VIR-7831(GSK4182136) Drug Product Stability Trend Report

Purpose:

The purpose of this study is to evaluate the stability of VIR-7831(GSK4182136) drug product batches (manufactured at WuXi Biologics, China using Gen1 and Gen2 2000 L DS) and commercial scale DP batches (manufactured at GSK Parma, Italy using Gen2 6 x 2000 L DS) at a concentration of 25 mg/mL and 62.5 mg/mL in a 10 mL vial, in accordance with ICH guideline Q1A (R2) "*Stability Testing of New Drug Substances and Products*", and ICH Q5C "*Stability Testing of Biotechnological/Biological Products*". The data will be collected to support the recommended storage condition and the drug product shelf life for regulatory filing.

Statement:

This report should be considered a historical document and statements made are accurate, at the time the report was authored. Any proposals (storage condition, retest date/shelf life statements, and label claims) in this report are recommendations based on the available data. All GMP storage conditions, retest date/shelf lives, and label claims are supported by the appropriate documentation and change controls. The official drug product storage condition, expiry date/shelf life, and label claims are documented in the appropriate controlled specification document.

Scope:

This study is designed to evaluate the stability of VIR-7831(GSK4182136) drug product, stored at the long-term 2°C – 8°C (5°C), accelerated 25°C/60% RH (25°C), and stress 40°C/75% RH storage conditions. The vials are stored in the inverted orientation. These stability data presented in this report supports a recommended storage condition of "store at 5 ± 3°C" and a proposed shelf life of 24 months. The official shelf life is documented on the appropriate specification document using the appropriate documentation and change control.

Summary:

The stability data for the VIR-7831(GSK4182136) drug product (62.5 mg/mL) batches (manufactured using the early stage process and commercial process), described in **Table 1** and **Table 2**, were entered into JMP Pro 15.2.0 Statistical Analysis Software. The data for each batch and storage condition was analyzed by bivariate analysis of the test results versus time to generate trend plots. These trend plots can be used to assess change in the results over time, in terms of empirical relationships. In addition, degradation model (Statistica 13.5.0) was used since the data could be pooled.

The data collected at the long-term (2°C – 8°C) storage condition and the accelerated (25°C/60% RH) condition are used to support the expiry date (clinical) and shelf life (commercial) of the material, according to ICH guidance Q1E "Evaluation for Stability Data" and Q5C "Stability Testing of Biological Products." This guidance applies to drug substance and drug product for use in humans. The data collected at the stress (40°C/75% RH) storage condition is used to support short-term temperature excursions and demonstrate comparability between the clinical batches and the commercial-scale material.

The commercial drug product process specification (VQD-SPEC-027213) is provided in **Table 3**. The details of the stability container are provided in **Table 4**.

The trend plots in Figure 10 - Figure 12 demonstrate that VIR-7831(GSK4182136) drug product (62.5 mg/mL) manufactured at WuXi and Parma in a 10 mL vial, have stability indicating attributes that are demonstrated to remain within specifications, at the recommended storage condition of “store at 2°C – 8°C” up to 24 months.

Table 1: Summary of VIR-7831 (GSK4182136) 25mg/mL and 62.5 mg/mL Drug Product Gen1 and Gen2 Scale Process Drug Product in a 10 mL Vial Manufactured at WuXi

Batch #	Description	Storage Conditions	Study Condition	Available Data	Length of Study	Stability Report
202006002	Clinical Gen1 25 mg/mL	5 ± 3°C 25 ± 2°C/60 ± 5% RH 40 ± 2°C/75 ± 5% RH	Long Term Accelerated Stress	18 Months Study Complete Study Complete	24 Months 6 Months 6 Months	VIR Report Number: 11034
202006004	Clinical Gen1 25 mg/mL	5 ± 3°C 25 ± 2°C/60 ± 5% RH 40 ± 2°C/75 ± 5% RH	Long Term Accelerated Stress	18 Months Study Complete Study Complete	24 Months 6 Months 6 Months	VIR Report Number: 11053
202009005	Clinical Gen2 62.5 mg/mL	5 ± 3°C 25 ± 2°C/60 ± 5% RH 40 ± 2°C/75 ± 5% RH	Long Term Accelerated Stress	12 Months Study Complete Study Complete	60 Months 6 Months 3 Months	VIR Report Number: 5836
202010006	Clinical Gen2 62.5 mg/mL	5 ± 3°C 25 ± 2°C/60 ± 5% RH 40 ± 2°C/75 ± 5% RH	Long Term Accelerated Stress	12 Months Study Complete Study Complete	60 Months 6 Months 3 Months	VIR Report Number: 6671
Clinical trial material has been demonstrated to be comparable to the commercial-scale material as described in the filing and supporting documentation.						

Table 2: Summary of VIR-7831 (GSK4182136) Commercial Scale Process Drug Product (62.5 mg/mL) Batches in a 10 mL Vial Manufactured at Parma

Batch #	Description	Storage Conditions	Study Condition	Available Data	Length of Study	Stability Report
202421682	Engineering batch	2 – 8°C 25 ± 2°C/60 ± 5%RH 40 ± 2°C/75 ± 5%RH	Long Term Accelerated Stress	9 Months Study Complete Study Complete	36 Months 6 Months 3 Months	VQD-RPT-056817
8H5D	GMP1 Clinical Emergency use	2 – 8°C 25 ± 2°C/60 ± 5%RH 40 ± 2°C/75 ± 5%RH	Long Term Accelerated Stress	9 Months Study Complete Study Complete	36 Months 6 Months 3 Months	VQD-RPT-065745
9G7S	GMP3 Clinical Emergency use	2 – 8°C 25 ± 2°C/60 ± 5%RH 40 ± 2°C/75 ± 5%RH	Long Term Accelerated Stress	9 Months Study Complete Study Complete	36 Months 6 Months 3 Months	VQD-RPT-065746
CF2J	PPQ1 Clinical Emergency use	2 – 8°C 25 ± 2°C/60 ± 5%RH 40 ± 2°C/75 ± 5%RH	Long Term Accelerated Stress	9 Months Study Complete Study Complete	36 Months 6 Months 3 Months	VQD-RPT-123341
FW9J	PPQ2 Clinical Emergency use	2 – 8°C 25 ± 2°C/60 ± 5%RH 40 ± 2°C/75 ± 5%RH	Long Term Accelerated Stress	9 Months Study Complete Study Complete	36 Months 6 Months 3 Months	VQD-RPT-123342
FX4A	PPQ3 Clinical Emergency use	2 – 8°C 25 ± 2°C/60 ± 5%RH 40 ± 2°C/75 ± 5%RH	Long Term Accelerated Stress	6 Months Study Complete Study Complete	36 Months 6 Months 3 Months	VQD-RPT-123343

PPQ = Process Performance Qualification

Table 3: VIR-7831 (GSK4182136) Drug Product Specifications	
Attribute	**VQD-SPEC-027213**
Appearance Color Clarity	Liquid essentially free of visible particles ≤ B4 ≤ 18.0 NTU
pH	5.5 – 6.5
Protein Conc.	56.3 – 68.7
SEC Monomer	≥ 92.5%
SEC HMW	≤ 6.0%
CE-SDS Reduced	(LC + HC) ³ 95.0%
CE-SDS Non Reduced	³ 95.0%
cIEF Main Peak	≥ 50.0%
cIEF Acidic Species	≤ 45.0%
cIEF Basic Species	≤ 20.0%
Potency (ELISA)	70 – 130%
Potency (PNA)	60 – 140%
Particulate Matter	≥ 10 µm: ≤ 6000 particles/container ≥ 25 µm: ≤ 600 particles/container
PS-80	0.010 – 0.070% (w/v)

1. According to the shelf life (Universal) specification VQD-SPEC-027213 Rev.5.0
2. LC = light chain, HC = heavy chain
HMW = high molecular weight
PNA = Pseudovirus Neutralization Assay

Table 4: VIR-7831(GSK4182136) Drug Product Container Closure Information		
Container Closure Component	**Description**	**Manufacturer**
Primary (vial)	10 mL Borosilicate glass injection vial (Type I glass)	Nuova Ompi SAP Code 62000000056322
Stopper	20mm/Chlorobutyl Rubber Serum Stopper with compound film, 20mm/Grey	West (SAP code 62000000055225)
Cap	20 mm Aluminum-plastic cap	West (SAP code 10000000095544)

STABILITY ANALYSIS

Data presented within this section will include the following:

- Trend plots profiling the stability test attributes for the VIR-7831 drug product batches evaluated at the long-term, accelerated, and stressed stability storage conditions listed in **Table 1**.
- Evaluation of product quality attributes that demonstrate statistically significant change with time.
- Extrapolation analysis of the stability data as function of storage time for product quality attributes demonstrating statistically significant change with time. This analysis is intended to determine if the width of the predicted confidence interval at the 24-month time point conforms to stability acceptance criteria for the VIR-7831 Gen2 GMP DP batches.

Stability Profiles of VIR-7831 DP Batches Using Graph Builder

- Stability plots for the following test attributes did not indicate any trend and meet the acceptance limits specified in Table 2: pH (**Figure 1**), Clarity (**Figure 2**), Subvisible Particles (**Figure 3**), and PS80 (**Figure 4**)

- Stability plots of Potency data from the long-term and accelerated storage conditions (**Figure 5**) did not exhibit any consistent trends. The stability plot of Potency data generated for the stressed storage condition displayed a clear and similar downward trend for all DP batches listed in **Table 1** and **Table 2**. All potency data have met the acceptance limit specified in **Table 3**.

- Purity by CE-SDS (Reduced and Non-Reduced) in **Figure 6** did not exhibit trends at 5°C storage condition while data plots from the accelerated and stressed conditions both displayed a downward trend similar to each other. All long-term stability data to date have met the acceptance criteria specified in **Table 3**.

- Purity by cIEF (Main Peak, Acidic species, Basic species) in **Figure 7** did exhibit similar trends across the VIR-7831 DP batches. The main peak exhibits clear decreases while the acidic charge variants increase as function of storage time at the stressed condition (40°C). Samples stored at the long-term temperature condition analyzed to date have met the acceptance limits specified in **Table 3** for DP purity by cIEF.

- Purity by SEC (Monomer and HMW) in **Figure 8** demonstrated similar trends across the VIR-7831 DP batches. A downward trend was observed in Monomer content together with an inverse increasing trend in HMW content. All data met the stability acceptance criteria listed in **Table 3** for DP purity by SEC.
- The protein concentration attribute did not exhibit trends across the DP batches as summarized in **Figure 9**. VIR-7831 Gen 1 and Gen 2 DP are formulated at different protein concentrations. Data for all batches of DP analyzed in this report met the acceptance limits as specified in **Table 3.**

Stability Profiles of VIR-7831 (GSK4182136) DP at 5C, 25C and 40C

Figure 1: Clarity for VIR-7831 (GSK4182136) DP

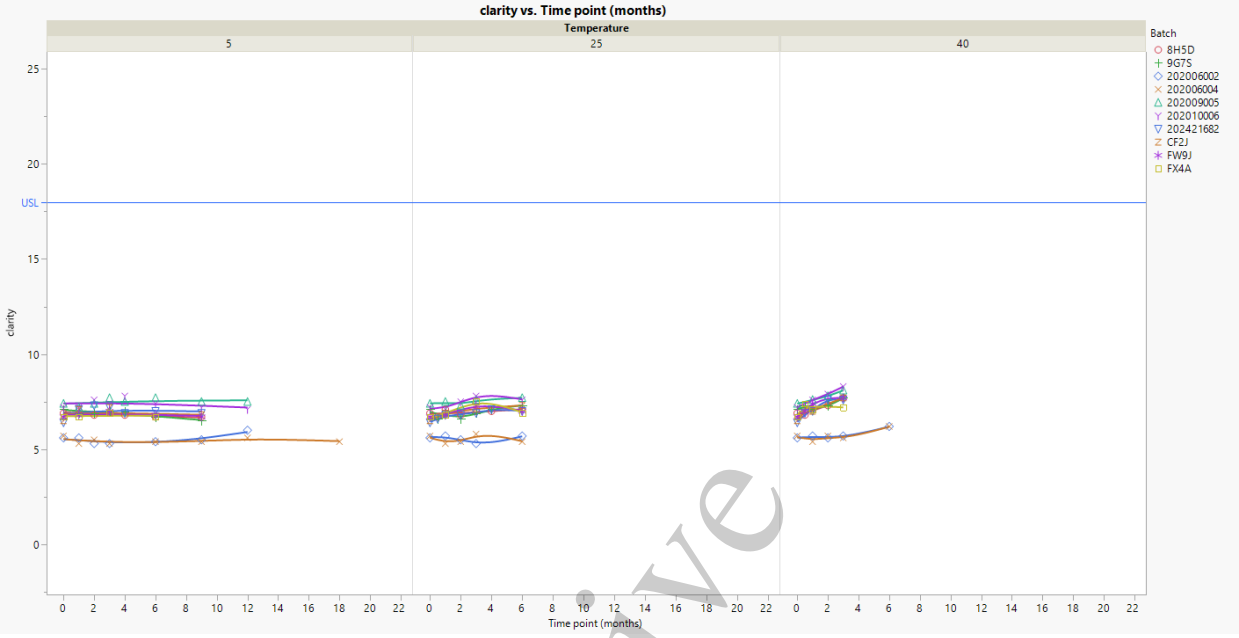


Figure 2: pH for VIR-7831 DP

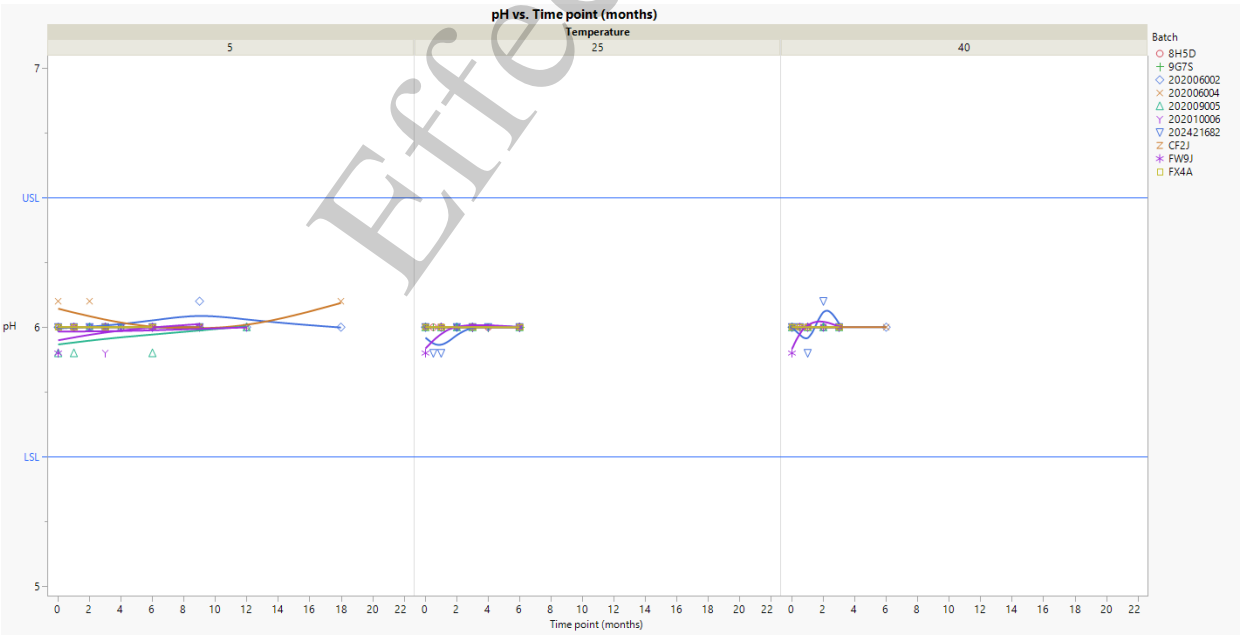
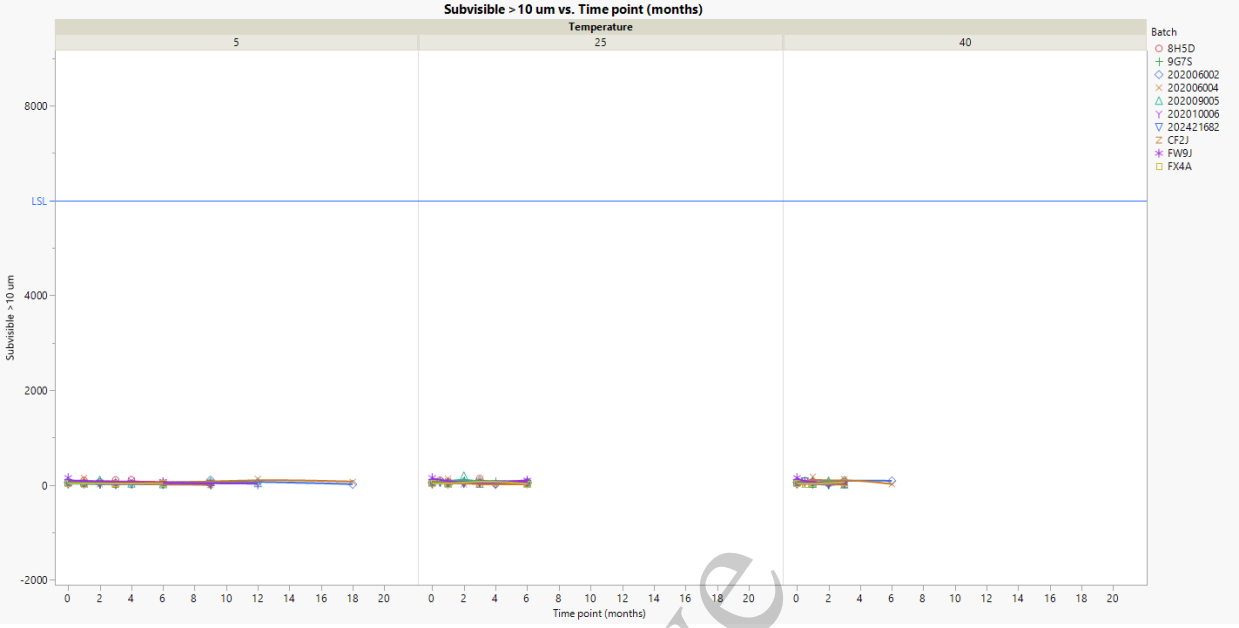


Figure 3: Subvisible Particulate for VIR-7831 (GSK4182136) DP



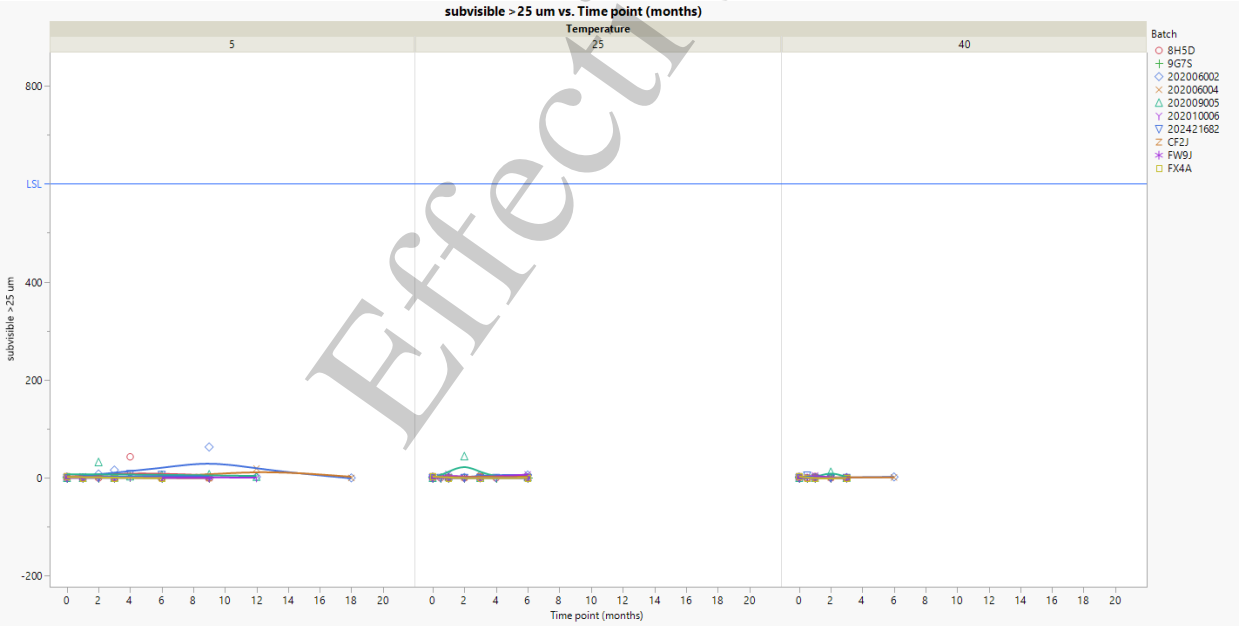


Figure 4: Polysorbate 80 for VIR-7831 (GSK4182136) DP

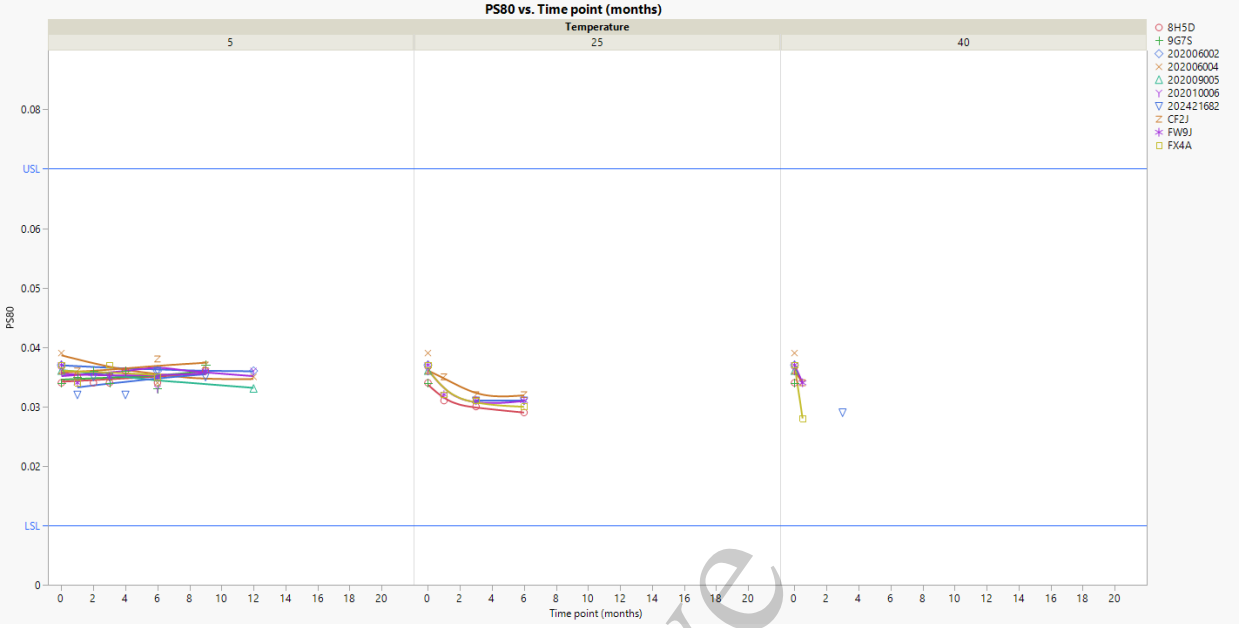


Figure 5: Potency for VIR-7831 (GSK4182136) DP

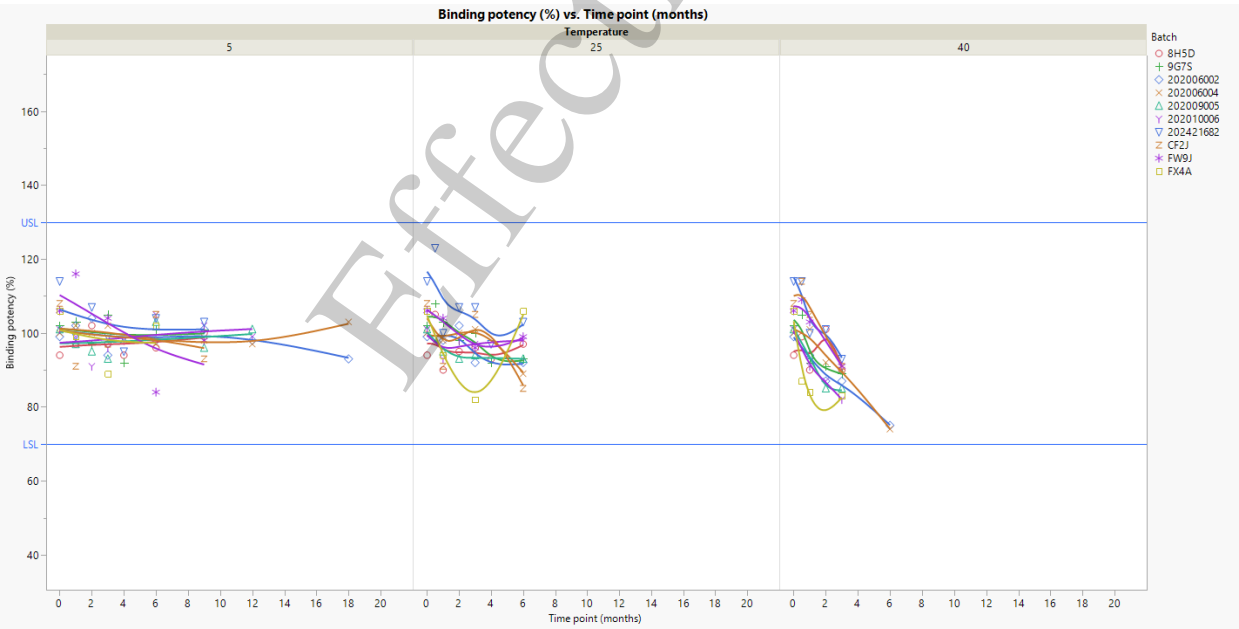
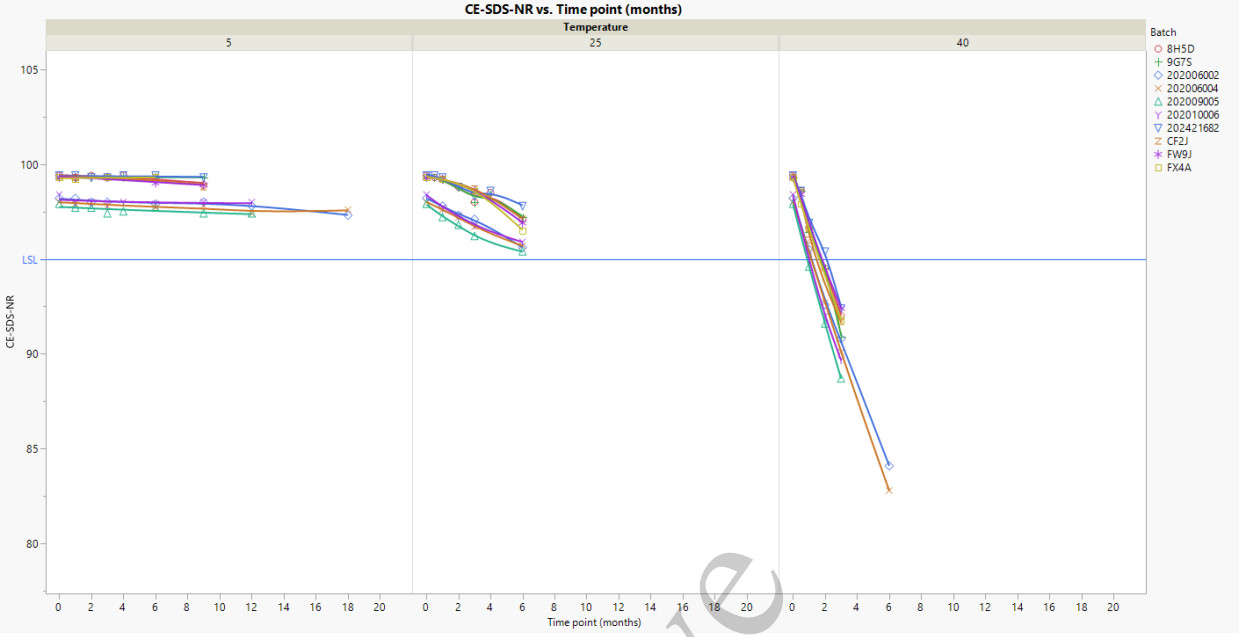


Figure 6: CE-SDS (Reduced and Non-Reduced) for VIR-7831 (GSK4182136) DP



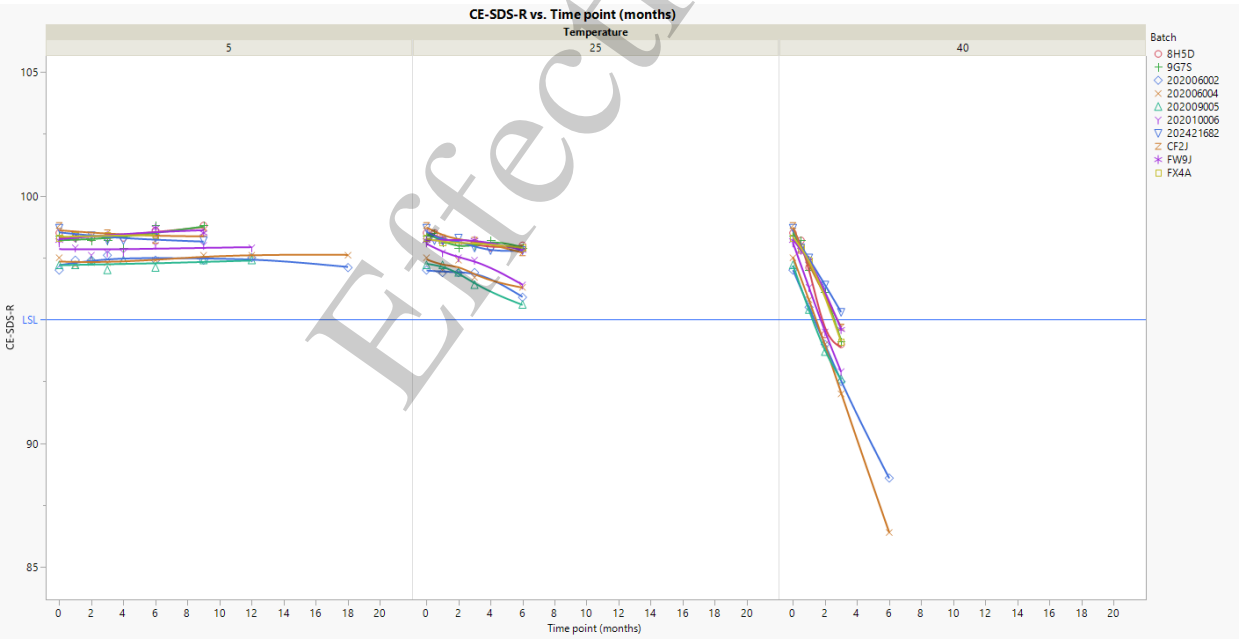


Figure 7: Charge Variant Analysis for VIR-7831 (GSK4182136) DP

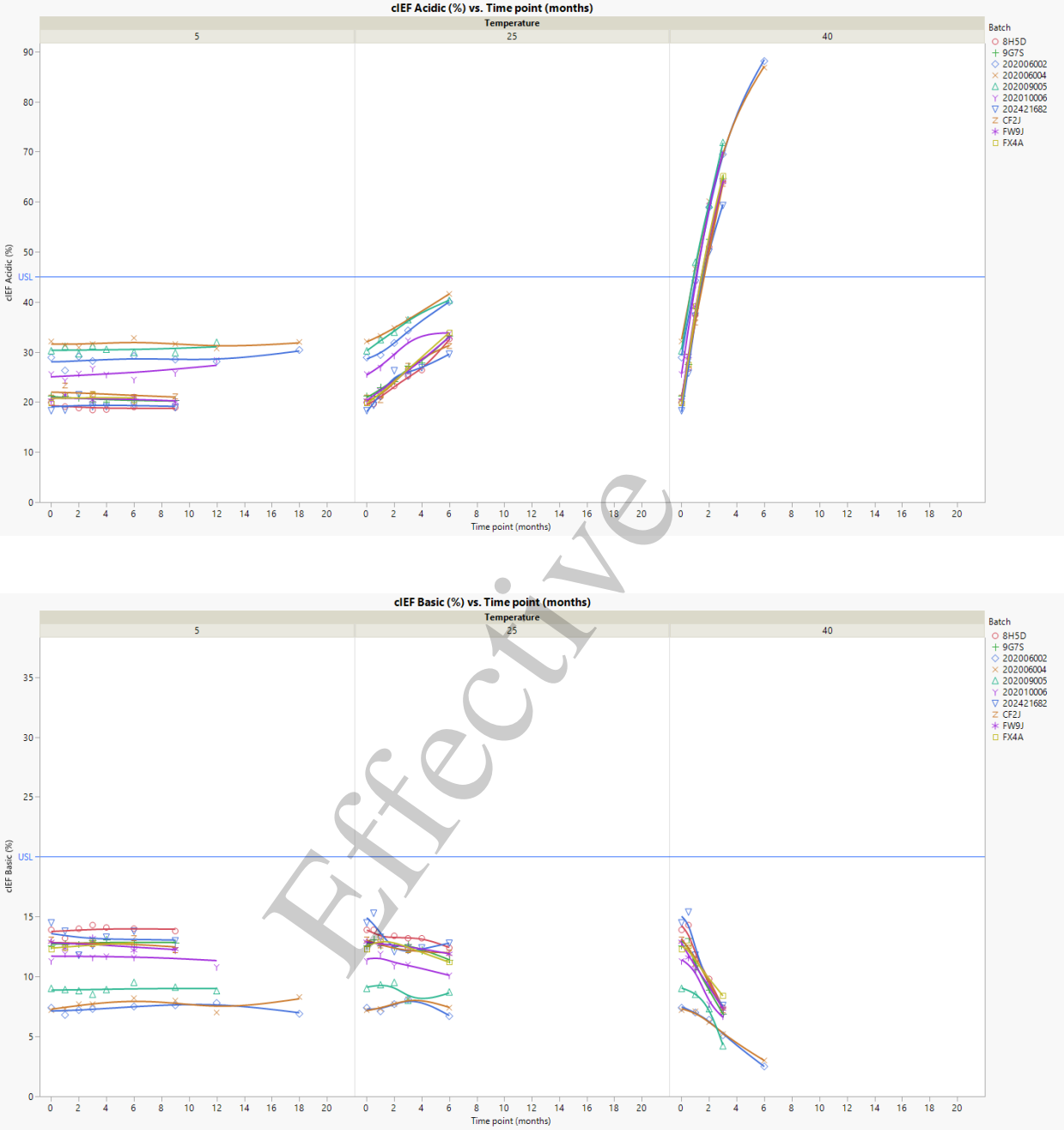
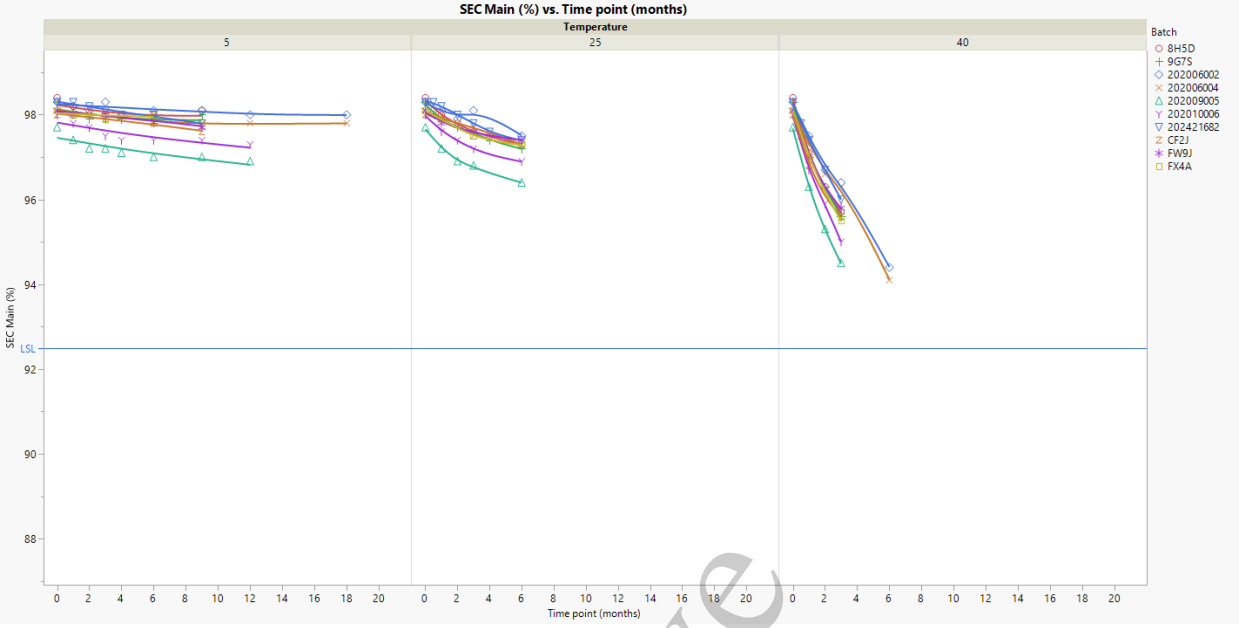


Figure 8: SEC HPLC for VIR-7831 (GSK4182136) DP



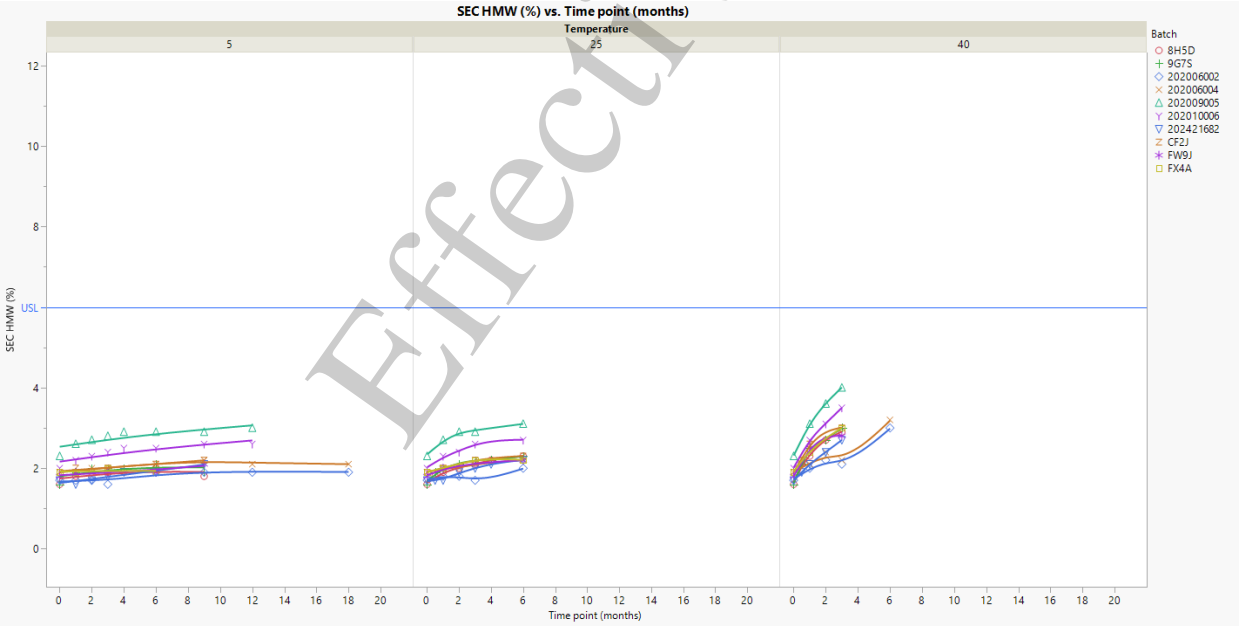
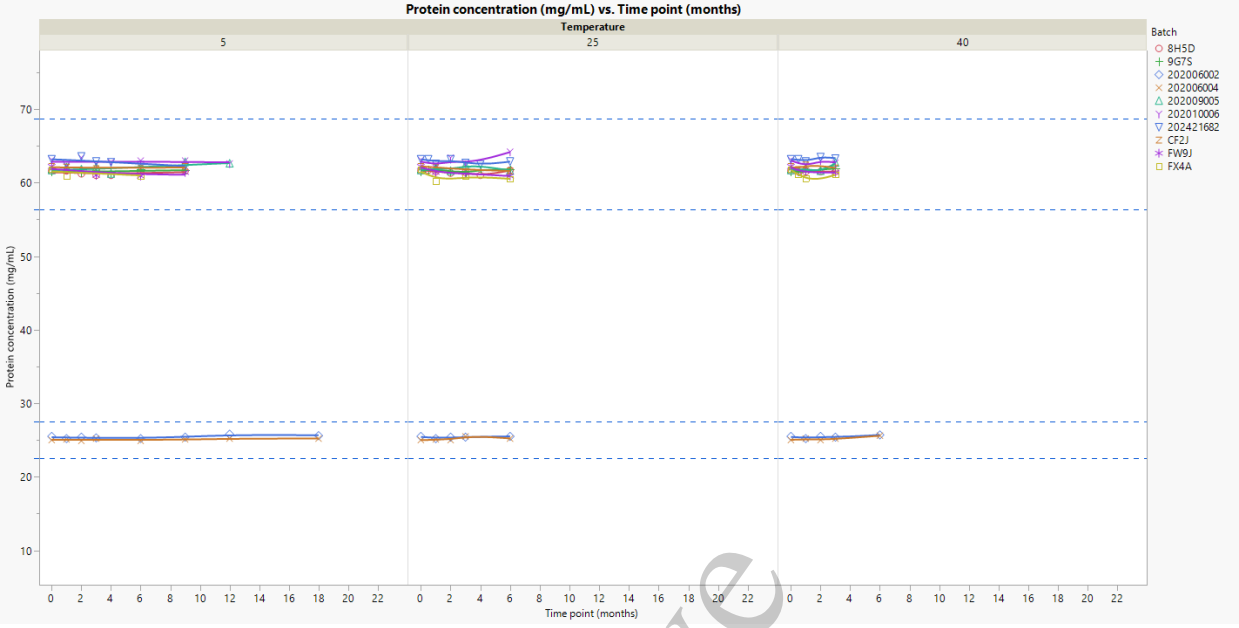


Figure 9: Protein Concentration for VIR-7831 (GSK4182136) DP



Evaluation of Nominal Storage Condition Stability Test Data for Statistically Significant Change with Time

Statistical analysis of stability data in **Table 1** and **Table 2** was performed using Statistica 13.5.0 to determine if assay results displayed statistically significant trends with storage time. Clinical and commercial batches were included since the data could be pooled. Slopes with a p-value ≤ 0.05 were considered statistically different from zero, while slopes with a p-value > 0.05 were considered not significantly different from zero. For assays with statistically significant trends (slope p-value <0.05), the predicted shelf life was taken as the time (in months) when either the upper or lower 95% prediction interval equalled the assay upper or lower specification acceptance criteria. Assays with an insignificant slope (p-value > 0.05) were not used to predict shelf life. **Table 5** summarizes the slope p-values and predicted shelf life from each assay

Table 5: SHELF-LIFE ANALYSIS SUMMARY

Evaluation of slopes and intercepts per Q1E using degradation modeling

Test	Stability Specification	p-value of slope	Predicted time to specification 95% CI at 5°C	p-value of slope	Predicted time to specification 95% CI at 25°C
Clarity	≤ 18.0 NTU	0.4995	NA*	0.0005	NA*
pH	6.0 ± 0.5	0.2731	NA*	0.1047	NA*
Charge Variants by cIEF	Main peak: ≥ 50.0%	0.9744	>72 months	<.0001	5 months
	Acidic peaks: ≤ 45.0%	0.9111	>72 months	<.0001	7 months
	Basic peaks: ≤ 20.0%	0.8766	>72 months	<.0001	>24 months
Purity by SEC-HPLC	Main Peak (monomer): ≥ 92.5%	<.0001	71 months	<.0001	21 months
	HMW ≤ 6.0%	<.0001	58 months	<.0001	23 months
CE-SDS (Non-Reduced)	Main Peak% ≥ 95.0%	<.0001	56 months	<.0001	6 months
CE-SDS (Reduced)	(Light Chain + Heavy Chain) ≥ 95.0%	0.0773	44 months	<.0001	7 months
Potency by ELISA	70%-130% relative potency	0.1087	62 months	0.0039	13 months
Subvisible Particulate Matters (≥ 10µm)	≤ 6000 particles/container	0.1314	NA*	0.5955	NA*
Subvisible Particulate Matters (≥ 25µm)	≤ 600 particles/container	0.9564	NA*	0.9282	NA*
Polysorbate 80	0.010 ± 0.070% (w/v)	0.9975	NA*	0.8996	NA*

* Analysis of the stability test results suggests that the data trend is not slated to reach the test limit at the lower 95% CI level; data does not indicate change with time or trends in the direction opposite the limit.

Full factorial analysis was performed to determine any significant change in the rate of degradation in the stability attributes for VIR-7831 DP batches at the nominal storage condition (5±3°C). The analysis showed P values for the 'Time (months)' effect to be statistically insignificant (P > 0.05) for the following attributes, confirming no significant change over time:

- pH (P=0.2731)
- Clarity (P=0.4995)
- Protein Concentration (P=0.2072)
- Potency (P=0.1087)
- Subvisible Particles ≥ 10 µm (P=0.1314)
- Subvisible Particles ≥ 25 µm (P=0.9564)
- cIEF (Main) (P=0.9744)
- cIEF (Acidic) (P=0.9111)
- cIEF (Basic) (P=0.8766)
- Reduced CE-SDS (Light + Heavy Chain) (P=0.0773)

Data analysis of the following product quality attributes yielded 'Time (months)' effect P-values < 0.05, indicating a statistically significant change in the attribute as function of storage time:

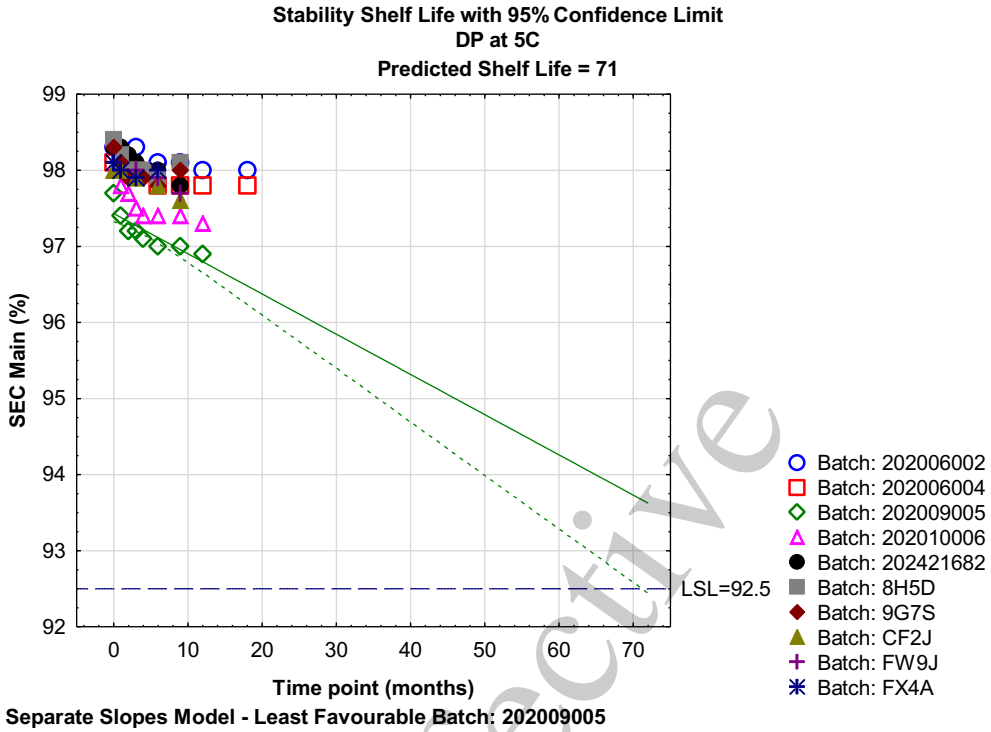
- SEC (Monomer) (P<0.0001)
- SEC (HMW) (P<0.0001)
- Non-reduced CE-SDS (Main Peak) (P<0.0001)

Data for the following product quality attributes which demonstrate statistically significant change as function of storage time at the nominal condition, were analyzed and extrapolated to the 24-month storage interval. The extrapolation is intended to determine continued conformance of the analyzed product quality attributes with stability acceptance criteria at the 24-month stability interval:

- SEC (Monomer) - **Figure 10**
- SEC (HMW) - **Figure 11**
- Non-reduced CE-SDS (Main Peak) - **Figure 12**

Statistical Analysis using Degradation Analysis for Composite Batches at 5°C and 25°C Storage Condition

Figure 10: Degradation Modeling for SEC HPLC (Main Peak)



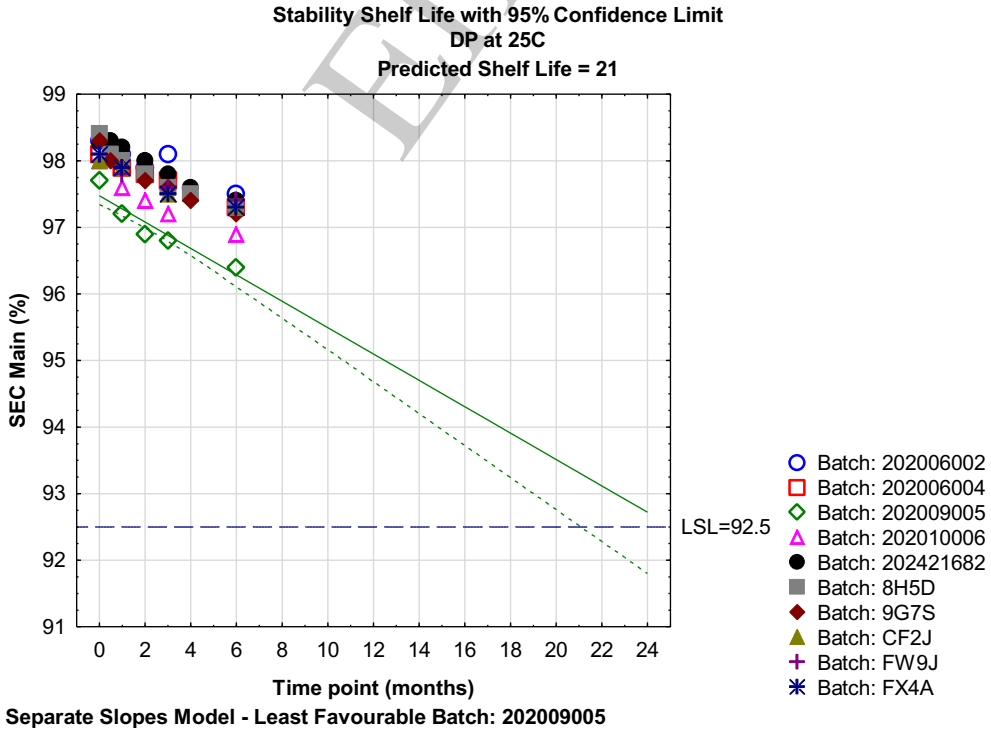
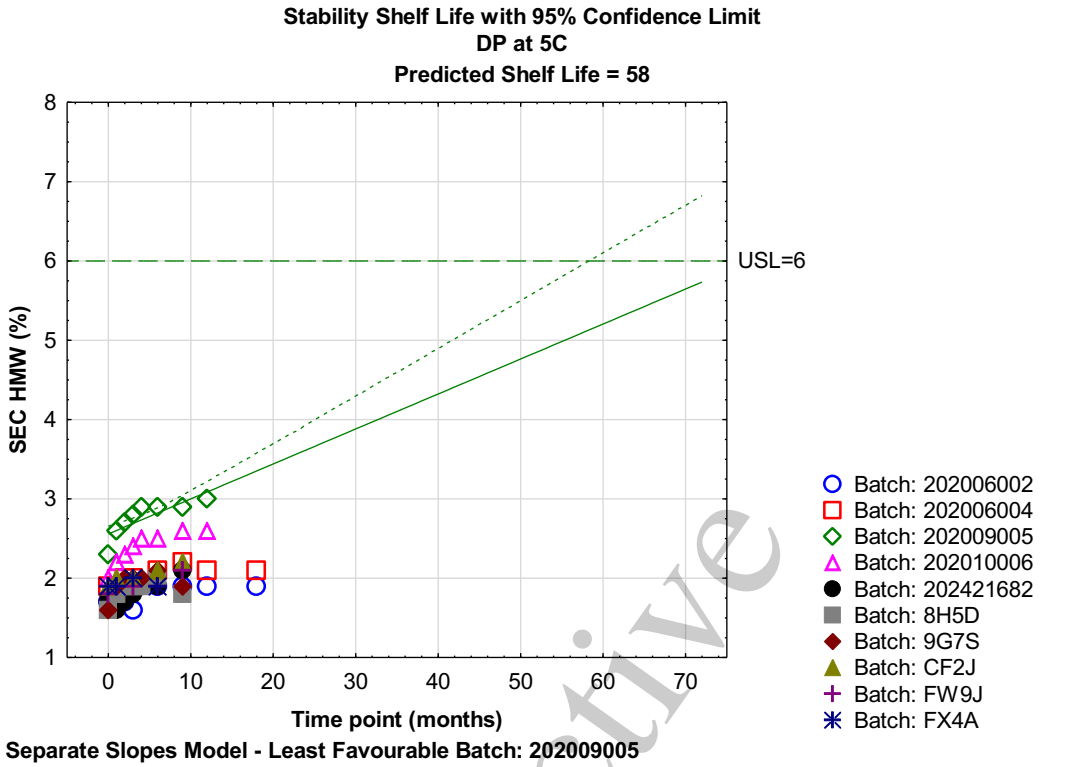


Figure 11: Degradation Modeling for HPLC SEC (HMW Peak)



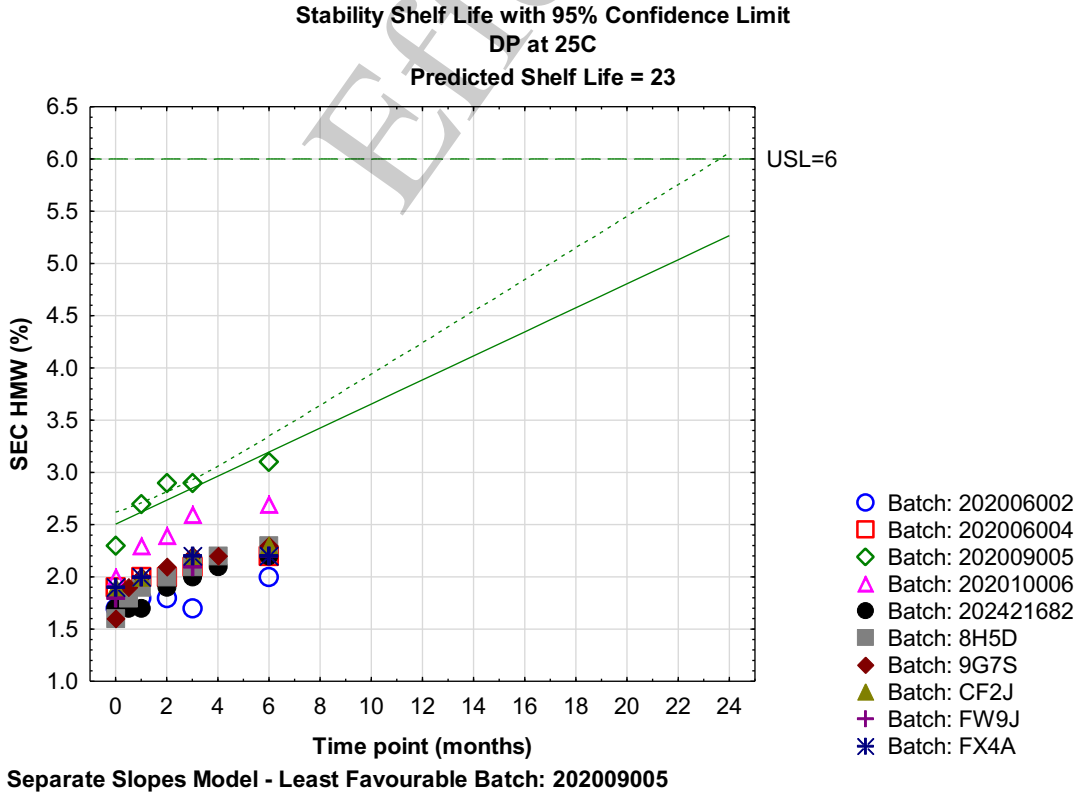
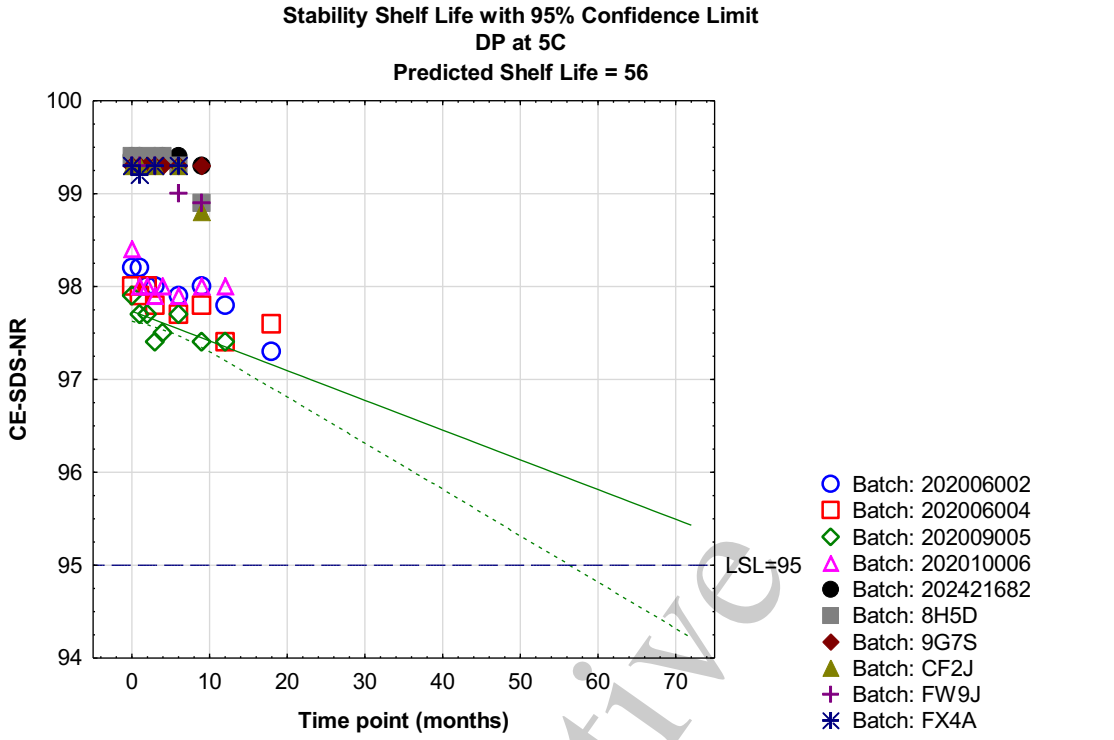
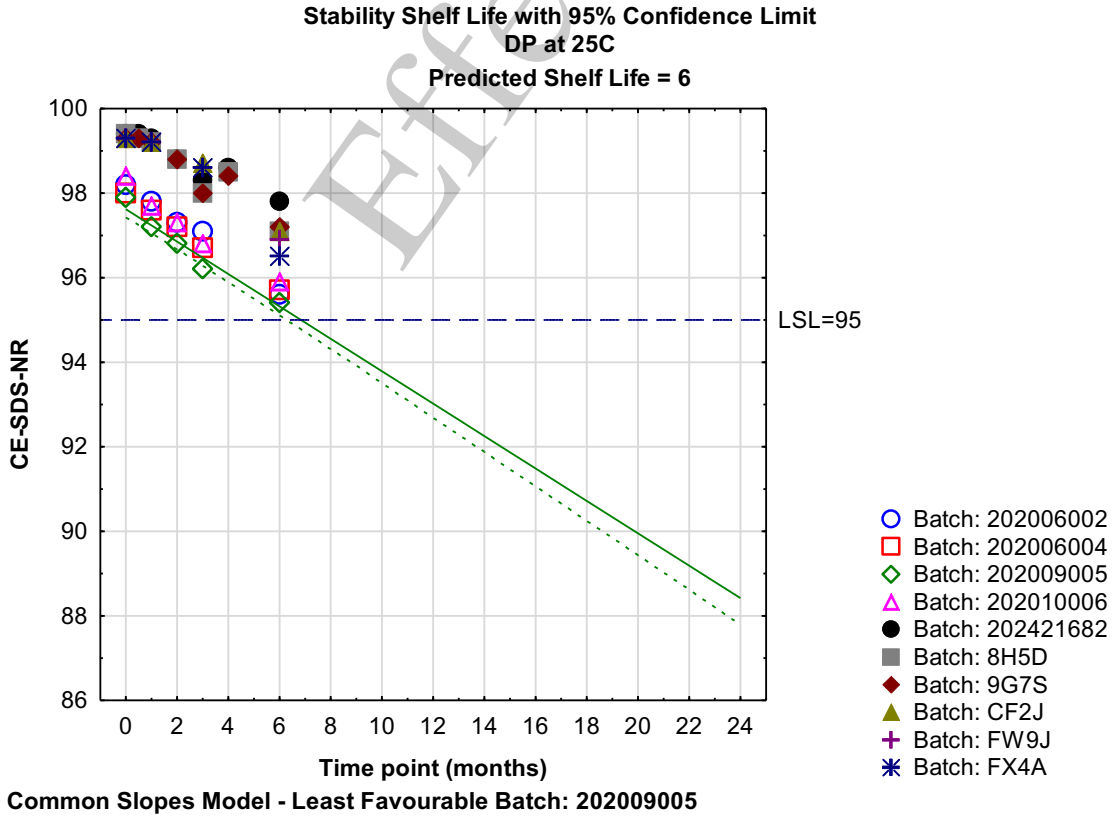


Figure 12: Degradation Modeling for CE-SDS (Non-Reduced)





Conclusion:

The shelf-life of VIR 7831 (GSK4182136) Drug Product was assessed using the following stability data available to date: 18-month time point data from analysis of VIR 7831 Gen 1 DP batches, 12-month time point data from analyses of the GMP Gen 2 WuXi DP batches, and 9- month time point data from analyses of the GMP Gen 2 Parma DP batches. The overall stability between VIR-7831 Gen 1 and Gen 2 WuXi and Parma DP batches has been deemed comparable (VQD-RPT-102561).

Data from this shelf-life assessment supports amending the expiry period for the Gen2 Parma drug product batches currently being used in ongoing studies out to 24 months. The data indicate that the earliest time the drug product (stored in recommended conditions of 2-8°C) will reach specification limit is 44 months with CE-SDS (Non-Reduced) test result being the limiting factor. Protein concentration test data was not appropriate for use for shelf-life extrapolation as the target protein concentration of the VIR-7831 Gen 1 (25 mg/mL) and Gen 2 Wuxi and Parma DP batches (62.5 mg/mL) are different, however the profiles trend similarly and would not impact the shelf life. Data from the ongoing stability studies at the long-term recommended storage condition will be monitored.

VERSION HISTORY:

Version	Change	Justification
2.0	Reformatted document.	To align with updated directive per VQD-WI-021249
	Updated Document Revision: Table 1: Removed batch# 2275S20200501	Pilot batch #2275S20200501 was not manufactured under GMP conditions and is not considered reflective of the current Gen2 DP manufacturing process. Expiry will be establish using GMP data.
	Updated Document Revision: **Table 3:** Specification **VQD-SPEC-027213** Rev.5.0 updated to universal specifications **Discussion of the Trend Charts Batch Update:** 202006002 18M @ 5C 202006004 18M @ 5C 202009005 12M @ 5C 202010006 12M @ 5C 202421682 6M, 9M @ 5C 8H5D 4M, 6M, 9M @ 5C 4M, 6M @ 25C 9G7S 4M, 6M, 9M @ 5C 4M, 6M @ 25C CF2J 3M,6M,9M @ 5C 3M, 6M @25C 3M @ 40C FW9J 3M,6M,9M @ 5C 3M, 6M @25C 3M @ 40C FX4A 3M,6M @ 5C 3M, 6M @25C 3M @ 40C	Align with updated specification document and reflect current stability data time points used in trending.

VIR-7831 Drug Product Stability Trend Report
Document Approvals by Electronic Signature

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