



VIR-7831(GSK4182136) Drug Product Stability Trend Report for Clinical and EUA Batches

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 for clinical and EUA. The trend report for the commercial product can be found at VQD-RPT-213667.

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This report should be considered a historical document and statements made are accurate, at the time the report was authored.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 (VQD-SPEC-027213).

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 2°C – 8°C” and a proposed shelf life of 36 months. The official shelf life is documented on the appropriate specification document (VQD-SPEC-027213) 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 Statistica Statistical Analysis Software. The data for each batch and storage condition was plotted using scatterplots 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 (EUA) 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 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 36 months.

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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	24Months Study Complete Study Complete	36 Months 6 Months 6 Months	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	24 Months Study Complete Study Complete	36 Months 6 Months 6 Months	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	24 Months Study Complete Study Complete	60 Months 6 Months 3 Months	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	24 Months Study Complete Study Complete	60 Months 6 Months 3 Months	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	18 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	18 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	18 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	12 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	12 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	12 Months Study Complete Study Complete	36 Months 6 Months 3 Months	VQD-RPT-123343
DV4T	PPQ1	2 – 8°C	Long Term Accelerated Stress	6 Months	36 Months	VQD-RPT-188140
	Clinical	25 ± 2°C/60 ± 5%RH		Study Complete	6 Months	
	Emergency Use	40 ± 2°C/75 ± 5%RH		Study Complete	3 Months	
DY9B	PPQ1	2 – 8°C	Long Term Accelerated Stress	6 Months	36 Months	VQD-RPT-188142
	Clinical	25 ± 2°C/60 ± 5%RH		Study Complete	6 Months	
	Emergency Use	40 ± 2°C/75 ± 5%RH		Study Complete	3 Months	
DV4U	PPQ1	2 – 8°C	Long Term Accelerated Stress	6 Months	36 Months	VQD-RPT-188141
	Clinical	25 ± 2°C/60 ± 5%RH		Study Complete	6 Months	
	Emergency Use	40 ± 2°C/75 ± 5%RH		Study Complete	3 Months	

PPQ = Process Performance Qualification

Table 3: VIR-7831 (GSK4182136) Drug Product Specifications

Attribute	VQD-SPEC-027213 ¹
Appearance	Liquid essentially free of visible particles
Color	≤ B5
Clarity	≤ 15.0 NTU
pH	5.5 – 6.5
Protein Conc.	56.3 – 68.7
SEC Monomer	≥ 95.0%
SEC HMW	≤ 5.0%
CE-SDS Reduced	(LC + HC) ² ≥ 95.0%
CE-SDS Non Reduced	≥ 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	0.02 – 0.06% (w/v)

1. According to the shelf life (Universal) specification VQD-SPEC-027213 Rev.9.0

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:

- Scatterplots 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 36-month time point conforms to stability acceptance criteria for the VIR-7831 Gen2 GMP DP batches.

Stability Profiles of VIR-7831 DP Batches Using Statistica

- Stability plots for the following test attributes did not indicate any trend and meet the acceptance limits specified in Table 2: Clarity (**Figure 1**), pH (**Figure 2**), Subvisible Particles (**Figure 3**).
- Stability plots for the following test attributes indicate a slight downward trend and meet the acceptance limits specified in Table 2: 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 and basic charge exhibit clear decreases while the acidic charge variants increase as a 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**.

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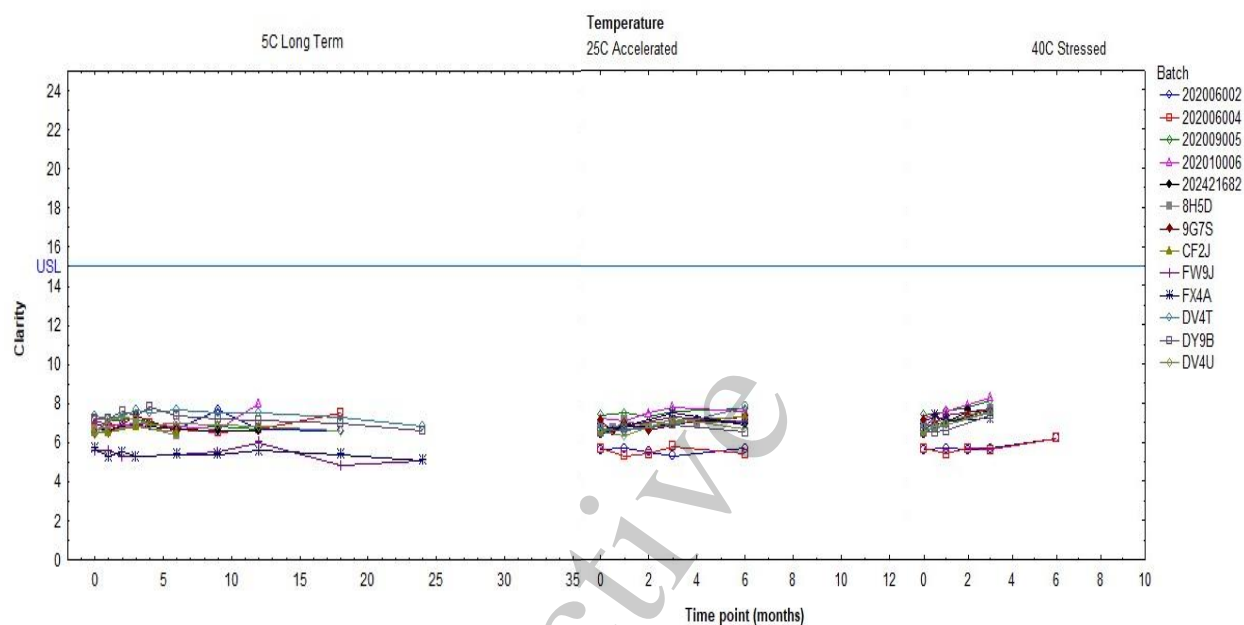
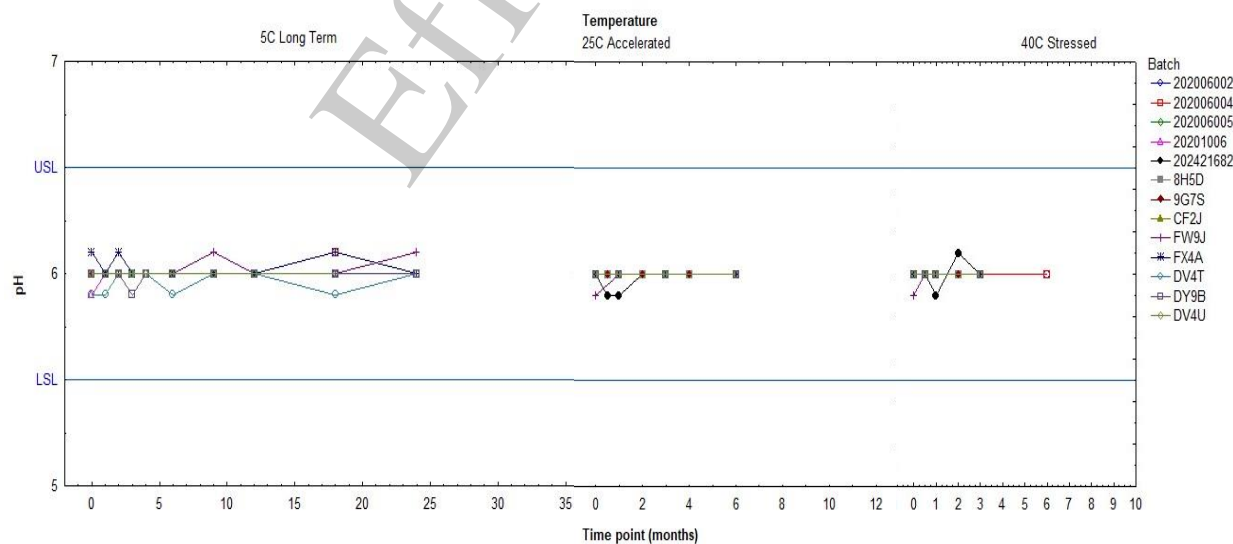
Stability Profiles of VIR-7831 (GSK4182136) DP at 5C, 25C and 40C**Figure 1: Clarity for VIR-7831 DP (GSK4182136)****Figure 2: pH for VIR-7831 DP (GSK4182136)**

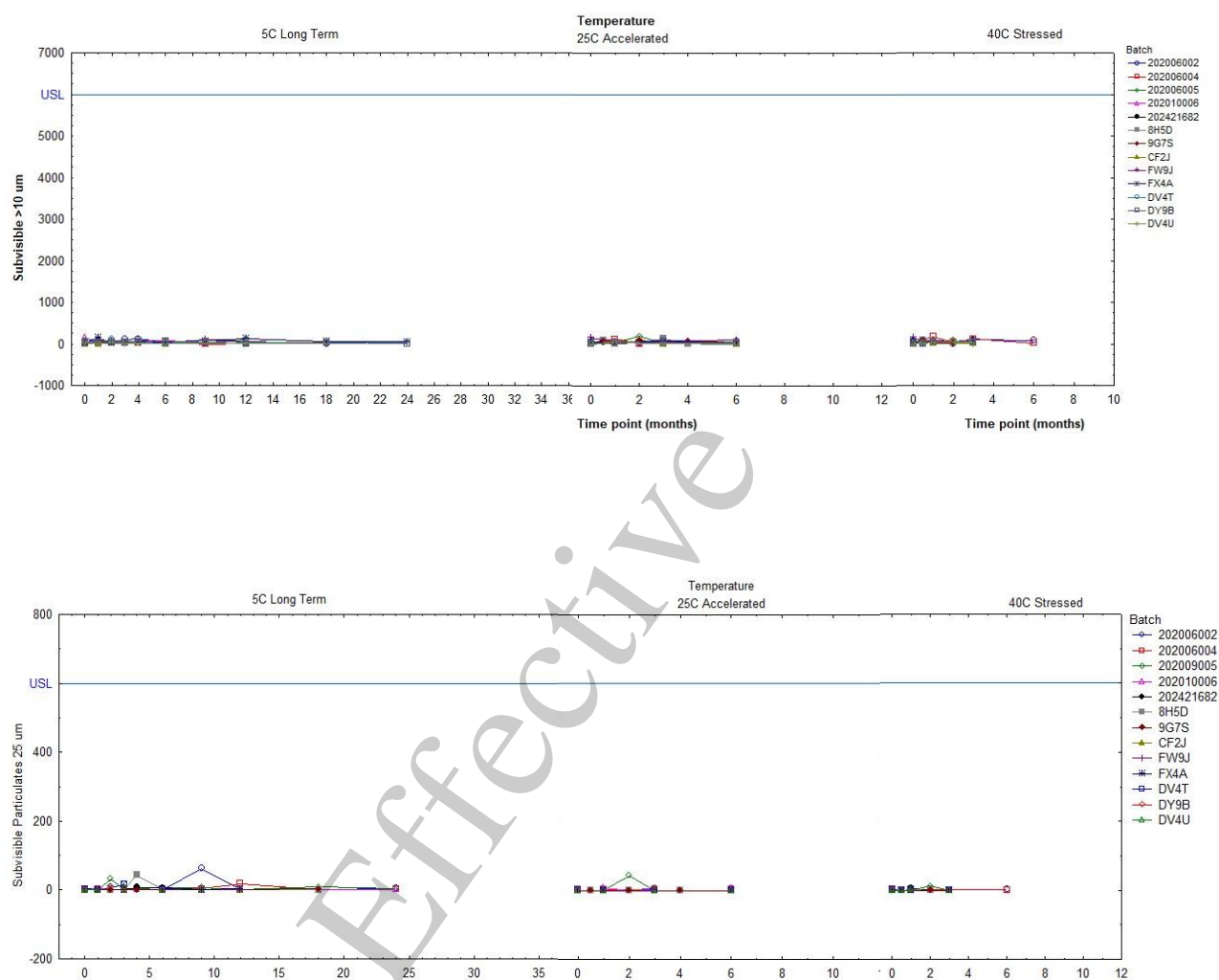
Figure 3: Subvisible Particulate for VIR-7831 (GSK4182136) DP

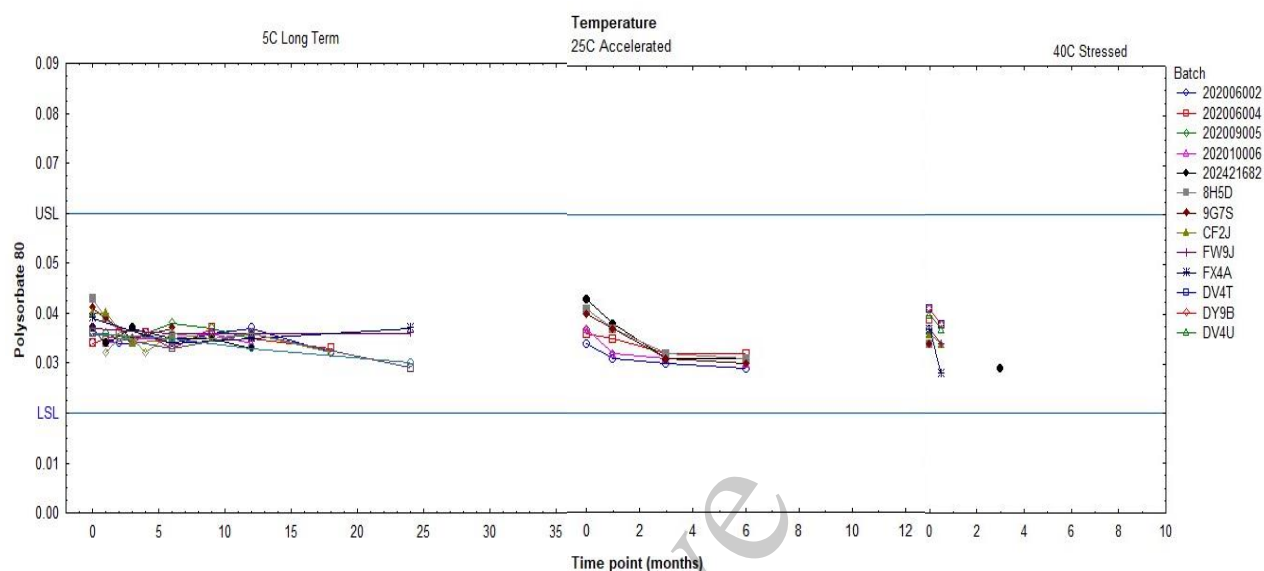
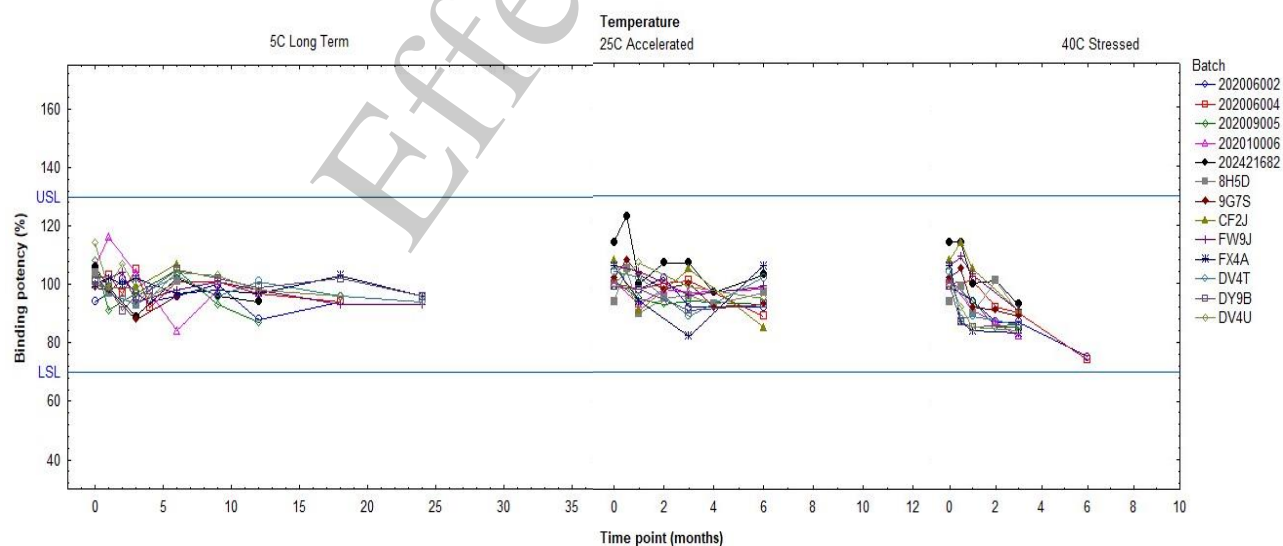
Figure 4: Polysorbate 80 for VIR-7831 (GSK4182136) DP**Figure 5: Potency for VIR-7831 (GSK4182136) DP**

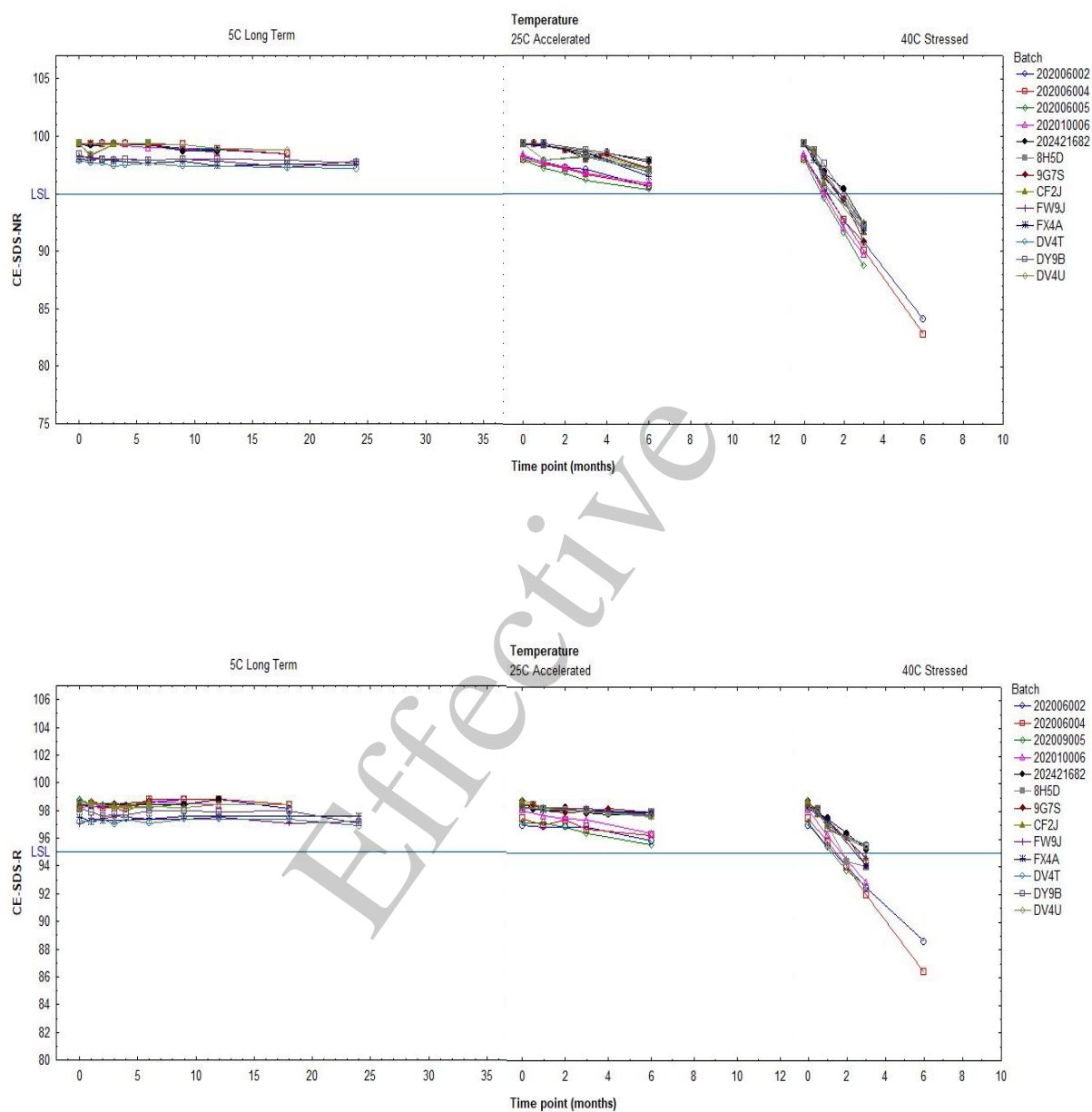
Figure 6: CE-SDS (Reduced and Non-Reduced) for VIR-7831 (GSK4182136) DP

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

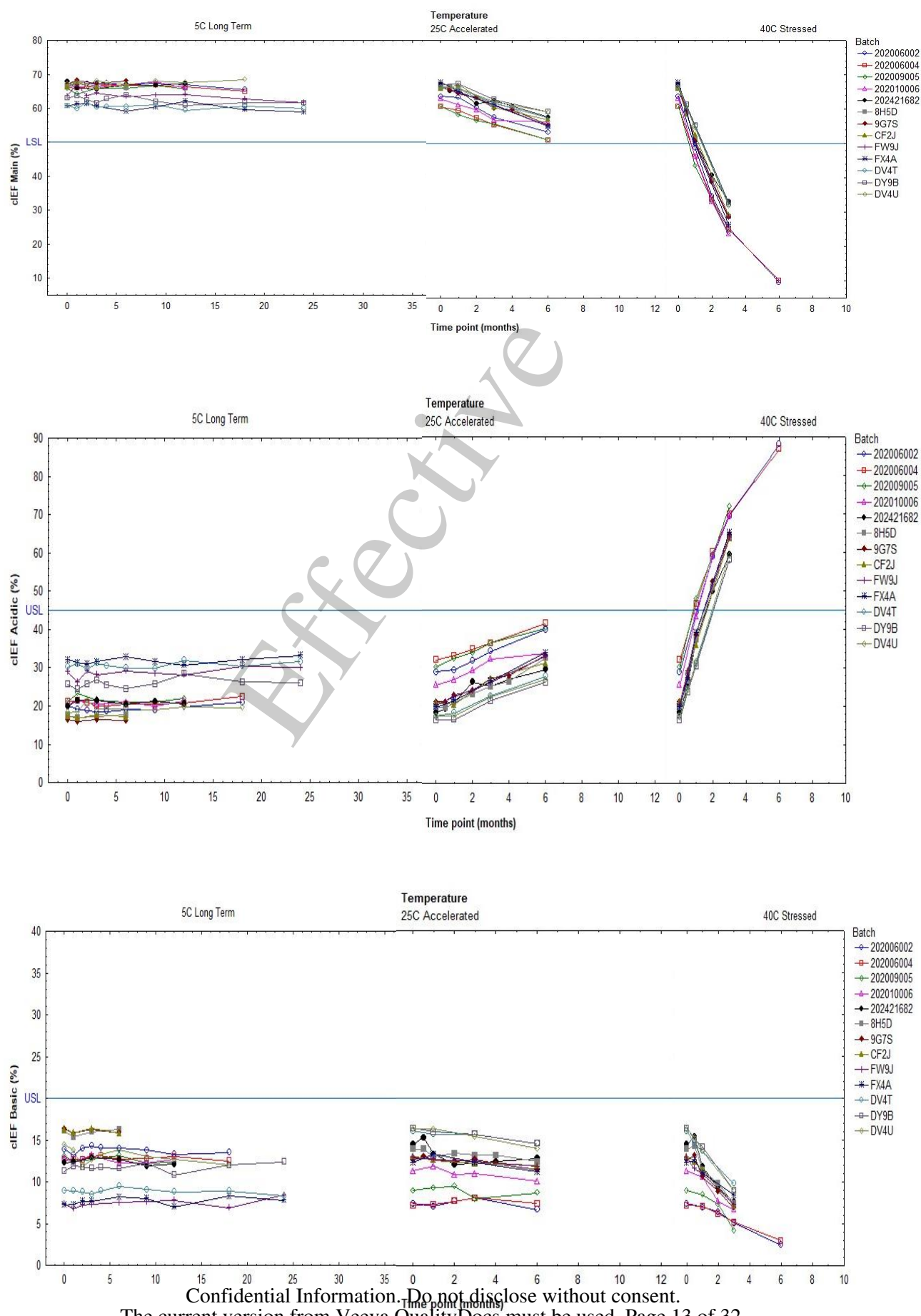


Figure 8: SEC HPLC for VIR-7831 (GSK4182136) DP

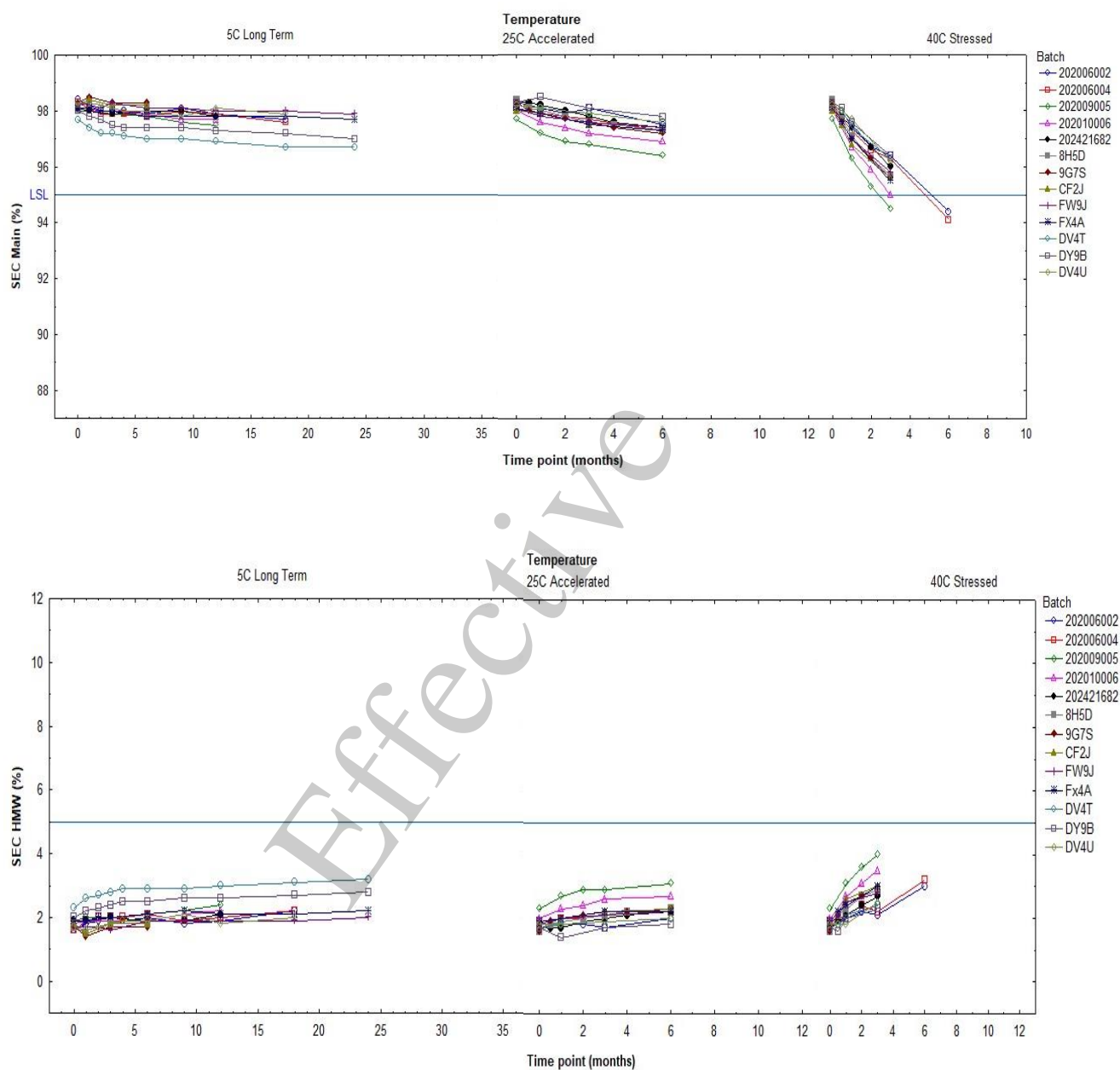
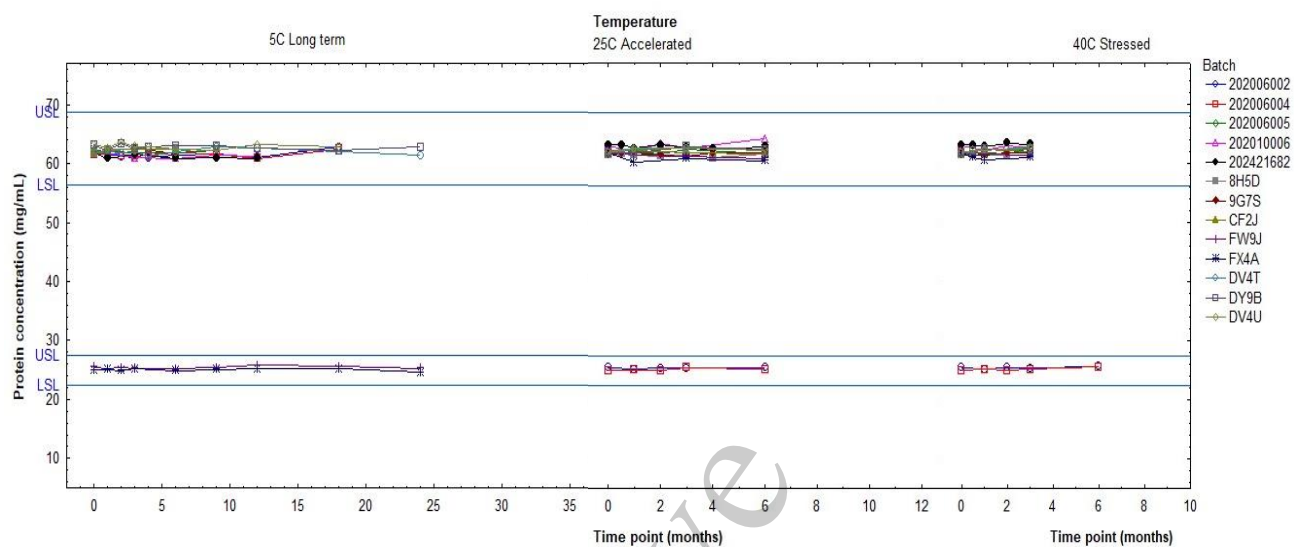


Figure 9: Protein Concentration for VIR-7831 (GSK4182136) DP

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

Statistical analysis of long-term 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. Batches with less than 5 testing points were not used in this statistical analysis. The Statistica stability macro was used to determine whether if a common slope could be used or if separate slopes should be used. Table 6 indicates when a common slope for all batches were used and when the separate slopes are used with the p-values of each batch. 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. The maximum allowable shelf-life was set to 96 months in this analysis. **Table 6** summarizes the slope p-values and predicted shelf life from each assay

Table 6: 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 n 95% CI at 5°C	Statistical Assessment per Test
Clarity	≤ 15.0 NTU	Common Slopes 0.010600	>96 months	Shelf-Life not found within maximum allowed extrapolation distance
pH	6.0 ± 0.5	Common Slopes 0.045288	>96 months	Shelf-Life not found within maximum allowed extrapolation distance
Charge Variants by cIEF	Main peak: $\geq 50.0\%$	Common Slopes 0.000809	>96 months	Shelf-Life not found within maximum allowed extrapolation distance
	Acidic peaks: $\leq 45.0\%$	Common Slopes 0.000644	>96 months	Shelf-Life not found within maximum allowed extrapolation distance
	Basic peaks: $\leq 20.0\%$	Separate Slopes Lots below p 0.05: 0.000639 Lot - 202421682	>96 months	Shelf-Life not found within maximum allowed extrapolation distance
Purity by SEC-HPLC	Main Peak (monomer): $\geq 95.0\%$	Separate Slopes Lots below p 0.05: 0.000240 Lot – 202006002 0.000033 Lot – 202006004 0.000000 Lot – 202009005	>96 months	Shelf-Life not found within maximum allowed extrapolation distance

		0.000000 Lot – 202010006 0.000049 Lot – 202421862 0.000001 Lot 8H5D 0.000003 Lot – 9G7S 0.000006 Lot – CF2J 0.000184 Lot – FW9J		
	HMW ≤ 5.0%	Separate Slopes Lots below p 0.05: 0.000438 Lot – 202006002 0.002114 Lot – 202006004 0.000000 Lot – 202009005 0.000000 Lot – 202010006 0.000393 Lot – 202421862 0.000110 Lot 8H5D 0.000104 Lot – 9G7S 0.000084 Lot – CF2J 0.001164 Lot – FW9J	>96 months	Shelf-Life not found within maximum allowed extrapolation distance
CE-SDS (Non-Reduced)	Main Peak% ≥ 95.0%	Separate Slopes Lots below p 0.05: 0.000088 Lot – 202006002 0.000686 Lot – 202006004 0.000194 Lot – 202009005 0.013637 Lot – 202010006 0.000087 Lot – 202421862 0.000000 Lot 8H5D 0.000003 Lot – 9G7S 0.002103 Lot – CF2J 0.000027 Lot – FW9J 0.000110 Lot – FX4A	55 months	Predicted Shelf Life 92 months - 202006002 >96 months – 202006004 85 months – 202009005 >96 months – 202010006 93 months – 202421862 67 months - Lot 8H5D 80 months - Lot – 9G7S 70 months - Lot – CF2J 55 months - Lot – FW9J 58 months - Lot – FX4A
CE-SDS (Reduced)	(Light Chain + Heavy Chain) ≥ 95.0%	Common Slopes 0.674632	N/A	No Trend

Potency by ELISA	70%-130% relative potency	Common Slopes 0.000572	>96 months	Shelf-Life not found within maximum allowed extrapolation distance
Subvisible Particulate Matters ($\geq 10\mu\text{m}$)	≤ 6000 particles/container	Common Slopes 0.012162	>96 months	Shelf-Life not found within maximum allowed extrapolation distance
Subvisible Particulate Matters ($\geq 25\mu\text{m}$)	≤ 600 particles/container	Common Slopes 0.937174	N/A	No Trend
Polysorbate 80	$0.02 \pm 0.06\%$ (w/v)	Common Slopes 0.004901	89 months	Lot 202009005
Protein Concentration	56.3 – 68.7 mg/mL	Common Slopes 0.879328	N/A	No Trend

Effective

Statistical 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 ($5\pm 3^{\circ}\text{C}$). 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:

- Reduced CE-SDS (Light + Heavy Chain)
- Subvisible Particles $\geq 25\ \mu\text{m}$
- Protein Concentration

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:

- pH
- Clarity
- Binding Potency
- Subvisible Particles $\geq 10\ \mu\text{m}$
- SEC (Monomer)
- SEC (HMW)
- Non-reduced CE-SDS
- cIEF (Main)
- cIEF (Acidic)
- cIEF (Basic)
- PS80

Data for the following product quality attributes which demonstrate statistically significant change as function of storage time at the nominal condition, were analysed and extrapolated to the 36-month storage interval. The extrapolation is intended to determine continued conformance of the analysed product quality attributes with stability acceptance criteria at the 24-month stability interval. Attributes that had no trend were not analysed and no graphs are presented:

- pH
- Clarity
- Binding Potency
- Subvisible Particles $\geq 10\ \mu\text{m}$
- SEC (Monomer)
- SEC (HMW)
- Non-reduced CE-SDS
- cIEF (Main)
- cIEF (Acidic)
- cIEF (Basic)
- PS80

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

Figure 10: Degradation Modeling for pH

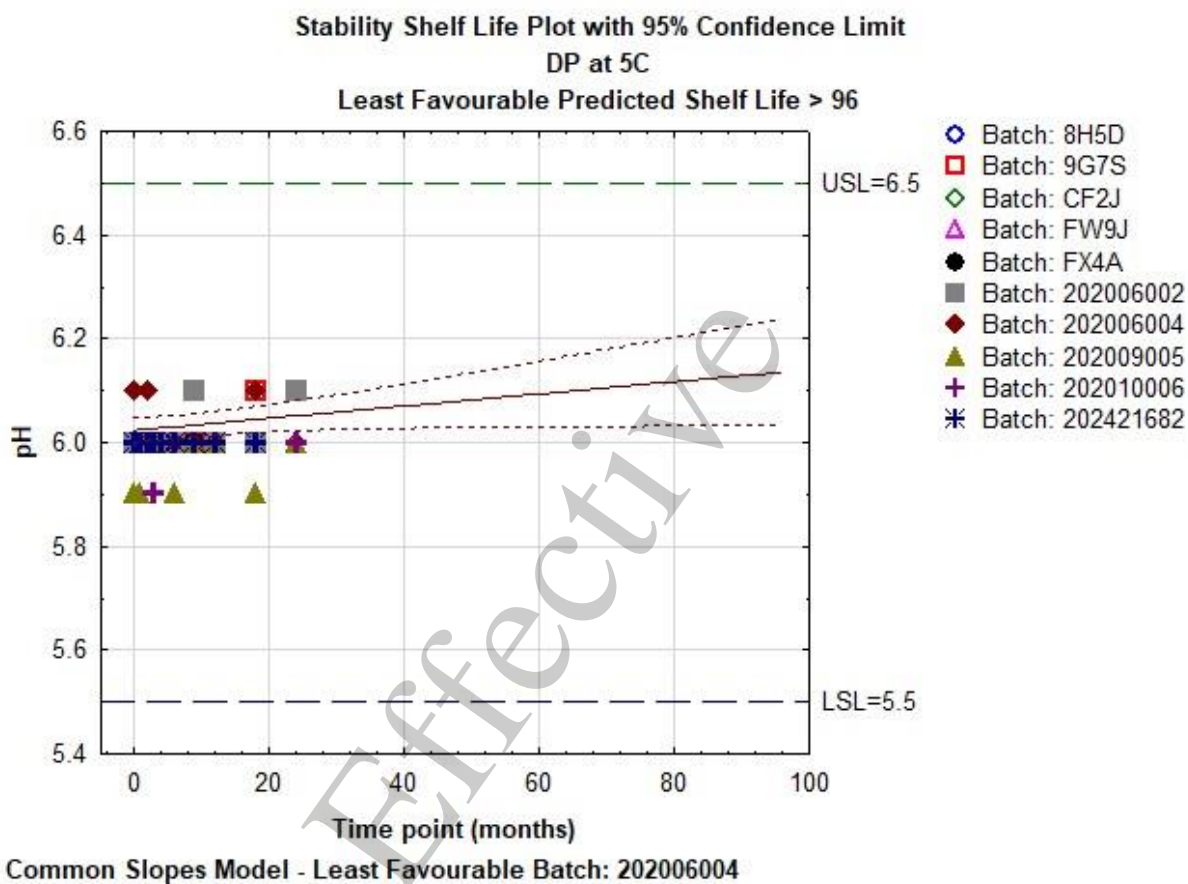


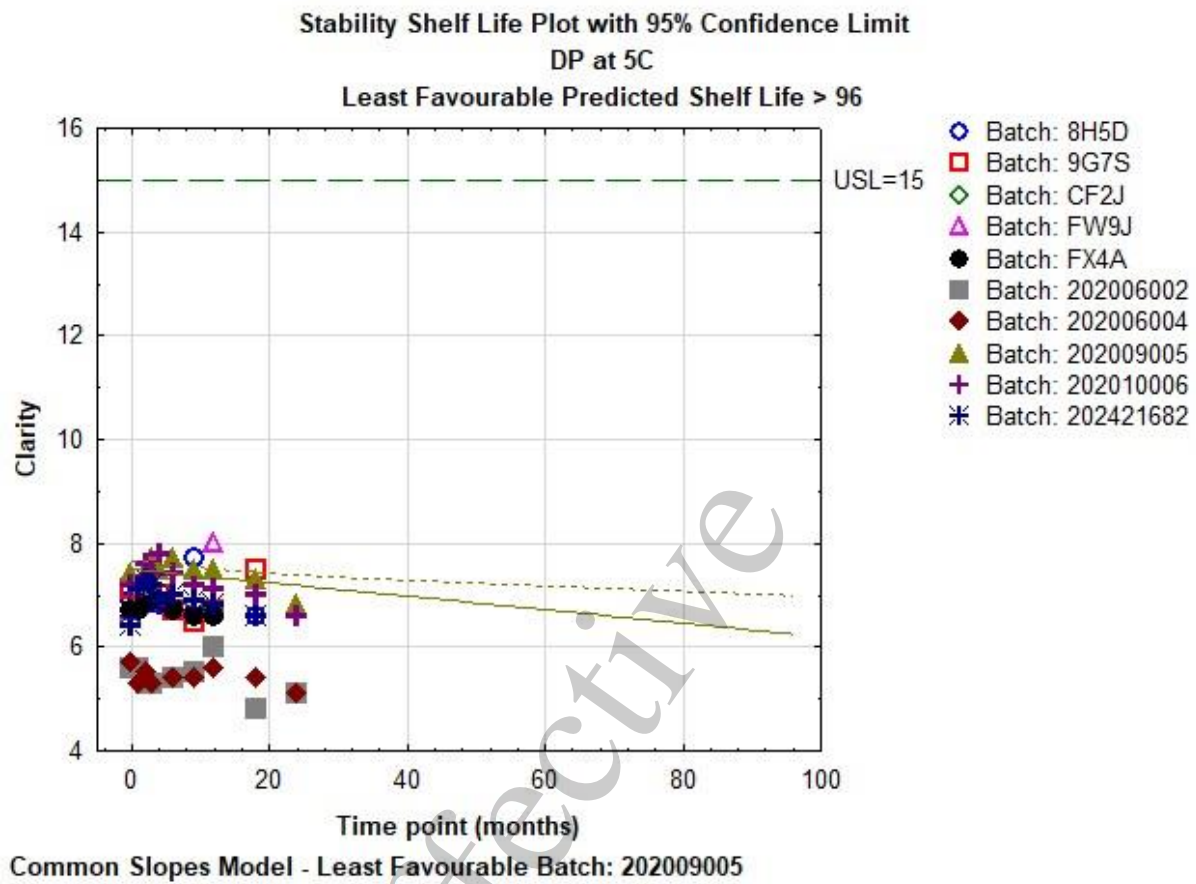
Figure 11: Degradation Modeling for Clarity

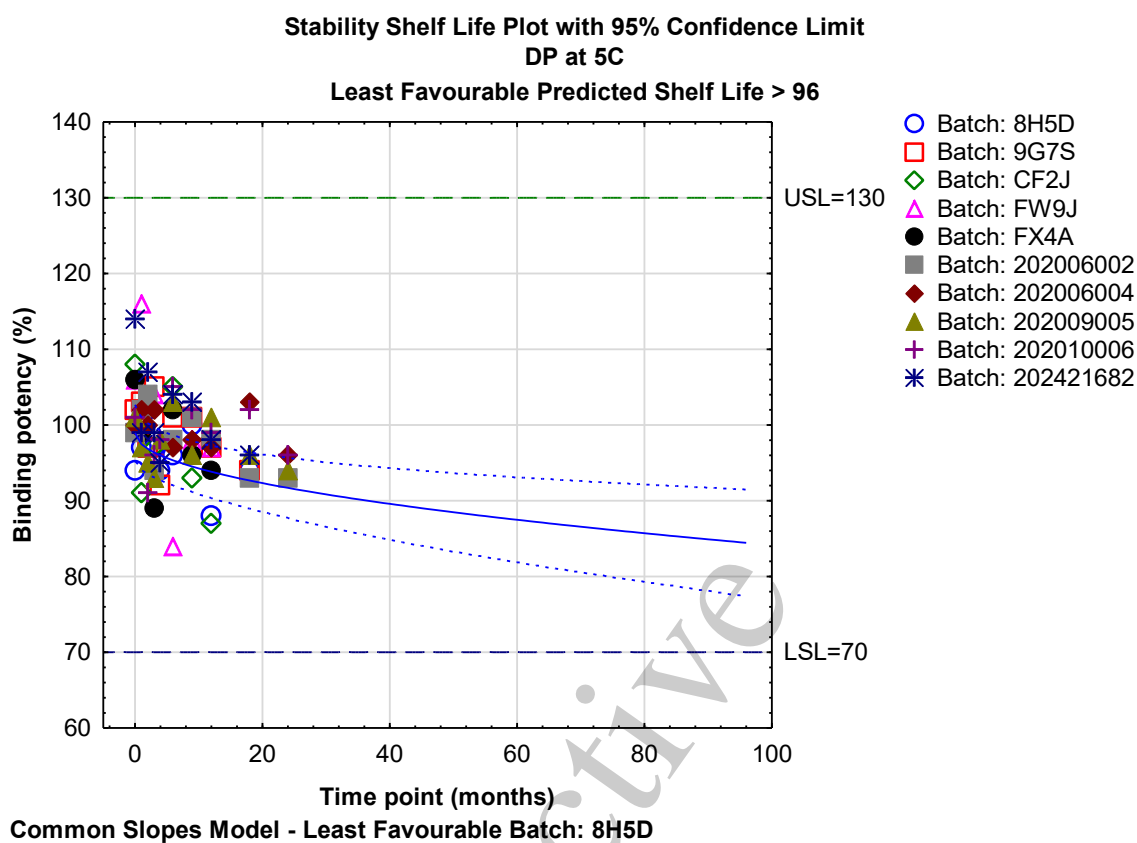
Figure 12 Degradation Modeling for Binding Potency

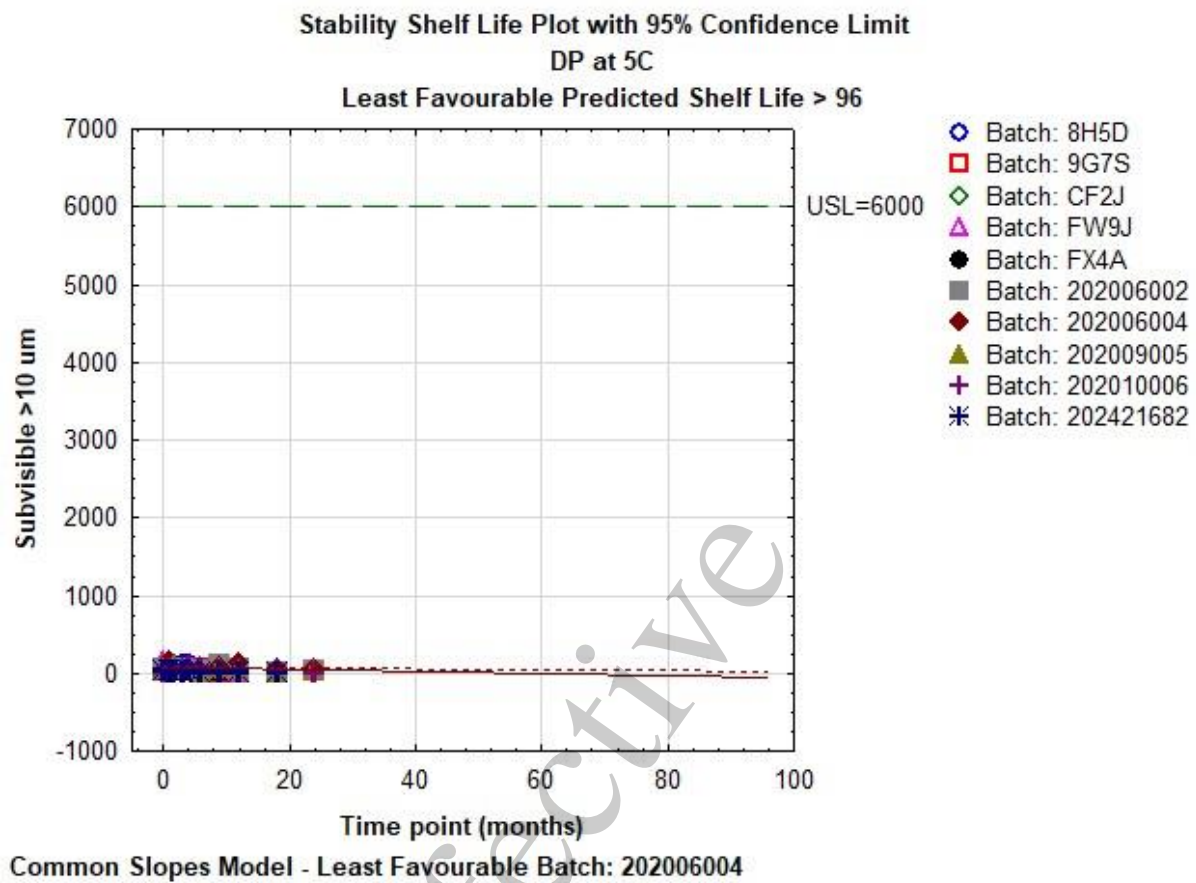
Figure 13: Degradation Modeling for Subvisible Particulates 10um

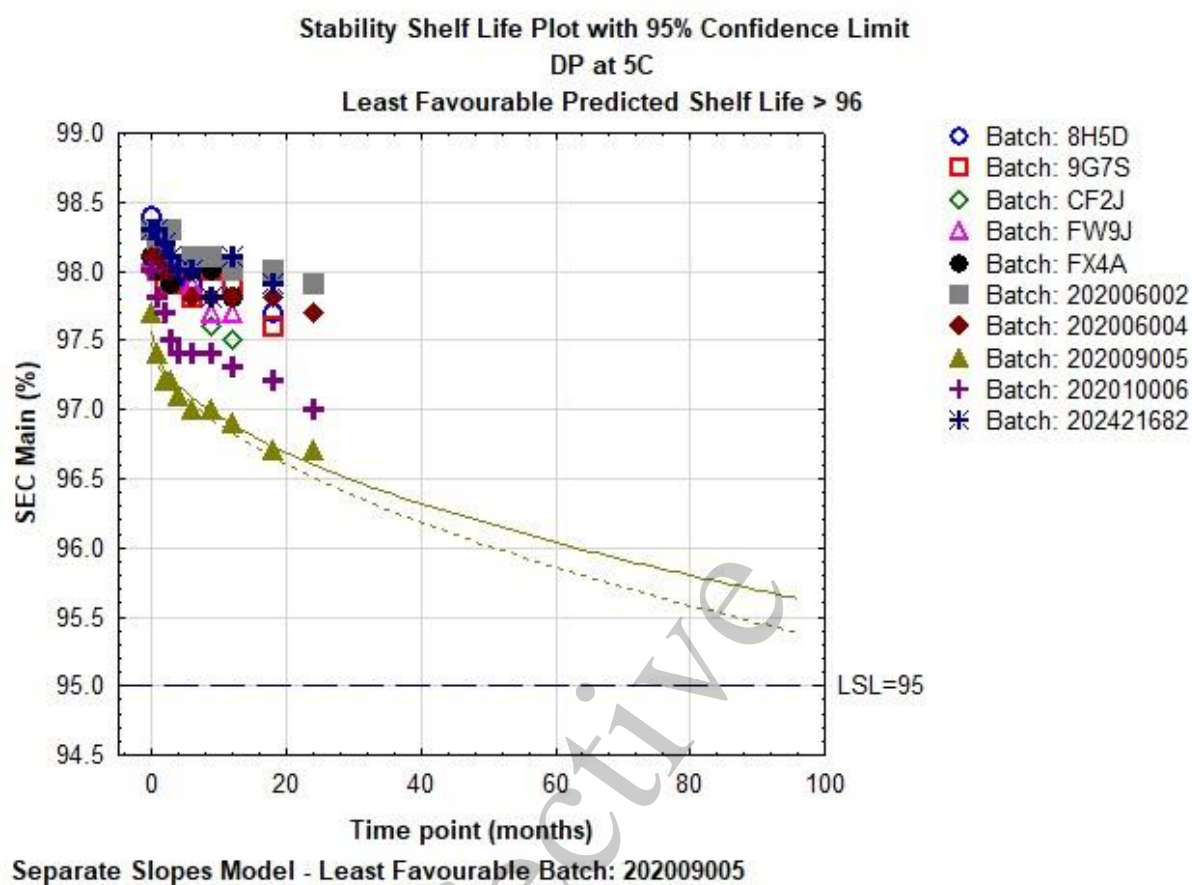
Figure 14: Degradation Modeling for SEC Main

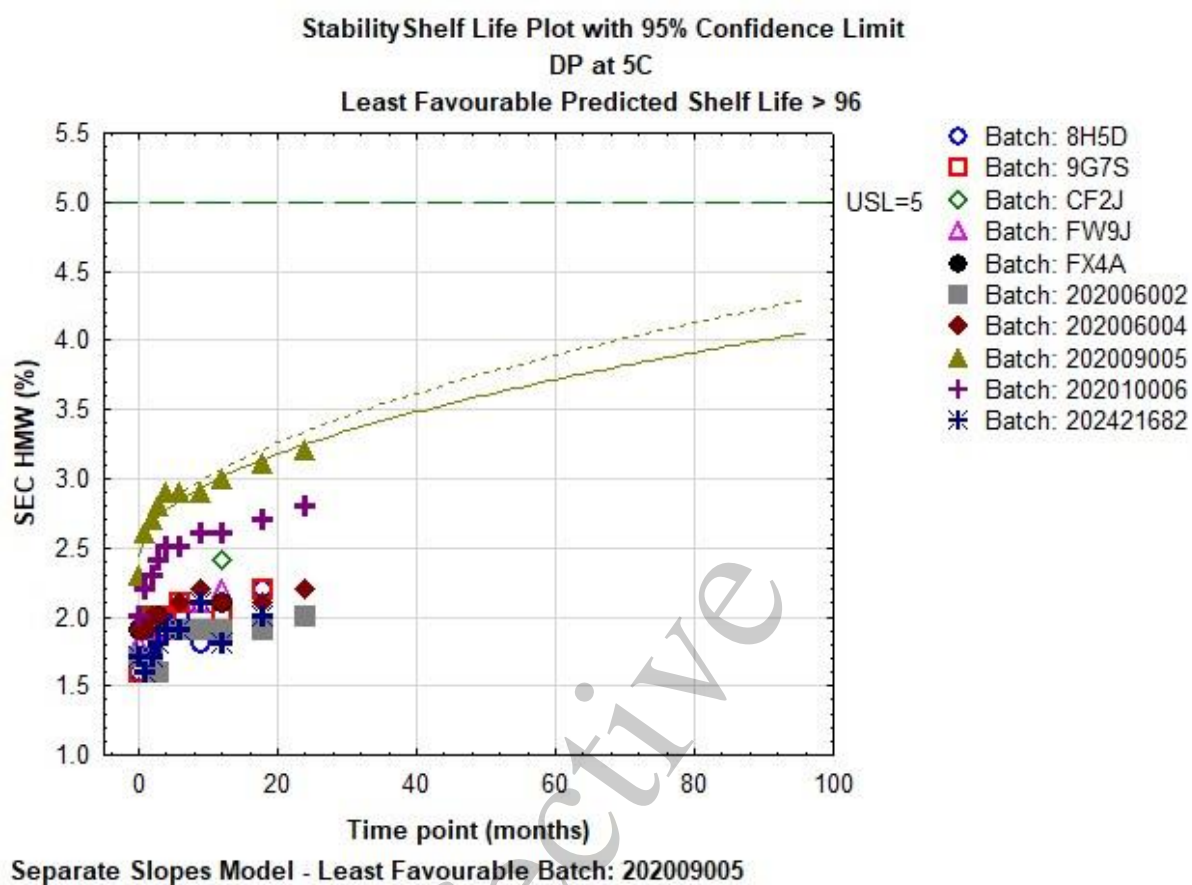
Figure 15: Degradation Modeling for SEC HMW

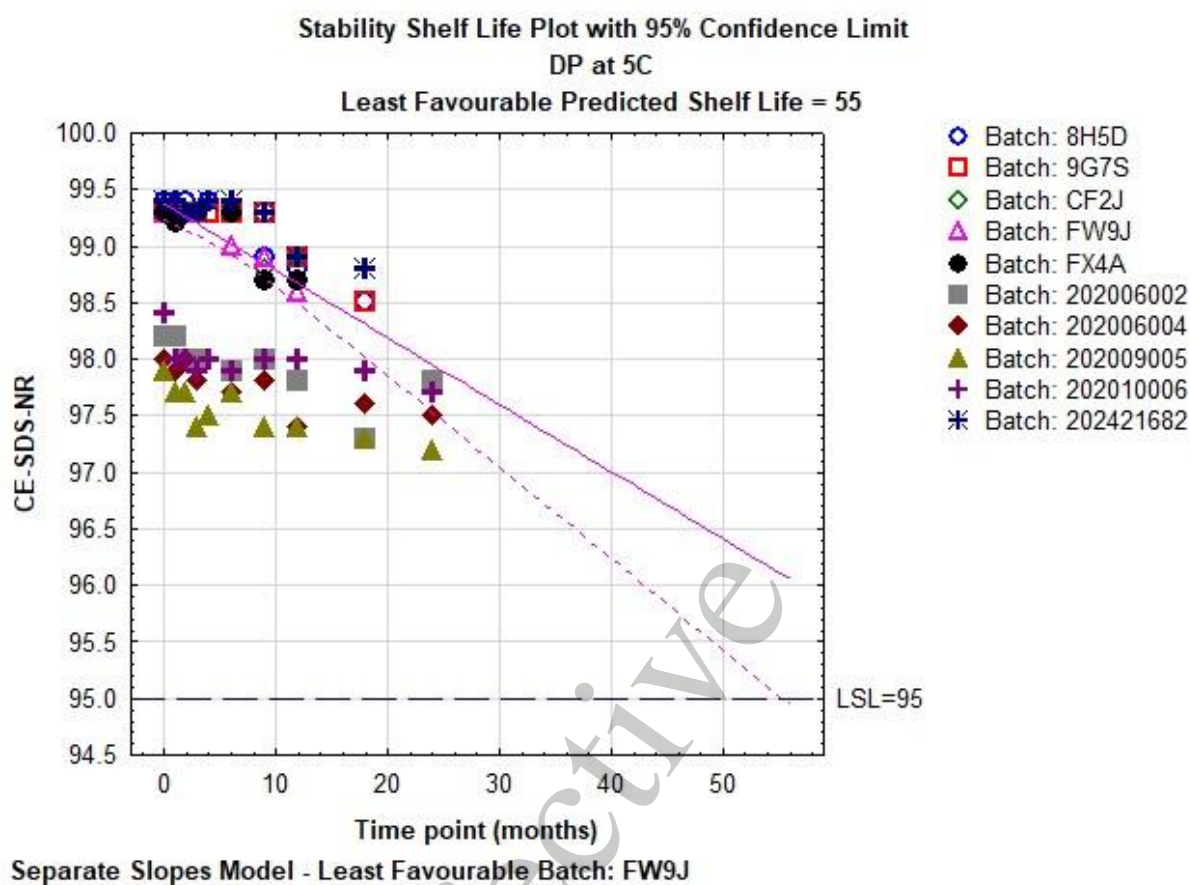
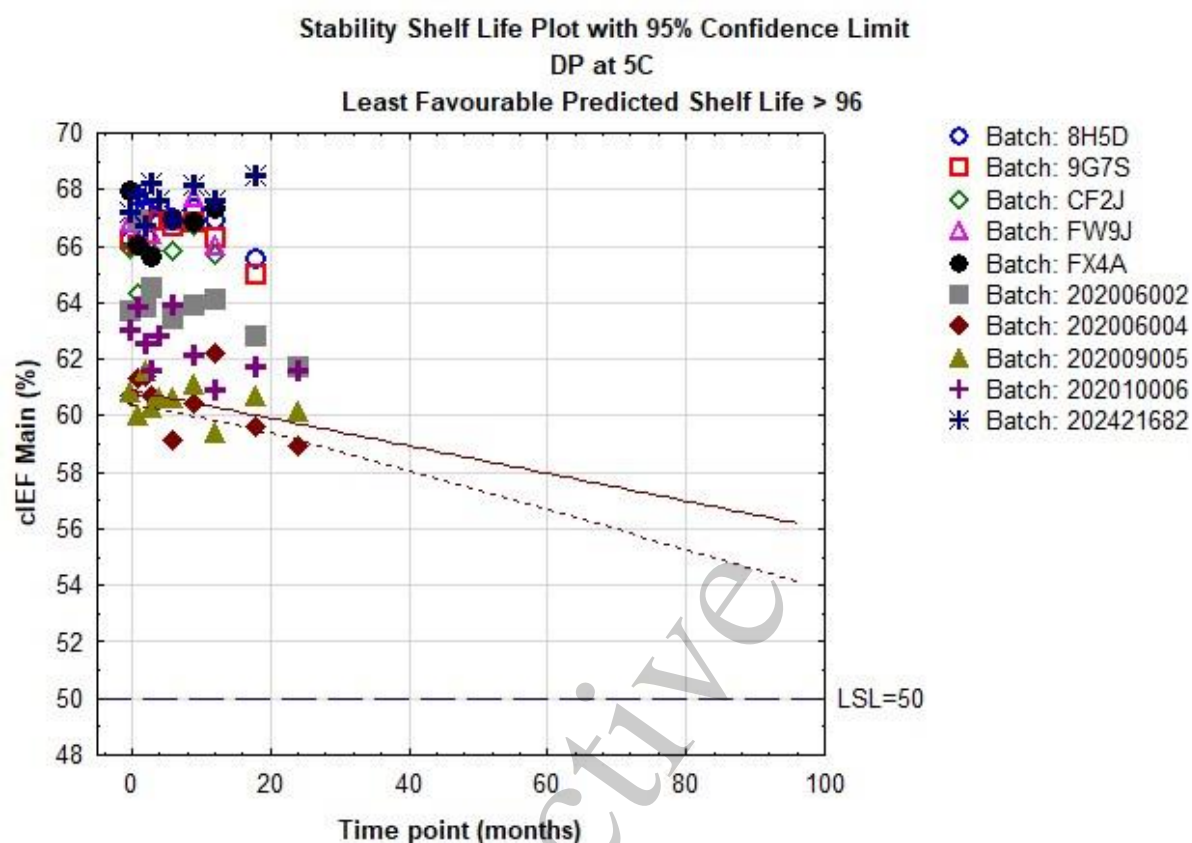
Figure 16: Degradation Modeling for CE-SDS-Non-Reduced

Figure 17: Degradation Modeling for cIEF Main



Common Slopes Model - Least Favourable Batch: 202006004

Figure 18: Degradation Modeling for cIEF Acidic

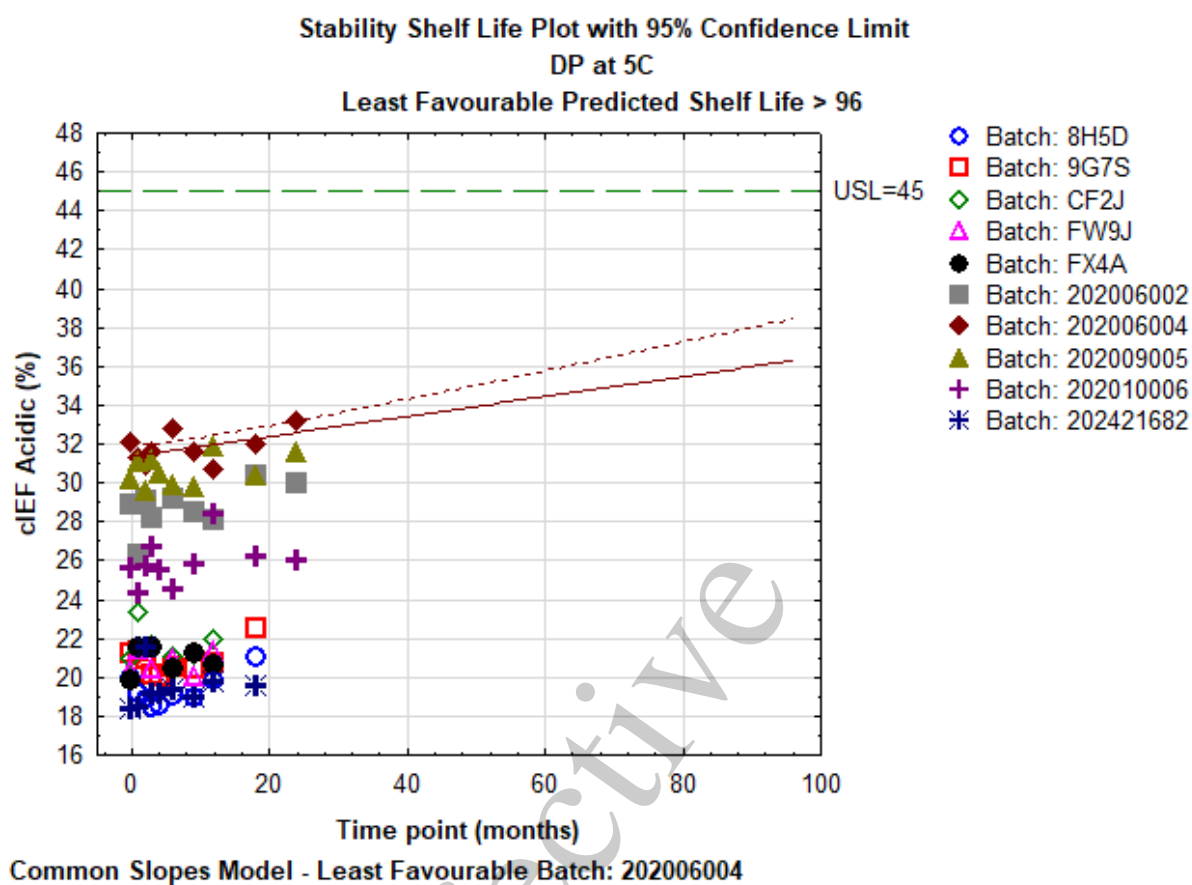


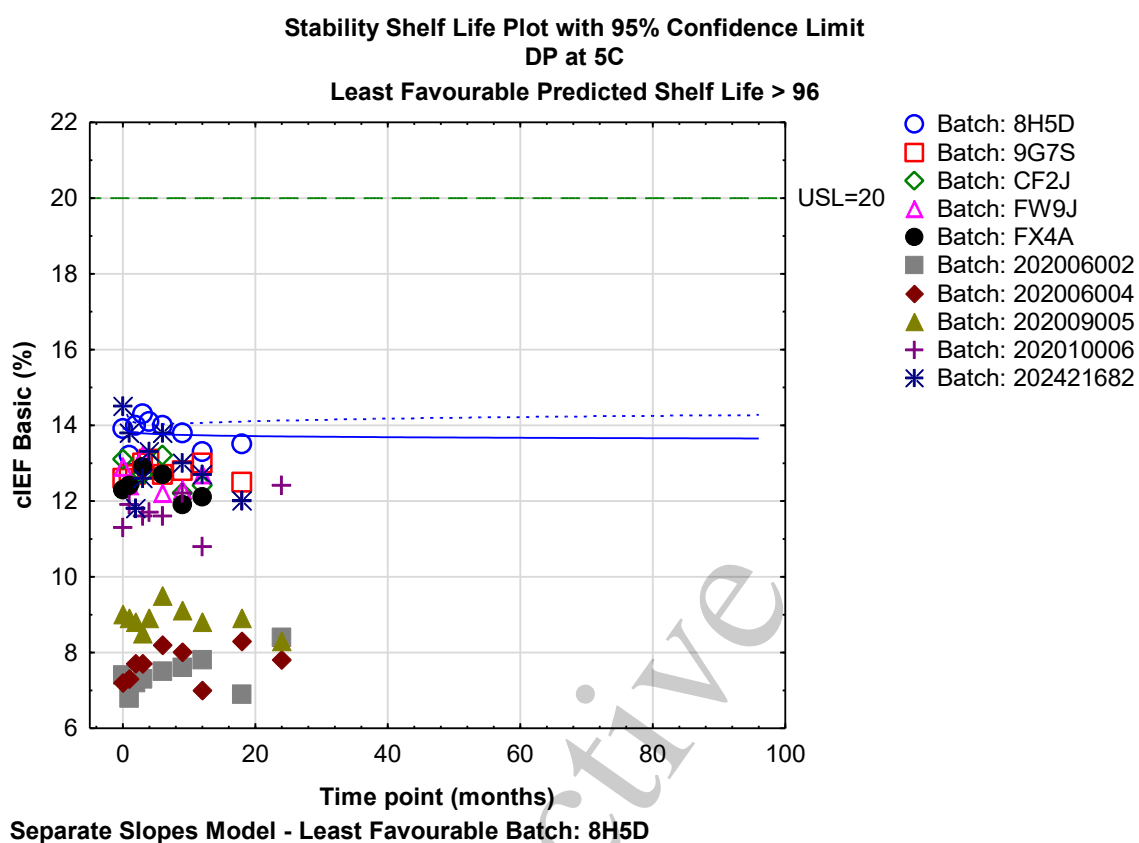
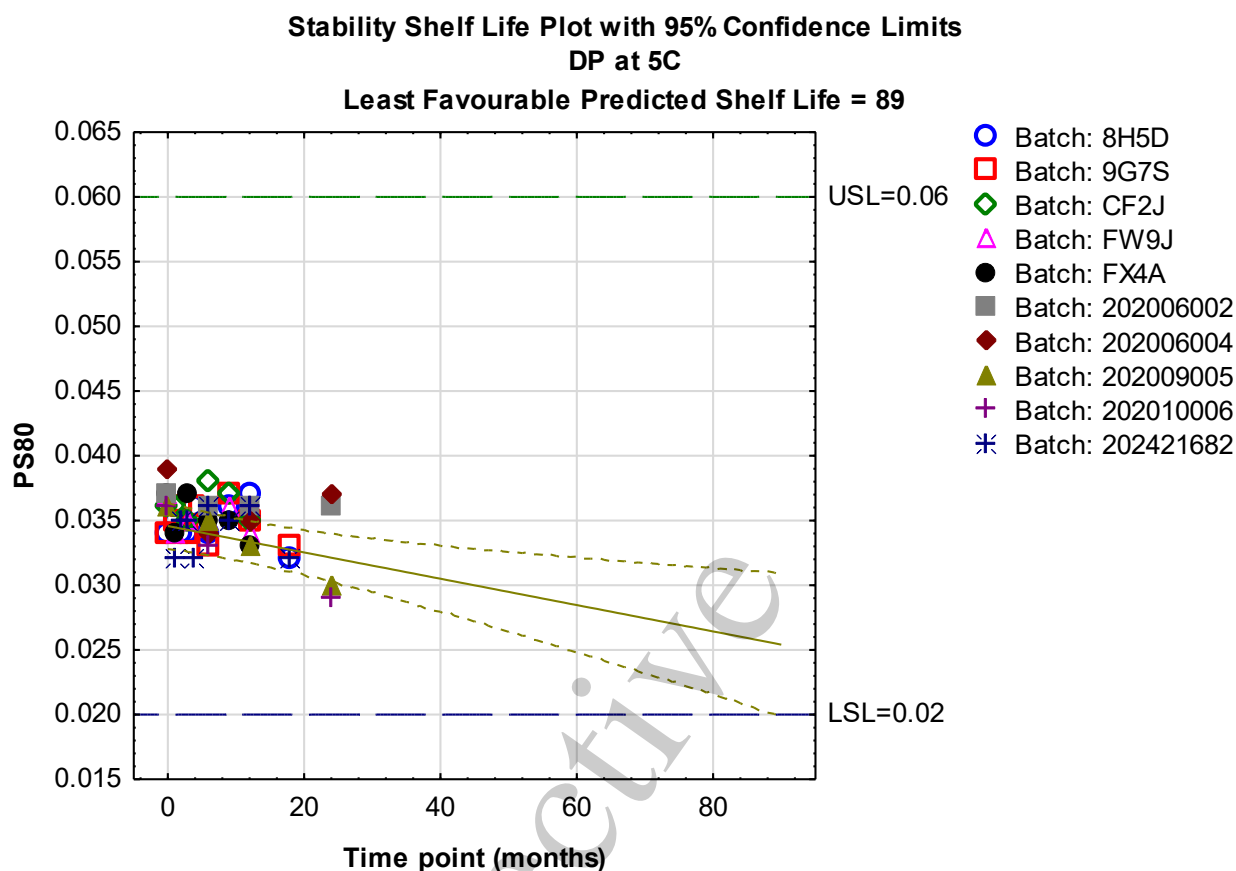
Figure 19 Degradation Modeling for cIEF Basic

Figure 20: Degradation Modeling for PS80

Common Slopes Model - Least Favourable Batch: 202009005

Conclusion:

The shelf-life of VIR 7831 (GSK4182136) Drug Product was assessed using the following stability data available to date: 24-month time point data from analysis of VIR 7831 Gen 1 DP batches, 24-month time point data from analyses of the GMP Gen 2 WuXi DP batches, 18-month time point data from analyses of the GMP Gen 2 Parma DP batches, and 12-month time point data from the PPQ 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 36 months. The data indicate that all attributes tested on stability are expected to remain within specifications through the 36-month shelf-life. The earliest time the drug product (stored in recommended conditions of 2-8°C) will reach specification limit is 55 months with CE-SDS (Non-Reduced) test result being the limiting factor. Data from the ongoing stability studies at the long-term recommended storage condition will be monitored.

VERSION HISTORY:

Version	Change	Justification
4.0	<p>Updated Data</p> <p>202009005 24M @ 5C 202010006 24M @ 5C 202421682 18M @ 5C 8H5D 18M @ 5C 9G7S 18M @ 5C CF2J 12M @ 5C FW9J 12M @ 5C FX4A 12M @ 5C</p> <p>Added batches DV4T, DY9B, DV4U up to 6 months</p>	<p>Updated all scatterplot graphs to reflect the new data, and updated the statistical analysis graphs with the new statistical assessment.</p> <p>Updated the conclusion for a 36 month expiry.</p>
3.0	<p>202006002 24M @ 5C 202006004 24M @ 5C 202009005 18M @ 5C 202010006 18M @ 5C 202421682 12M @ 5C 8H5D 12M @ 5C 9G7S 12M @ 5C CF2J 12M @ 5C FW9J 12M @ 5C FX4A 12M @ 5C</p>	<p>Align with updated specification document and reflect current stability data time points used in trending.</p>

VIR-7831 Drug Product Stability Trend Report

Document Approvals by Electronic Signature

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Verdict: Approve	Azita Adli aja21857 (azita.j.adli@gsk.com) Quality Assurance Approval 04-Apr-2023 15:45:27 GMT+0000
Verdict: Approve	Jing Capucao jjc22425 (jing.j.capucao@gsk.com) Management Approval 05-Apr-2023 01:08:14 GMT+0000
Verdict: Approve	Bree Crossley baw80181 (bree.a.crossley@gsk.com) Quality Assurance Approval 07-Apr-2023 11:43:00 GMT+0000
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