STABILITY TESTING DESIGN & DATA ANALYSIS

Stability study design and data analysis to determine shelf life for drug product

Background

For every drug product on the market, the regulatory bodies require that an expiration dating period (or shelf-life or expiration date) be indicated on the immediate container label. The expiration date provides the consumer with the confidence that the drug product will retain its identity, strength, quality, and purity throughout the expiration period of the drug product.

If the drug fails to remain within the approved specifications for the identity, strength, quality, and purity, the drug product is considered unsafe and subject to recall. The US Food and Drug Administration's Report to the Nation in 2004 and 2005 indicated that one of the top reasons for drug recall was that stability data did not support existing expiration dates.

Since 1979, the Food and Drug Administration (FDA) has required that all prescription drugs have a shelf life indicated directly on the container label. Similar requirements are in place in the European Union and around the world. The International Conference on Harmonization (ICH) of Technical Requirements for the Registration of Pharmaceuticals for Human Use guidance document Q1A(R2) (ICH Q1A) defines shelf life as, "The time period during which a drug product is expected to remain within the approved shelf life specification, provided that it is stored under the conditions defined on the container label."

To provide such assurance, pharmaceutical companies usually conduct stability studies to collect, analyze, and interpret data on the stability of their drug products throughout the expiration period.

Therefore, we wish to illustrate Statistical Design and Analysis of Stability data to predict shelf life of drug product.

Objective

The experimental objective of this study was to evaluation of stability data in order to determine the shelf-life of pharmaceutical product.

Main objective of Stability Testing Studies in general are summarized in table below (as per World Health Organization, WHO Technical Report Series, No. 863, 1996)

Objective	Type of study	Use
To select adequate (from the viewpoint of stability) formulations and containerclosure systems	Accelerated	Development of the product
To determine shelf-life and storage conditions	Accelerated and/or Long term / real-time	Development of the product and of the registration dossier
To substantiate the claimed shelf-life	Real-time	Registration dossier
To verify that no changes have been introduced in the formulation or manufacturing process that can adversely affect the stability of the product	Accelerated and real-time	Quality assurance in general, including quality control

This example is based on a model injectable drug product parenteral drug formulation was subjected to stability studies. The long-term stability data of three different production batches of the same product are evaluated by linear regression analysis. The shelf-life is determined based on confidence interval of selected linear model. Stability specifications and numerical limits of the responses and factors have been moderated to suit the needs of the example.

Scope

In the pharmaceutical industry stability programs are usually applied at various stages of drug development. For example, early stage of drug development, late stage dug development and toxicology, preclinical and clinical studies, and commercial manufacturing I.e.

- at an early stage of drug development, a stability program is necessarily carried out to study the stability of bulk drug substances. The purpose is to evaluate excipient compatibility under various storage factors, such as heat, humidity, light, and container type.
- at a later stage it is required to conduct a stability program for the formulations used in toxicology, preclinical and clinical studies to make sure the drug product is within specifications during the entire study.
- for the proposed market formulation, a stability program is required to establish an expiration dating period applicable to all future batches of the drug product. For the production batches, it is a common practice to have a stability monitoring program in place to ensure that all drug characteristics remain within desired specifications.

The design of a stability study is intended to establish an expiration dating period, the design should be chosen so that it can reduce bias and at the same time identify and control any expected or unexpected sources of variations. The goal for selection of an appropriate stability design is to improve the accuracy and precision of the established shelf-life.

The scope of this illustration is applicable to all these stages subjected to relevant regulatory guidelines with respect to type of product, allowed extrapolation, number of batches required etc.

Data

Stability studies on a finished pharmaceutical product are generally designed in the light of the physical, chemical, biological, biopharmaceutical and microbiological characteristics of a drug, during and beyond the expected shelf-life and storage periods of samples under the storage conditions expected in the intended market.

Typical stability indicating parameters are Assay, Content Uniformity, Residual Solvent, Moisture, Product degradation impurities (individual and total) etc. but not limited to. Measurements are done at predetermined timepoints with validated or acceptable method of analysis.

In this illustration long-term storage temperature (i.e. at 2°C to 8°C) stability data of three different production batches i.e. Batch 1, Batch 2, Batch 3, of the same parenteral drug product was generated for 0, 3,6 and 9 months.

For purpose of this example, we are only analyzing data generated for % Drug assay (Stability indicating parameter) for active pharmaceutical ingredient in drug product. The upper and lower specification limits for % Drug assay are 95 and 105 respectively. In additional two

possible vail orientations like inverted and upright were also considered in this study planning.

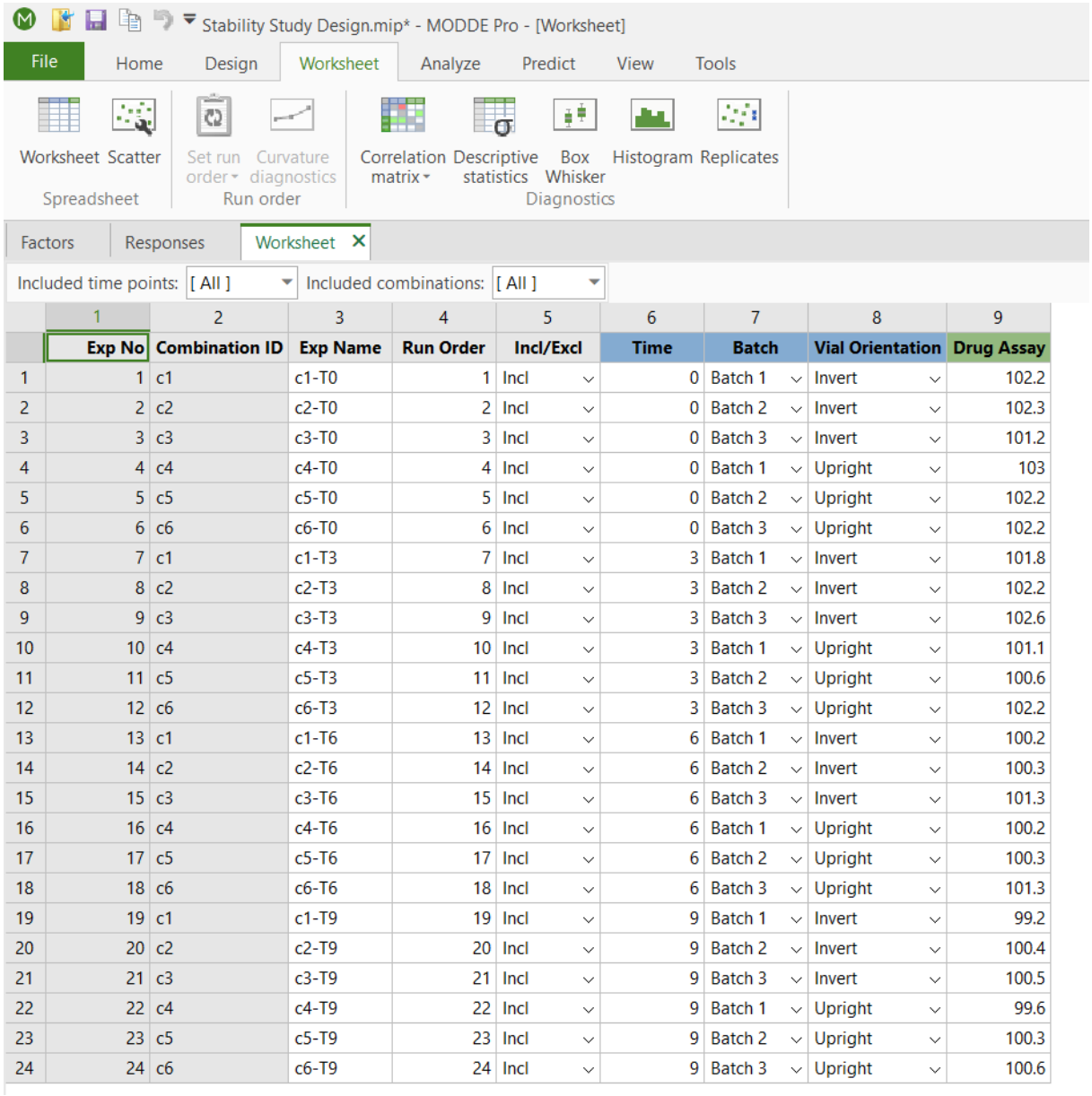
Vial Orientation: Upright & Inverted

Factors

	Name	Abbreviation	Units	Type	Settings
1	**Time**	T	month	Time	0, 3, 6, 9
2	**Batch**	Bat		Qualitative	Batch 1, Batch 2, Batch 3
3	**Vial Orientation**	VO		Qualitative	Invert, Upright
+	*Add...*				

Responses

	Name	Abbreviation	Units	Condition	Objective	Min	Target	Max
1	**Drug Assay**	DA	%	Required	Inside	95		105
+	*Add...*							



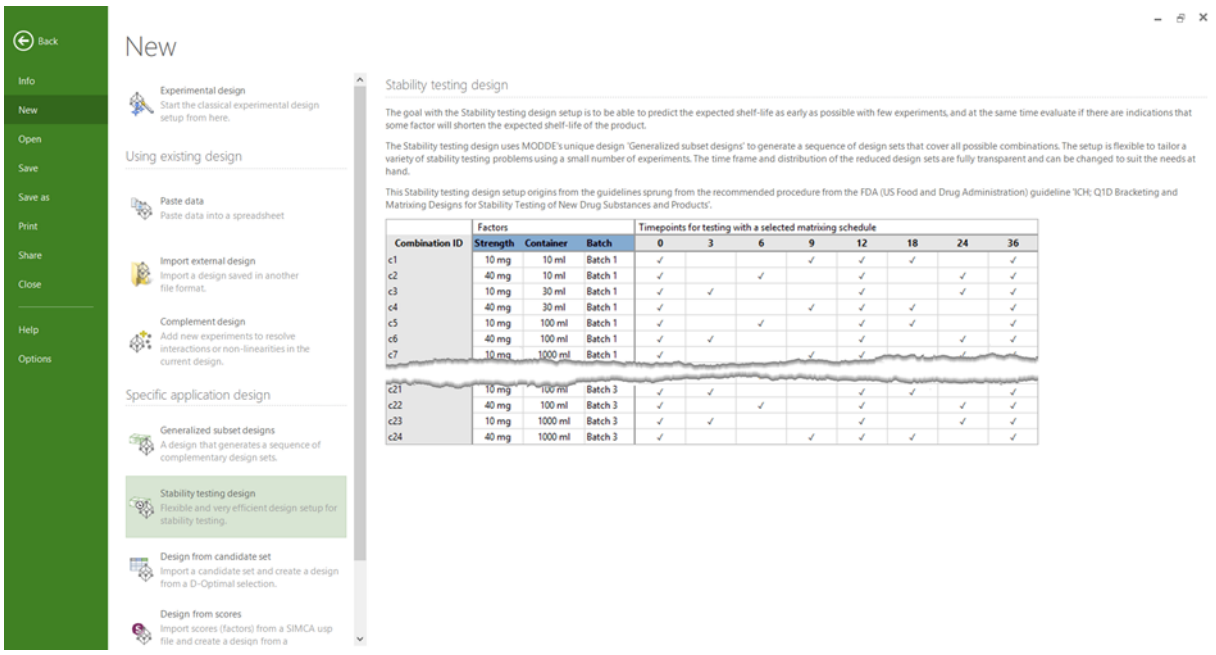
	1	2	3	4	5	6	7	8	9
	Exp No	Combination ID	Exp Name	Run Order	Incl/Excl	Time	Batch	Vial Orientation	Drug Assay
1	1	c1	c1-T0	1	Incl	0	Batch 1	Invert	102.2
2	2	c2	c2-T0	2	Incl	0	Batch 2	Invert	102.3
3	3	c3	c3-T0	3	Incl	0	Batch 3	Invert	101.2
4	4	c4	c4-T0	4	Incl	0	Batch 1	Upright	103
5	5	c5	c5-T0	5	Incl	0	Batch 2	Upright	102.2
6	6	c6	c6-T0	6	Incl	0	Batch 3	Upright	102.2
7	7	c1	c1-T3	7	Incl	3	Batch 1	Invert	101.8
8	8	c2	c2-T3	8	Incl	3	Batch 2	Invert	102.2
9	9	c3	c3-T3	9	Incl	3	Batch 3	Invert	102.6
10	10	c4	c4-T3	10	Incl	3	Batch 1	Upright	101.1
11	11	c5	c5-T3	11	Incl	3	Batch 2	Upright	100.6
12	12	c6	c6-T3	12	Incl	3	Batch 3	Upright	102.2
13	13	c1	c1-T6	13	Incl	6	Batch 1	Invert	100.2
14	14	c2	c2-T6	14	Incl	6	Batch 2	Invert	100.3
15	15	c3	c3-T6	15	Incl	6	Batch 3	Invert	101.3
16	16	c4	c4-T6	16	Incl	6	Batch 1	Upright	100.2
17	17	c5	c5-T6	17	Incl	6	Batch 2	Upright	100.3
18	18	c6	c6-T6	18	Incl	6	Batch 3	Upright	101.3
19	19	c1	c1-T9	19	Incl	9	Batch 1	Invert	99.2
20	20	c2	c2-T9	20	Incl	9	Batch 2	Invert	100.4
21	21	c3	c3-T9	21	Incl	9	Batch 3	Invert	100.5
22	22	c4	c4-T9	22	Incl	9	Batch 1	Upright	99.6
23	23	c5	c5-T9	23	Incl	9	Batch 2	Upright	100.3
24	24	c6	c6-T9	24	Incl	9	Batch 3	Upright	100.6

Setting Up the Design

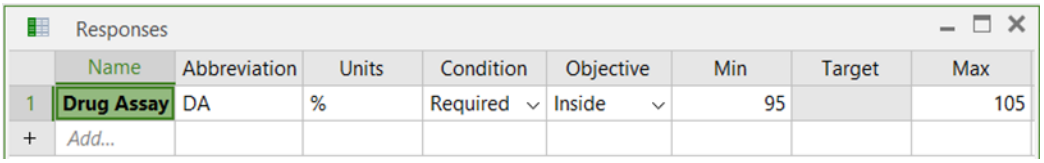
Design Wizard

Initiate a new investigation in MODDE®.

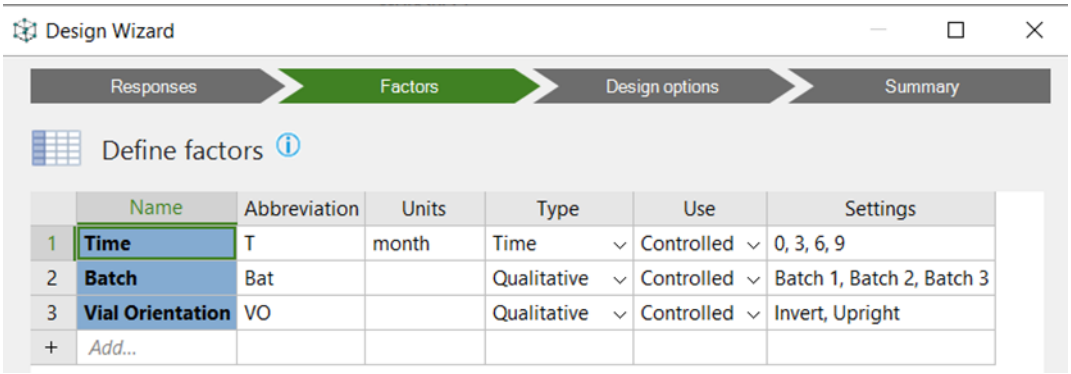
Select File/New/Stability testing design and step through the Design Wizard as shown below. Click Next.



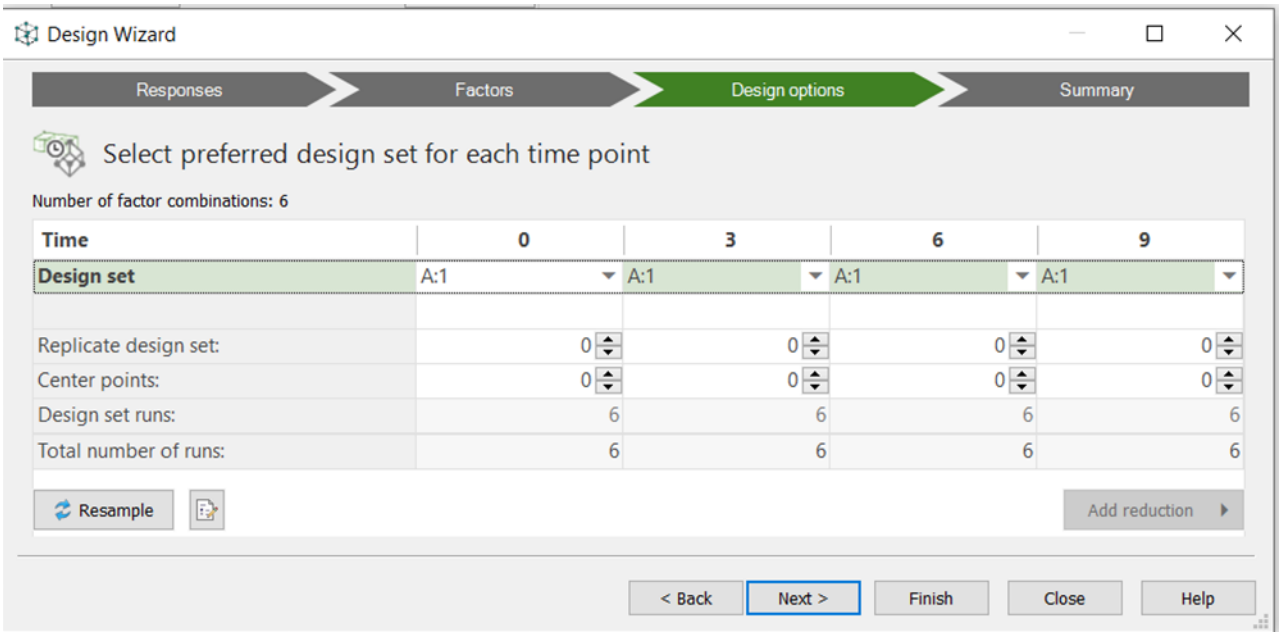
On the responses page, Click New and enter the name of the response. Set Condition to Required and Objective to Inside. Enter the value Min = 95 and Max = 105. Click OK. The response has now been defined. Click Next.



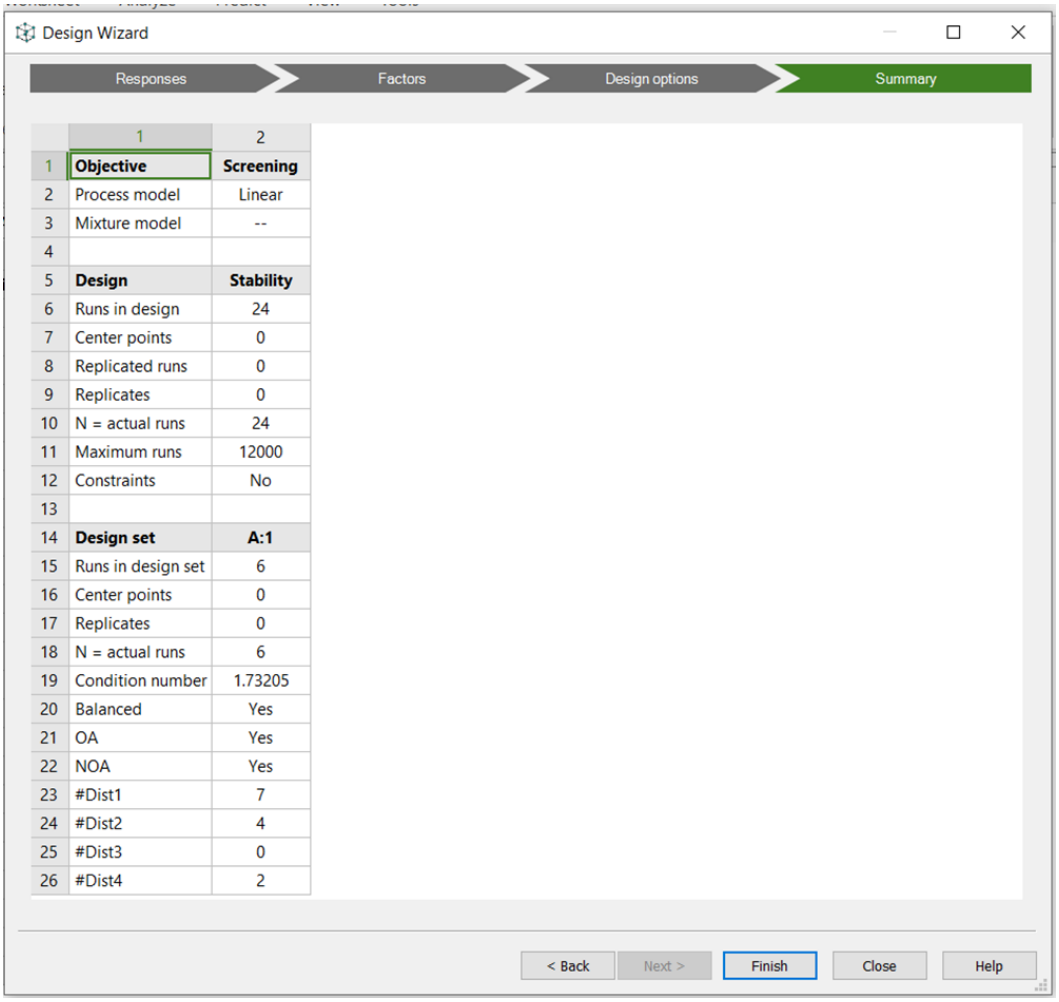
On the factors page, Click New and enter the name, abbreviation, unit, settings for the first factor. Click Add another and fill in the name, abbreviation, unit, settings second and third factor. Click on OK. The three factors have now been defined. Click Next.



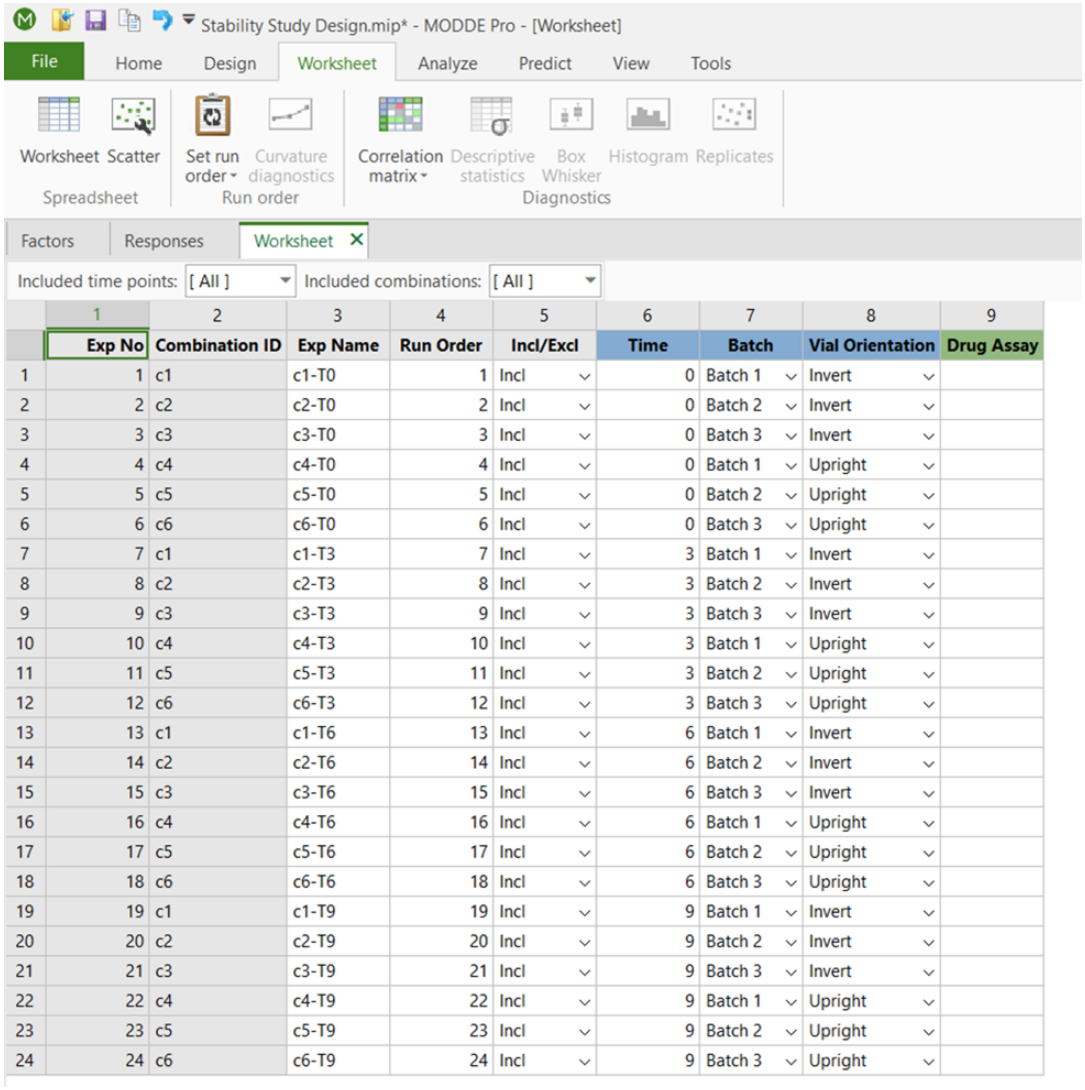
Select the proposed design with 24 design runs or samples. Click Next.



On the final Summary page, you can review your selections and settings, which should look like the screenshot below.



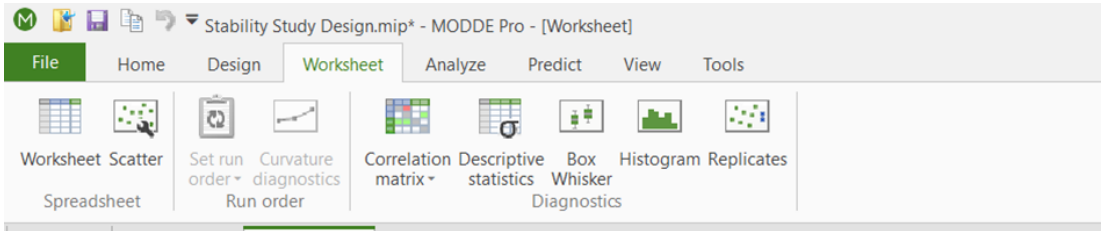
Click Finish to exit the design wizard.



	1	2	3	4	5	6	7	8	9
	Exp No	Combination ID	Exp Name	Run Order	Incl/Excl	Time	Batch	Vial Orientation	Drug Assay
1	1	c1	c1-T0	1	Incl	0	Batch 1	Invert	
2	2	c2	c2-T0	2	Incl	0	Batch 2	Invert	
3	3	c3	c3-T0	3	Incl	0	Batch 3	Invert	
4	4	c4	c4-T0	4	Incl	0	Batch 1	Upright	
5	5	c5	c5-T0	5	Incl	0	Batch 2	Upright	
6	6	c6	c6-T0	6	Incl	0	Batch 3	Upright	
7	7	c1	c1-T3	7	Incl	3	Batch 1	Invert	
8	8	c2	c2-T3	8	Incl	3	Batch 2	Invert	
9	9	c3	c3-T3	9	Incl	3	Batch 3	Invert	
10	10	c4	c4-T3	10	Incl	3	Batch 1	Upright	
11	11	c5	c5-T3	11	Incl	3	Batch 2	Upright	
12	12	c6	c6-T3	12	Incl	3	Batch 3	Upright	
13	13	c1	c1-T6	13	Incl	6	Batch 1	Invert	
14	14	c2	c2-T6	14	Incl	6	Batch 2	Invert	
15	15	c3	c3-T6	15	Incl	6	Batch 3	Invert	
16	16	c4	c4-T6	16	Incl	6	Batch 1	Upright	
17	17	c5	c5-T6	17	Incl	6	Batch 2	Upright	
18	18	c6	c6-T6	18	Incl	6	Batch 3	Upright	
19	19	c1	c1-T9	19	Incl	9	Batch 1	Invert	
20	20	c2	c2-T9	20	Incl	9	Batch 2	Invert	
21	21	c3	c3-T9	21	Incl	9	Batch 3	Invert	
22	22	c4	c4-T9	22	Incl	9	Batch 1	Upright	
23	23	c5	c5-T9	23	Incl	9	Batch 2	Upright	
24	24	c6	c6-T9	24	Incl	9	Batch 3	Upright	

Enter the response data or copy them from the file Raw data.XLS sheet.

After copying and pasting the data the updated worksheet should look like the screenshot below. Now you are ready to start analyzing the data.



Factors | Responses | Worksheet

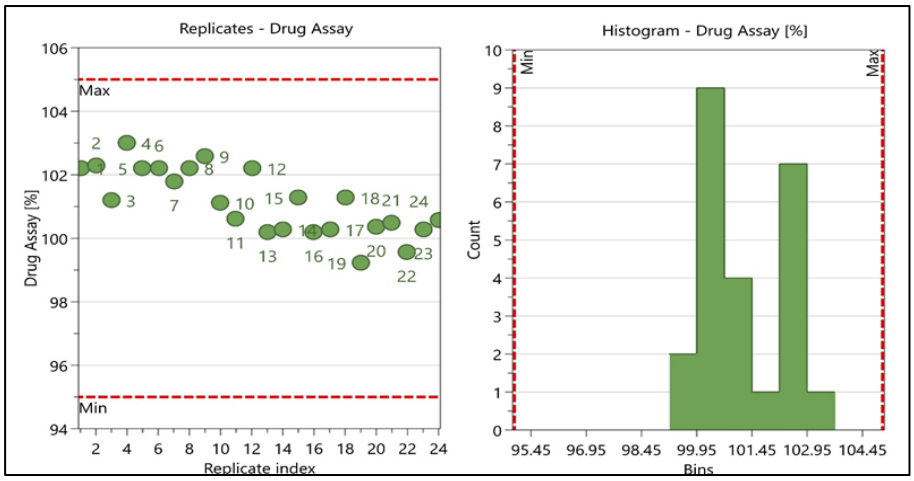
Included time points: [All] Included combinations: [All]

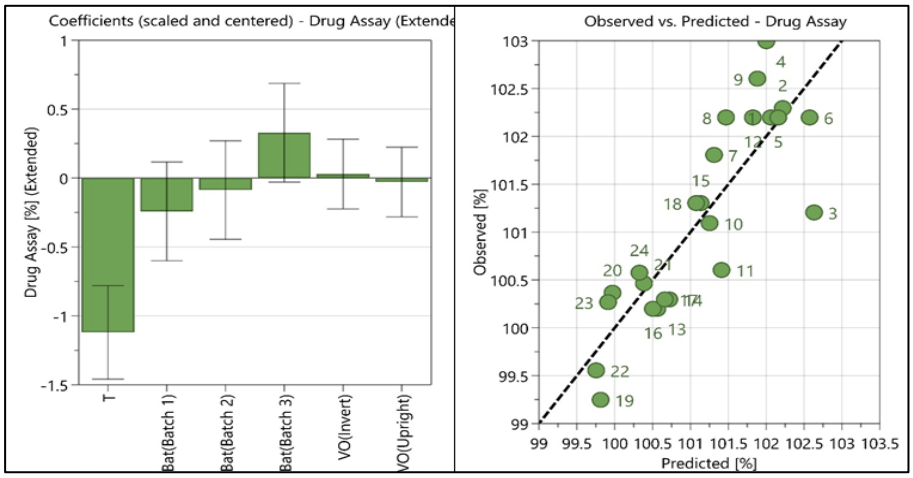
	1	2	3	4	5	6	7	8	9
	Exp No	Combination ID	Exp Name	Run Order	Incl/Excl	Time	Batch	Vial Orientation	Drug Assay
1	1	c1	c1-T0	1	Incl	0	Batch 1	Invert	102.2
2	2	c2	c2-T0	2	Incl	0	Batch 2	Invert	102.3
3	3	c3	c3-T0	3	Incl	0	Batch 3	Invert	101.2
4	4	c4	c4-T0	4	Incl	0	Batch 1	Upright	103
5	5	c5	c5-T0	5	Incl	0	Batch 2	Upright	102.2
6	6	c6	c6-T0	6	Incl	0	Batch 3	Upright	102.2
7	7	c1	c1-T3	7	Incl	3	Batch 1	Invert	101.8
8	8	c2	c2-T3	8	Incl	3	Batch 2	Invert	102.2
9	9	c3	c3-T3	9	Incl	3	Batch 3	Invert	102.6
10	10	c4	c4-T3	10	Incl	3	Batch 1	Upright	101.1
11	11	c5	c5-T3	11	Incl	3	Batch 2	Upright	100.6
12	12	c6	c6-T3	12	Incl	3	Batch 3	Upright	102.2
13	13	c1	c1-T6	13	Incl	6	Batch 1	Invert	100.2
14	14	c2	c2-T6	14	Incl	6	Batch 2	Invert	100.3
15	15	c3	c3-T6	15	Incl	6	Batch 3	Invert	101.3
16	16	c4	c4-T6	16	Incl	6	Batch 1	Upright	100.2
17	17	c5	c5-T6	17	Incl	6	Batch 2	Upright	100.3
18	18	c6	c6-T6	18	Incl	6	Batch 3	Upright	101.3
19	19	c1	c1-T9	19	Incl	9	Batch 1	Invert	99.2
20	20	c2	c2-T9	20	Incl	9	Batch 2	Invert	100.4
21	21	c3	c3-T9	21	Incl	9	Batch 3	Invert	100.5
22	22	c4	c4-T9	22	Incl	9	Batch 1	Upright	99.6
23	23	c5	c5-T9	23	Incl	9	Batch 2	Upright	100.3
24	24	c6	c6-T9	24	Incl	9	Batch 3	Upright	100.6

Stability Data Analysis and Prediction of Shelf Life

Use the Analysis wizard to analyze the data.

Use the analysis wizard to work through the responses. Evaluate the raw data. Is there any need for data pretreatment, for example transforming the response data? Try to find best model? Which factors are important? Are there any non-significant model terms? Are the residuals normally distributed? Refine the model, if necessary.





The model looks fairly good. However, the coefficient plot shows, most of the terms are small, so these can be removed to simplify the model, gain Df, and get the most accurate predictions (good Q2).

Visualize the Model

- Storage time is the key influencing factor which contributes in change in drug assay % value.
- Batch 1 and Batch 3 appears contributing little with respect to change in drug assay % value. Ideally It is expected that all three batches supposed to behave fairly similar and do not contribute to change in drug assay % value over the time or contribute at statistically insignificant level. If certain batch has considerable differences with respect to process performance or raw material etc. then it might reflect in coefficient plot as a significant contributor.

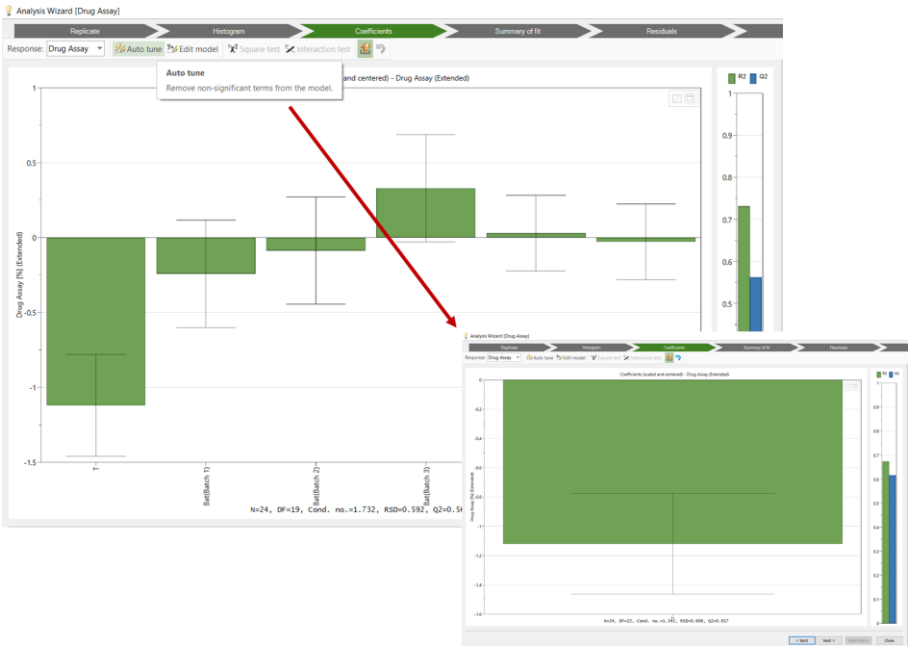
- Both vial orientations Invert and upright showed almost no impact on change in drug assay % value over the time or contribute at statistically insignificant level.

In the coefficient plot page, the exclude tool was used to remove the small and insignificant interaction terms, starting with the smallest coefficient, and excluding them one at a time.

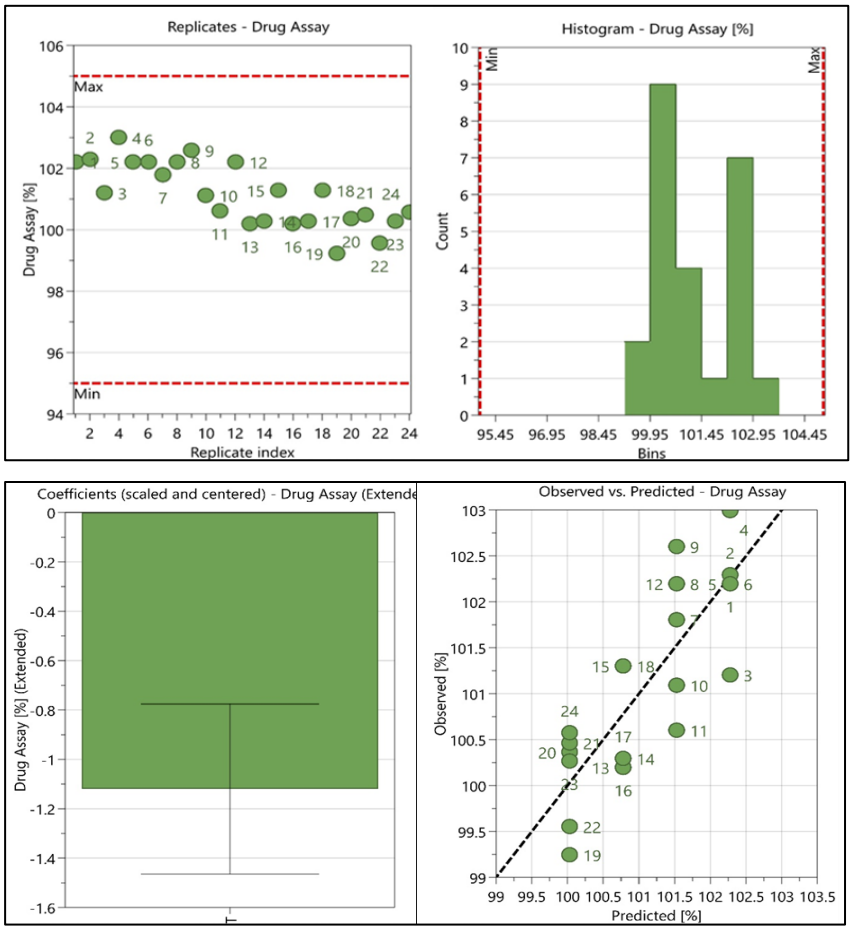
This can be done in two ways:

1. Remove all non-significant parameters or terms one by one and see if their significant change in mode performance i.e. R2 or Q2
2. Use Auto tune option in inbuilt into coefficient plot in Analysis wizard to remove all non-significant parameters or terms in one click, i.e.

With either of above approaches we will find that Time is the only factor appears contributing on change in drug assay % value



This procedure resulted in the following model diagnostics

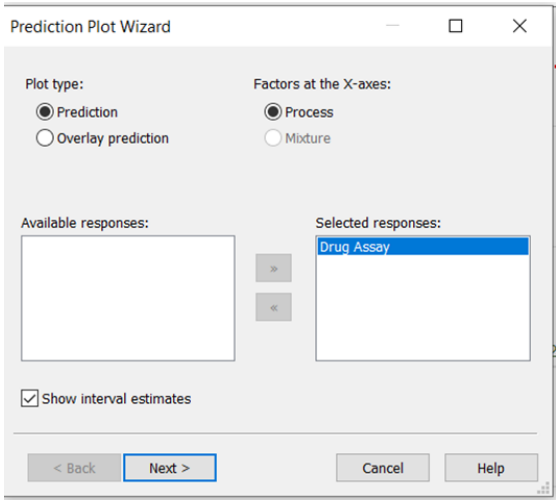


The model looks fairly like earlier model with respect to R2 and Q2. However, the number of coefficients is reduced to just one and we have simplified model, more Df.

Estimation of Predicted Shelf Life or Expiration Period

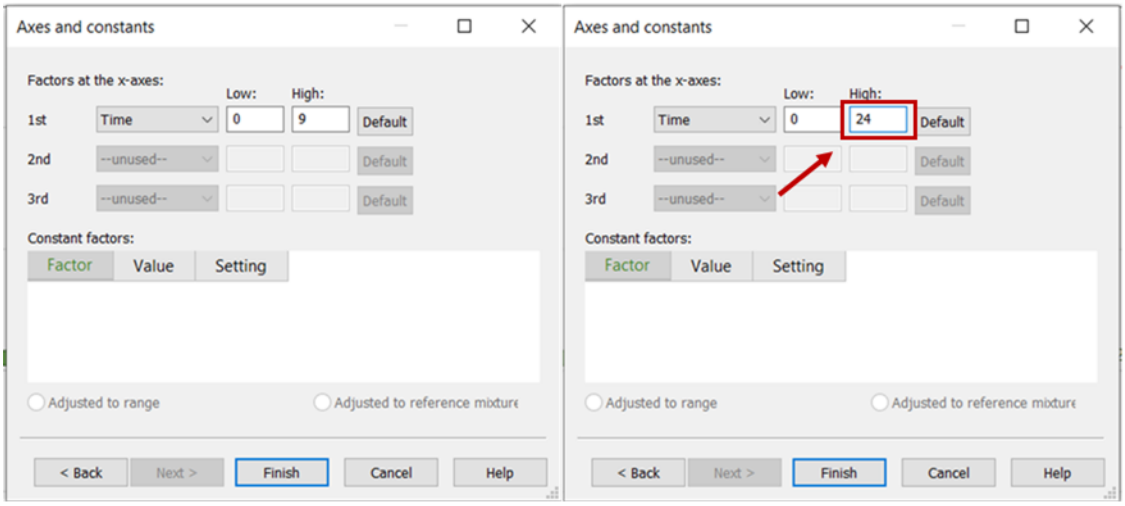
Create a prediction plot in MODDE®.

Select Predict/Prediction plot and step through the plot settings as shown below. Click Next.



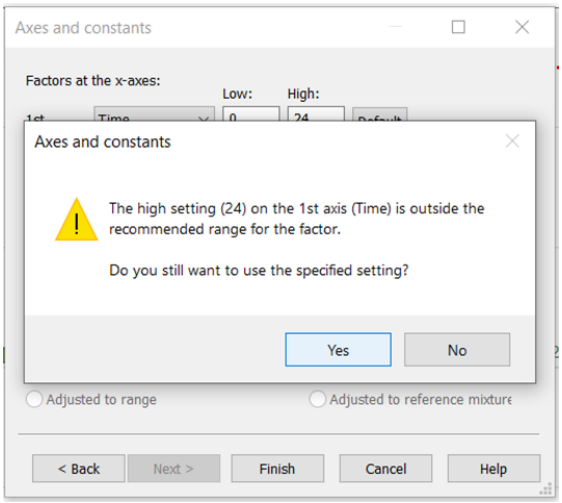
On Axes and Constants window modify the factors at X-axes based on need or until what

time we want extrapolate the dug assay %. In this case we would like to see extrapolated prediction of drug assay % for 24 months. Change the high limit to 24 as shown below.



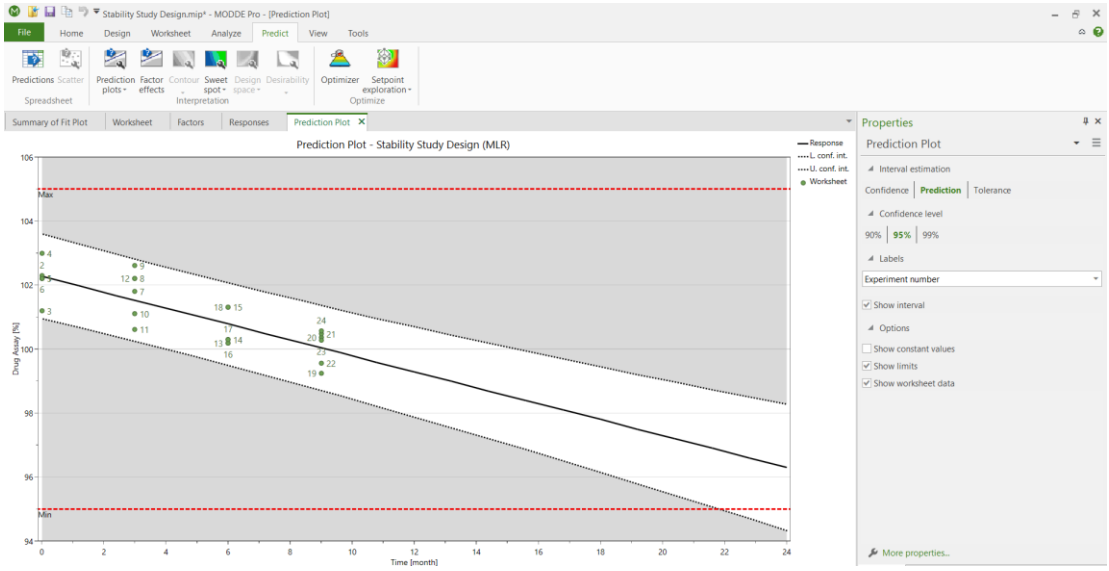
Many times, country specific regulatory guidelines and product under study can define how much maximum prediction one can go for i.e. 2X (2*9=18 months) or 1.5X (1.5*9 =13.5 months) etc. Click Finish

You might see warning sign based on the value you have entered for higher limit of extrapolation.



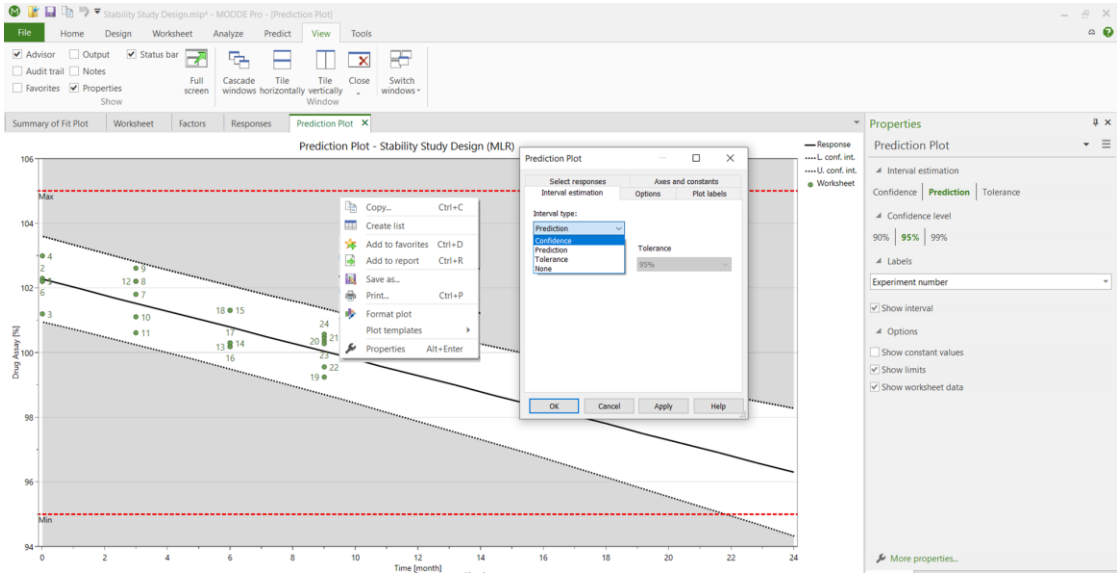
Click Yes and then Click Finish

You can see extrapolated prediction plot till 24 months for drug assay % with Prediction interval at 95% confidence level by default. You will also see predefines minimum and maximum acceptable settings for drug assay %.

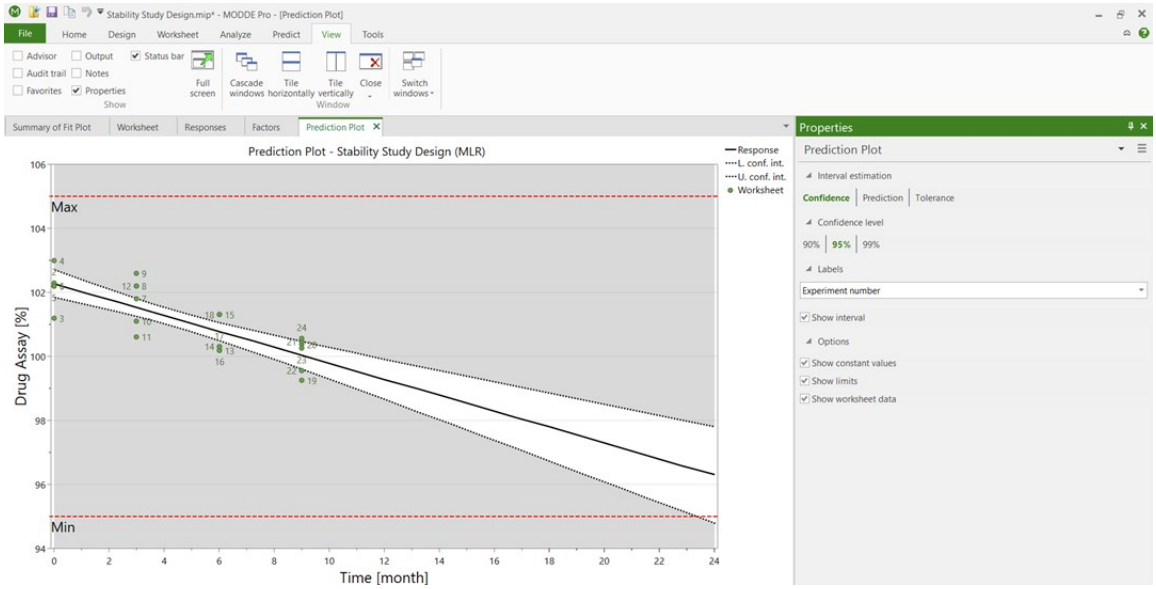


Many of the regulatory guideline including ICH (Q1A(R2) (ICH Q1A)) and WHO, recommends use of Confidence interval at 95% confidence level for estimation of shelf life.

To change the interval to Confidence interval, Right click on the above graph, Select Properties/ Interval Estimation/Choose Interval Type as “Confidence”. Click Apply.



You will see now extrapolated prediction plot till 24 months for drug assay % with Confidence interval at 95% confidence level.

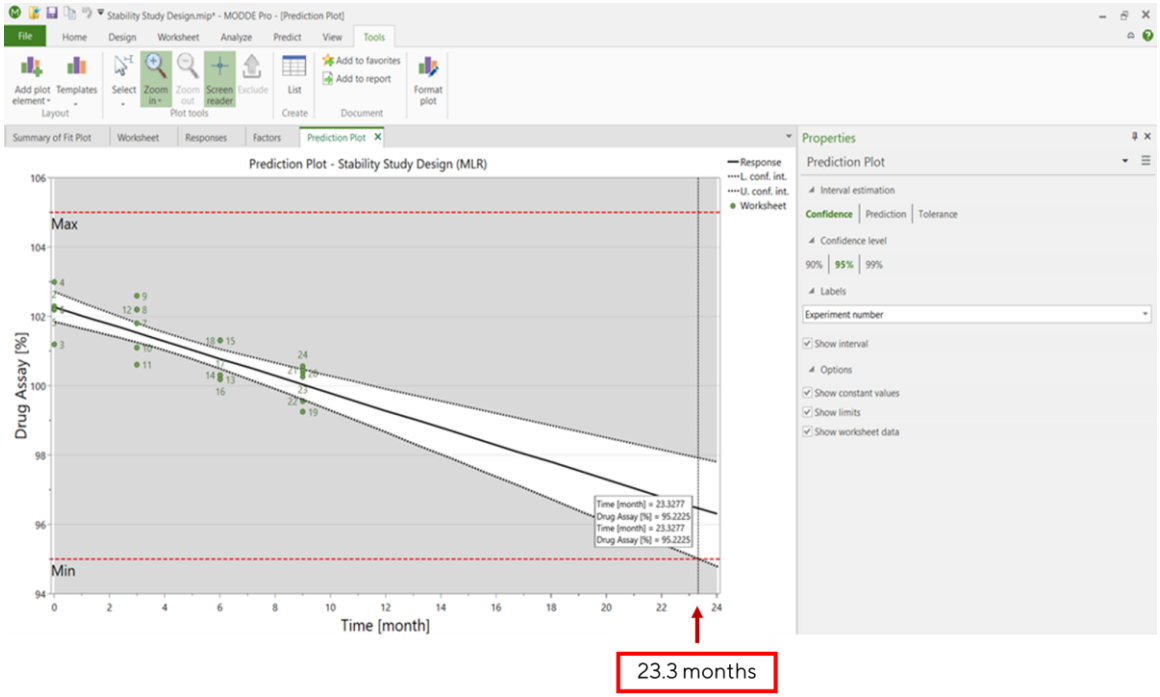


Predicted Shelf Life is estimated with reference to intersection of specification limits and Confidence interval at 95% confidence level. Different scenarios are possible based on behaviors of stability indicating parameter i.e.

- If it is decreasing over the time like drug assay % or vial volume, then lower interval will intersect with lower limit
- If it is increasing over the time like impurity etc. then upper interval will intersect with upper limit
- If it is uncertain trend over the time like some impurities, initial increases and then decreased because of its own degradation etc. then we might see both upper and lower intervals intersect with respective upper and lower limits

In this case we have drug assay % decreasing over the time and we can see lower interval will intersect with lower limit.

To estimate supported shelf life, Select Tool/Screen Reader and point at intersection of lower interval & lower specification limit as shown below. Timestamp at intersection is 23.3 months.



Conclusions

The Design wizard helped in setting up Stability Study design in quick and guided workflow. The Analysis wizard assisted in understanding role of different factors developing strong models for stability indicating parameter. Prediction plot with confidence interval helped in quick estimation of predicted shelf life.

Supported maximum shelf life is 23.3 months based on the above data analysis of stability indicating parameter drug assay %.

If one has multiple stability indicating parameters being evaluated, then lowest of all predicted shelf life will be considered as a predicted shelf life for that drug product.