Modernizing Quality Assessment through Automation: ONDP/Division of Biopharmaceutics Automation Tool Application

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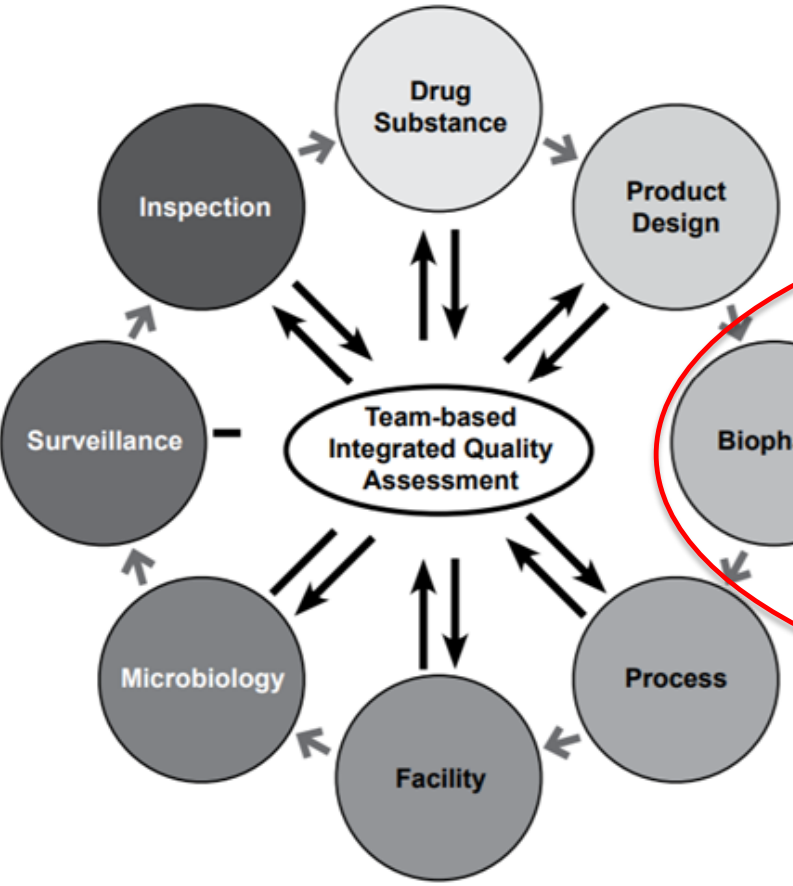
Outline

- Overview: review responsibilities in the **Division of Biopharmaceutics**
- Dissolution test and product quality assessment
- Automation tool for dissolution evaluation
  - Dissolution profiles comparison
  - Simulation to help assess dissolution acceptance criteria
- Summary
- Looking forward

FDA Pharmaceutical Quality
One Quality Voice



Our Goal

Establishing:
Patient Focused Quality Standard

Finding:
***In Vitro-In Vivo* Link for Pharmaceutical Manufacturing and Quality**

Figure modified from: https://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/UCM442666.pdf

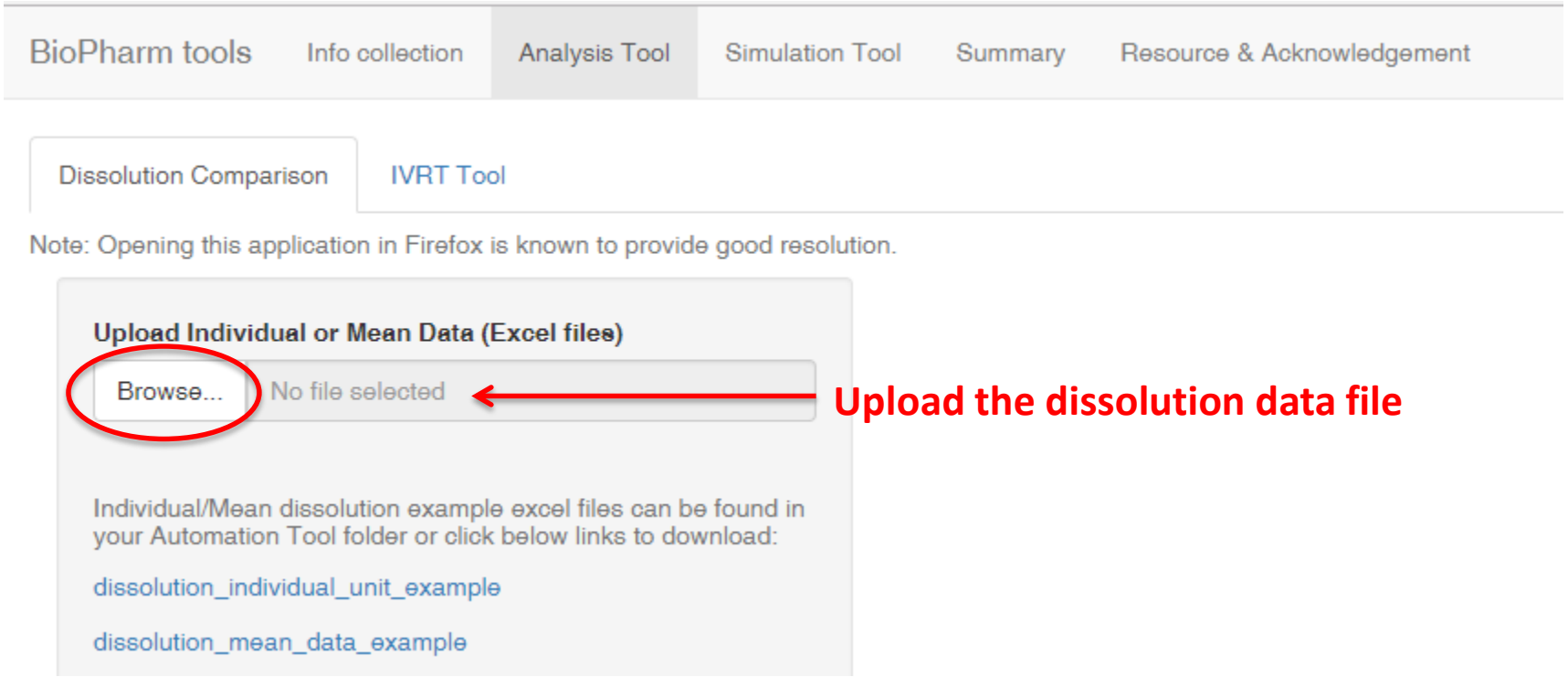
Dissolution Test:
Crucial in Product Quality Assessment

Applicable to multiple dosage forms:

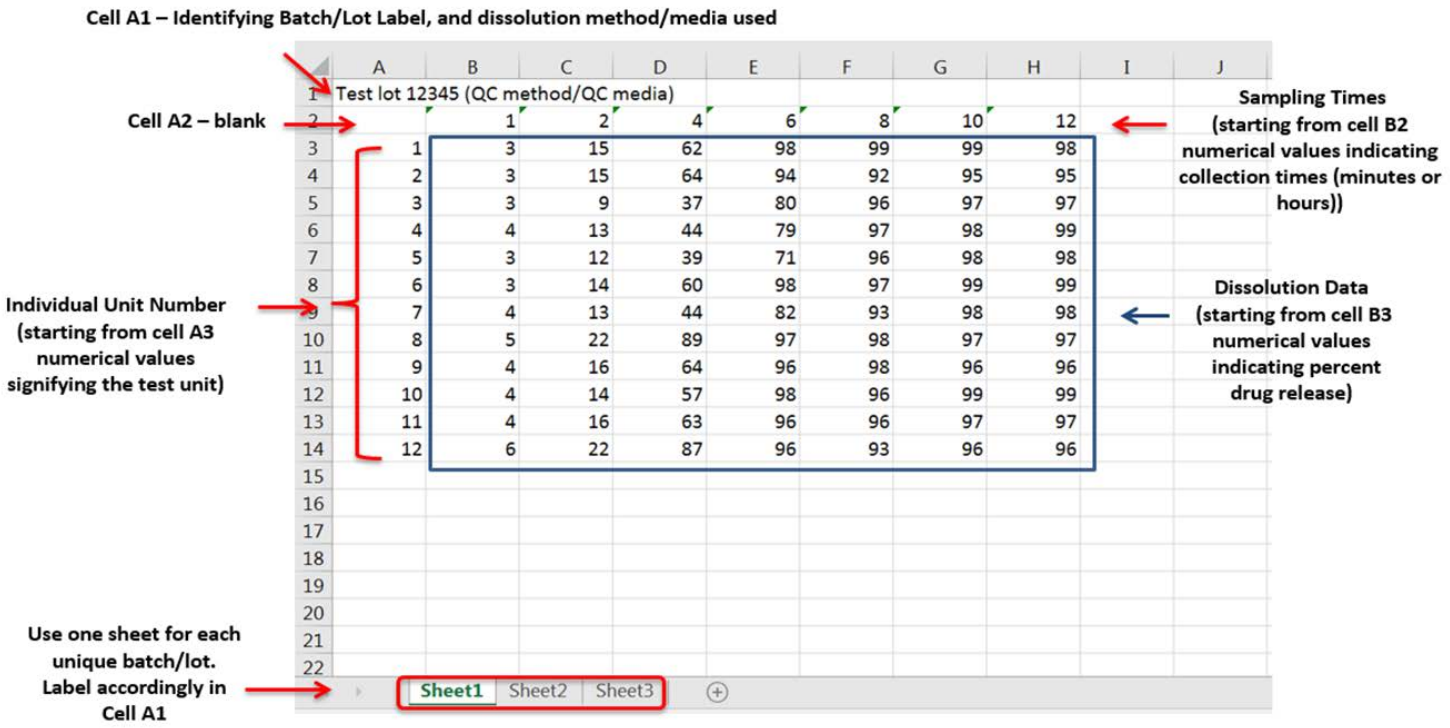
Tablets, Capsules, Implants, Powders, inserts, suspensions, etc.

Assessment involved	Frequently used in
Dissolution profiles comparison • f2 testing for highly variable dissolution: • Multivariate confidence region procedure (MVA Test) • f2 bootstrapping	• Pharmaceutical Development • Biowaivers • Interchangeability Evaluation • Scale-up and Post-Approval Changes (SUPAC)
Dissolution acceptance criteria	• Routine Quality Control • Stability Studies

Dissolution Profiles Comparison



Dissolution data input in Excel spreadsheet



	A	B	C	D	E	F	G	H	I	J
1	Test lot 12345 (QC method/QC media)									
2		1	2	4	6	8	10	12		
3	1	3	15	62	98	99	99	98		
4	2	3	15	64	94	92	95	95		
5	3	3	9	37	80	96	97	97		
6	4	4	13	44	79	97	98	99		
7	5	3	12	39	71	96	98	98		
8	6	3	14	60	98	97	99	99		
9	7	4	13	44	82	93	98	98		
10	8	5	22	89	97	98	97	97		
11	9	4	16	64	96	98	96	96		
12	10	4	14	57	98	96	99	99		
13	11	4	16	63	96	96	97	97		
14	12	6	22	87	96	93	96	96		
15										
16										
17										
18										
19										
20										
21										
22										

Dissolution Profiles Comparison (Cont.)

Upload Individual or Mean Data (Excel files)

Browse... example_s.xls

Upload complete

Individual data uploaded

Individual/Mean dissolution example excel files can be found in your Automation Tool folder or click below links to download:

dissolution_individual_unit_example

dissolution_mean_data_example

Download mean profiles overlay plot

☑ Show Error bar (1 standard deviation) in mean profile overlay plot

Choose time unit for the dissolution data

○ min ◉ hr

Select dissolution data sets for pairwise F2 calculations

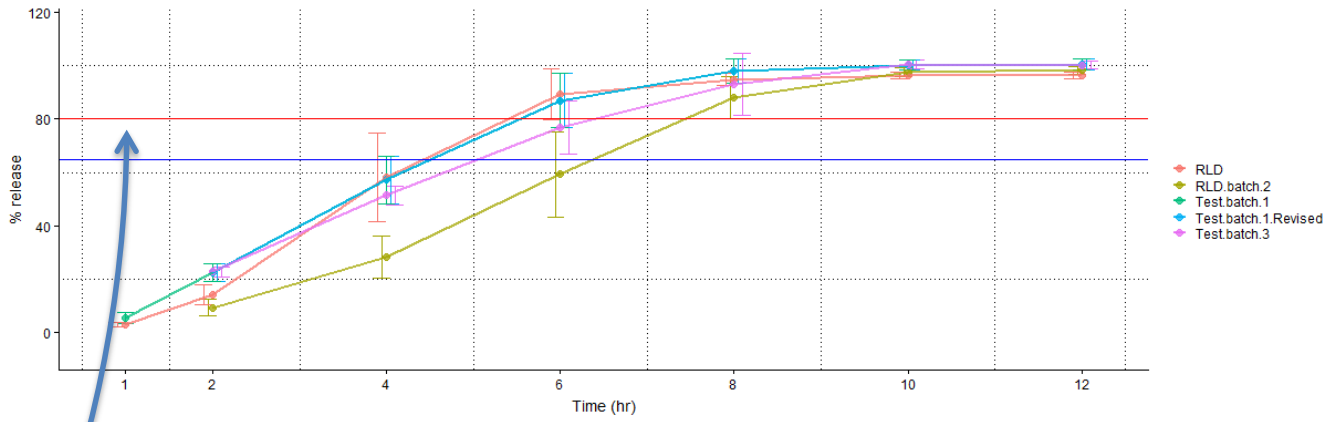
☑ RLD
☑ Test.batch.1
☑ Test.batch.1.Revised
☑ RLD.batch.2
☑ Test.batch.3

Choose time points for pairwise F2 calculations

☑ 1 ☑ 2 ☑ 4 ☑ 6 ☑ 8 ☑ 10 ☑ 12

specification of dissolution: Q (%)

80



Mean plot; Red horizontal line: Q(%); Blue horizontal line: Q-15%

Name	F2-Value
RLD Vs RLD.batch.2	37.62
RLD Vs Test.batch.1	68.08
RLD Vs Test.batch.1.Revised	67.09
RLD Vs Test.batch.3	56.86
RLD.batch.2 Vs Test.batch.1	37.57
RLD.batch.2 Vs Test.batch.1.Revised	37.57
RLD.batch.2 Vs Test.batch.3	43.82
Test.batch.1 Vs Test.batch.1.Revised	100.00
Test.batch.1 Vs Test.batch.3	63.83
Test.batch.1.Revised Vs Test.batch.3	63.83

MEAN	1	2	4	6	8	10	12
RLD	2.83	14.08	58.17	89.42	94.92	96.42	96.42
RLD.batch.2		9.33	28.42	59.25	88	97.67	98.33
Test.batch.1	5.5	22.33	57.17	87	98.08	100.33	100.67
Test.batch.1.Revised		22.33	57.17	87	98.08	100.33	100.67
Test.batch.3		22.75	51.33	76.92	93	100.42	100.33

CV(%)	1	2	4	6	8	10	12
RLD	33.09	26.65	28.85	10.71	2.31	1.36	1.36
RLD.batch.2		33.36	27.65	26.87	8.95	1.87	1.58
Test.batch.1	35.95	15.19	15.91	11.6	4.67	1.92	2.09
Test.batch.1.Revised		15.19	15.91	11.6	4.67	1.92	2.09
Test.batch.3		7.98	7.02	12.76	12.58	1.61	1.37

Dissolution Profiles Comparison (Cont.)

Select 1st dissolution profile:

RLD

Select 2nd dissolution profile:

Test.batch.1

Choose time points for MAV and bootstrapping

☑ 1 ☑ 2 ☑ 4 ☑ 6 ☑ 8 ☑ 10 ☑ 12

Number of replications for the bootstrapping

500

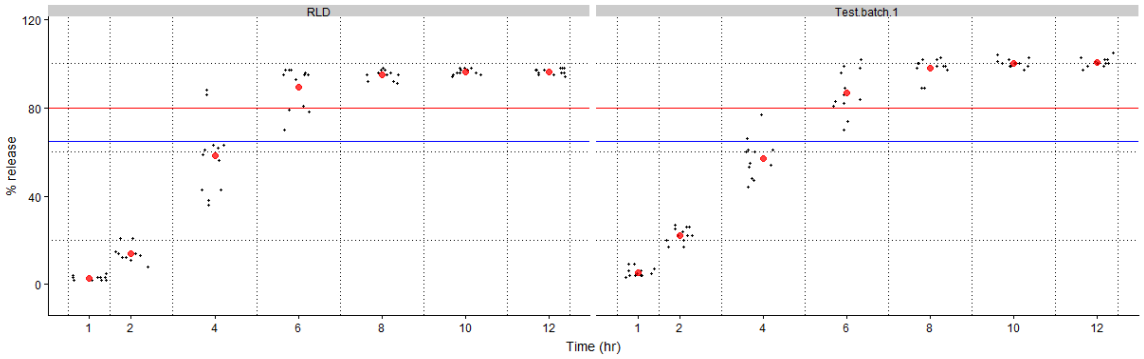
Press for bootstrapping

Select download file type

pdf

Download comparison plots

Download data file



Red line: Q(%); Blue line: Q-15%; Red dot: mean value for all units per time point. Note, the whole column represents the same time point.

MVA test

Compare	Time points	Dosage unit	Mahalanobis Distance (MSD)	Upper 90% CI (MSD)	MAX MSD	Similarity limit
RLD vs Test.batch.1	7	12	7.19025795174293	9.03786970435277	10.0736619344423	10

In MVA, the similarity can be verified if the upper bound of the confidence interval is smaller or equal to the MAX MSD

Bootstrapping test

Compare	Time points	Dosage unit	Lower 90% CI (BCA)	Upper 90% CI (BCA)	Mean from bootstrapping	Original f2
RLD vs Test.batch.1	7	12	66.6449371536966	70.8917688237604	66.8100396054361	68.0766073512341

In bootstrapping, the similarity can be verified if the lower bound of the confidence interval is larger or equal to 50

Dissolution Acceptance Criteria Assessment Simulation Tool

- To visualize appropriateness of a proposed/recommended acceptance criteria
- To estimate the pass rate (as per USP guidelines) for a proposed/recommended acceptance criteria

Assumptions:

- The dissolution data of BE/clinical batch (mean and %CV) is representative
- Normal distribution of the dissolution data

Simulation Tool: Immediate release formulation

BioPharm tools | Info collection | Analysis Tool | Simulation Tool | Summary | Resource & Acknowledgement

Immediate Release | Extended Release | Delayed Release

Change the default numbers to display graphical results based on user inputs and the assumption of normal distribution.

specification of dissolution: Q (%)

80

Size of each batch

1e+05

mean dissolution (%) of each batch

83

i.e. 80 means mean percent dissolution is 80%

CV% of dissolution of each batch

10

i.e. 10 means CV is 10%

Resample

graphic presentation will change according to new sampling

Estimate pass rate based on mean and CV

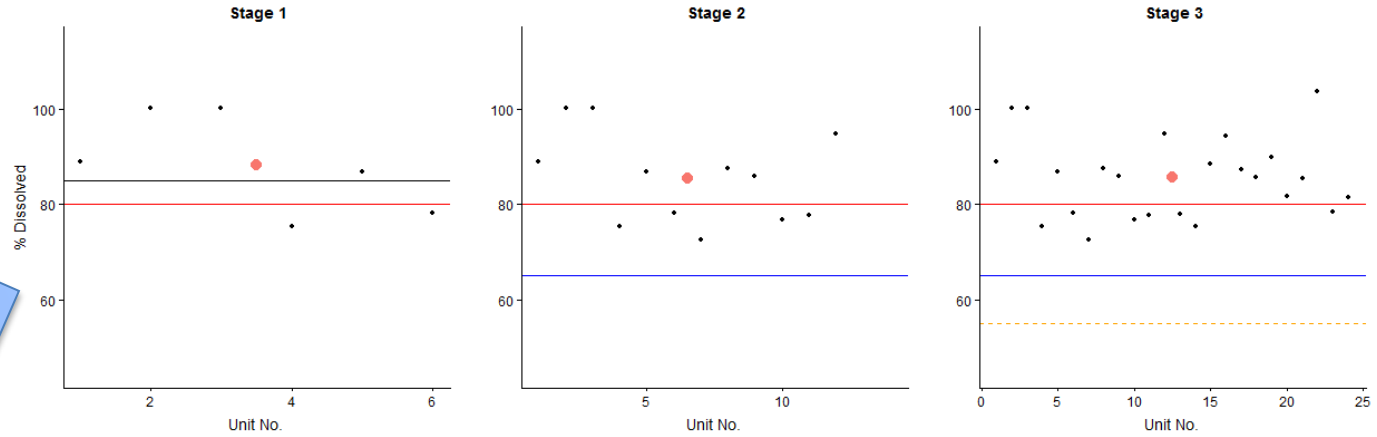
Number of batches simulated

50

Simulate to see batch pass rate

Per USP, for IR formulation, to pass stage 1: each unit is not less than Q+5%; To pass stage 2: Average (S1+S2) is equal to or greater than Q, and no unit is less than Q-15%; To pass stage 3: Average (S1+S2+S3) is equal to or greater than Q, not more than 2 units are less than Q-15%, and no unit is less than Q-25%

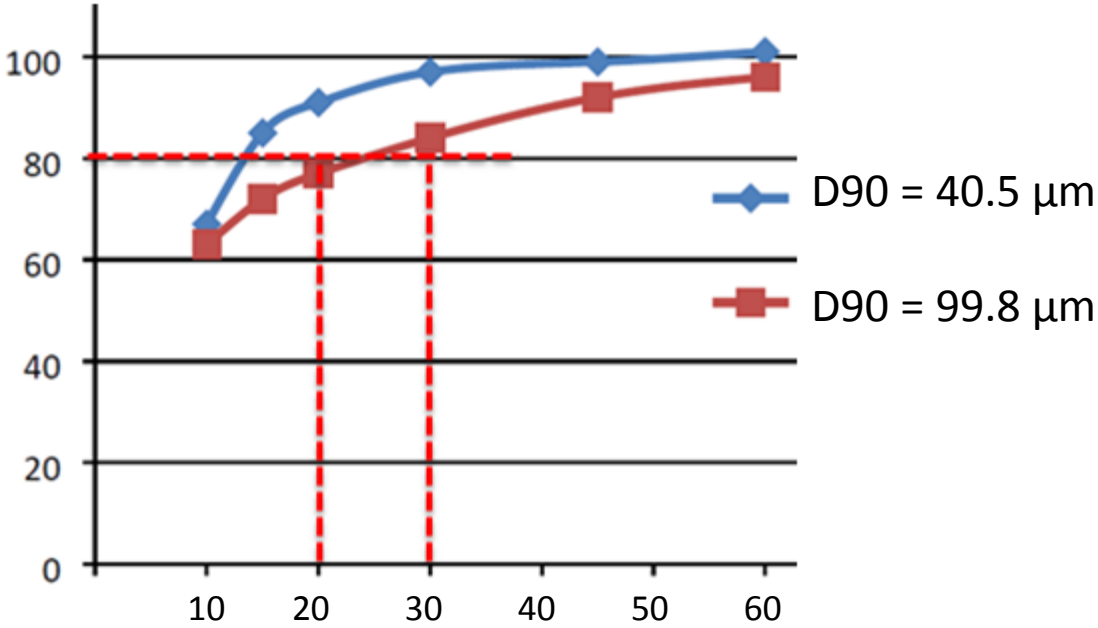
Graph displays the simulated results based on user defined dissolution specs, mean, and %CV



Black line: User defined specs(Q)+5%; Red line: Q(%); Blue line: Q-15%; dash red line: Q-25%; Red dot: mean value for all units per time point

Pass rate (%) based on number of simulations specified

Example: IR product (BCS Class II API)



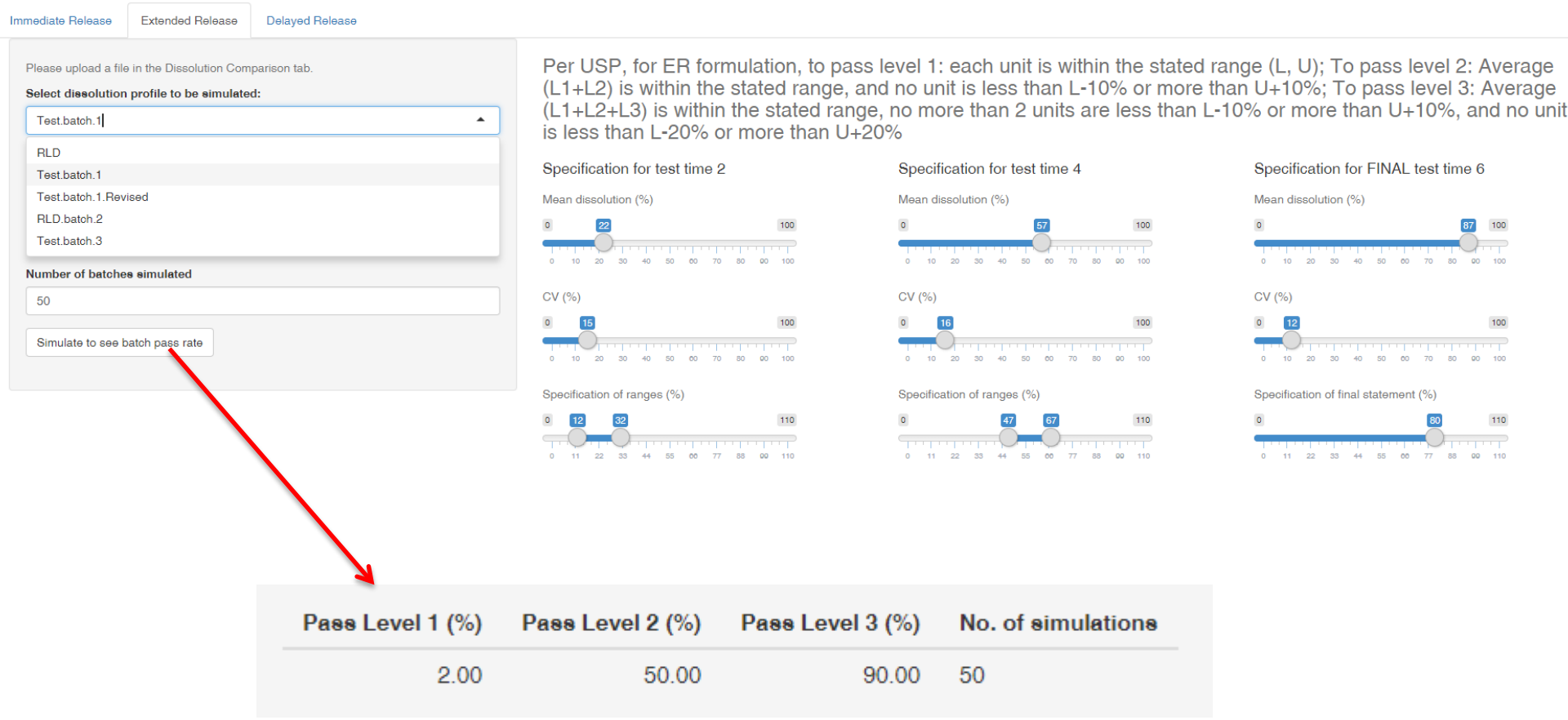
With the acceptance criterion set at "Q=80% at 20 minutes"

Pass Stage 1 (%)	Pass Stage 2 (%)	Pass Stage 3 (%)	No. of simulations	Mean release (%)	CV (%)	Q (%)
0.00	4.00	4.2	500	77	8.4	80

With the acceptance criterion set at "Q=80% at 30 minutes"

Pass Stage 1 (%)	Pass Stage 2 (%)	Pass Stage 3 (%)	No. of simulations	Mean release (%)	CV (%)	Q (%)
0.00	98.00	100.00	500	83	6.2	80

Simulation Tool: Extended release formulation



Pass Level 1 (%)	Pass Level 2 (%)	Pass Level 3 (%)	No. of simulations
2.00	50.00	90.00	50

Summary

- OPQ/ONDP/Division of Biopharmaceutics utilizes automation to streamline, improve efficiency and homogenize the review process

- The Automation Tool provides:
  - ❑ graphical output for dissolution profiles
  - ❑ automatic statistical analyses for profiles comparison
  - ❑ simulation to help determine clinical relevant dissolution acceptance criteria

Looking Forward

Division of Biopharmaceutics in Office of New Drug Products continues to explore ways to establish the in vitro – in vivo link for pharmaceutical manufacturing quality

- G-SRS provides a comprehensive framework, where quality specifications and corresponding clinical information can be captured

- Division of Biopharmaceutics is looking for ways to leverage the power of the G-SRS framework, and develop functionalities tailored to meet the needs of quality assessment, i.e. evaluating linkage between product quality attributes and clinical performances (PK data and quality related adverse events)

Acknowledgments

(arranged alphabetically by first names)

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