0.15] between Mean_Test and Mean_Reference		No
Similarity of Test and Reference		Reject



4 DEFINITIONS, ABBREVIATIONS, AND ACRONYMS

Blocker – Severity assigned to a Failed test case. Cannot proceed with any testing with the entire application or several features because of this issue.

Critical – Severity assigned to a failed test case. A required feature or functionality is not working at all.

Major – Severity assigned to a failed test case – A required feature or functionality cannot be demonstrated to be working as per the requirement. It is working partially or not working correctly.

Minor – Severity assigned to a failed Test case – Feature or functionality works but has an issue that is causing a user annoyance, is only cosmetic in nature.

5 APPEXDIX

This section contains attachments of related documents and results from the verification and validation testing.

5.1 ITERATION -1 RESULTS:

A copy of iteration 1 results can be provided on request.

5.2 ITERATION -2 RESULTS:

A copy of iteration 2 results can be provided on request.

5.3 ITERATION-3 RESULTS:

A copy of iteration 3 results can be provided on request.

5.4 ITERATION-4 RESULT:

A copy of iteration 4 results can be provided on request