

A case validation study: GC headspace determination of residual solvents in a drug substance

Document authorization:

Name & Title/Function	Action	Signature	Date

Document distribution list:

Date	Version	Distribution	Subject

Table of Contents

Document authorization:	1
Document distribution list:	1
1. Introduction.....	3
2. Purpose validation	3
3. Validation requirements	3
4. Validation results	4
4.1. Specificity	4
4.2. Linearity.....	5
4.2.2. Linearity of Heptane.....	6
4.3. Accuracy	7
4.4. Repeatability	9
4.5. Range.....	11
4.6. Limit of Detection and Limit of Quantitation	12
4.7. Robustness	14
4.8. System Suitability Test	16
5. Conclusions.....	20
Document change history:	21

1. Introduction

This validation report presents case study results for an Assay determination of residual solvents Ethanol and Heptane in a drug substance XXX.

2. Purpose of validation

The objective of this validation is to demonstrate that the given GC headspace method is suitable for the intended purpose, i.e. for the Assay determination of residual Methanol and residual Heptane in a drug substance of interest.

The validation was executed according to ICH Q2(R1) requirements. The limits for residual Methanol and residual Heptane were taken from ICH Q3C(R5), Class 3 solvents, limit 5000 ppm, i.e. 0.5%.

3. Validation requirements

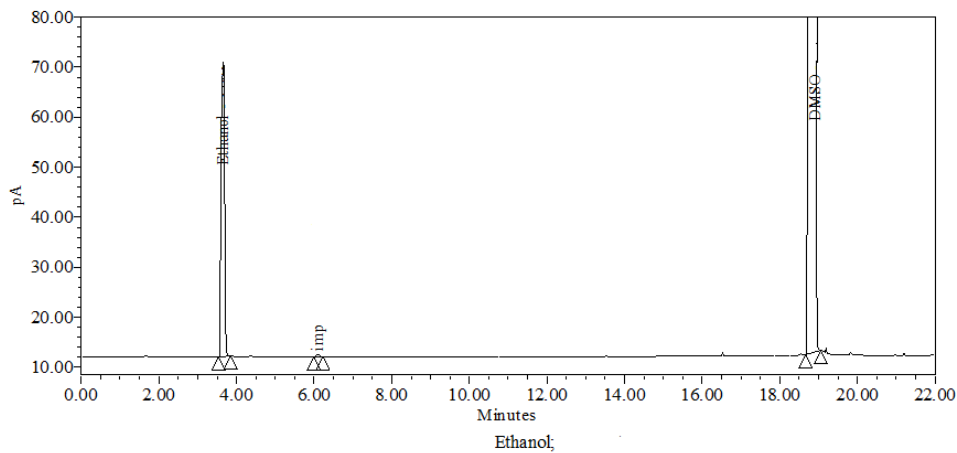
The validation protocol defined the following requirements and acceptance criteria:

Validation parameter	Requirements and acceptance criteria for Ethanol and Heptane
4.1. Specificity	Sufficient separation of Ethanol and Heptane from each other; no interference with the peaks from the Blank. Peak resolution > 1.5
4.2. Linearity	R > 0.99 QC coefficient > 5.0%
4.3. Accuracy	80% < Recovery < 120%
4.4. Repeatability	Repeatability < 15%
4.5. Range	Range determined based on Linearity, Accuracy and Precision
4.6. Limit of Detection and Limit of Quantitation	To be determined based on the calibration line (Linearity data)
4.7. Robustness	Influence of oven temperature, column pressure, incubation temperature and incubation time are to be evaluated
4.8. System Suitability Test	Plate number, Tailing and Peak area repeatability to be determined

4. Validation results

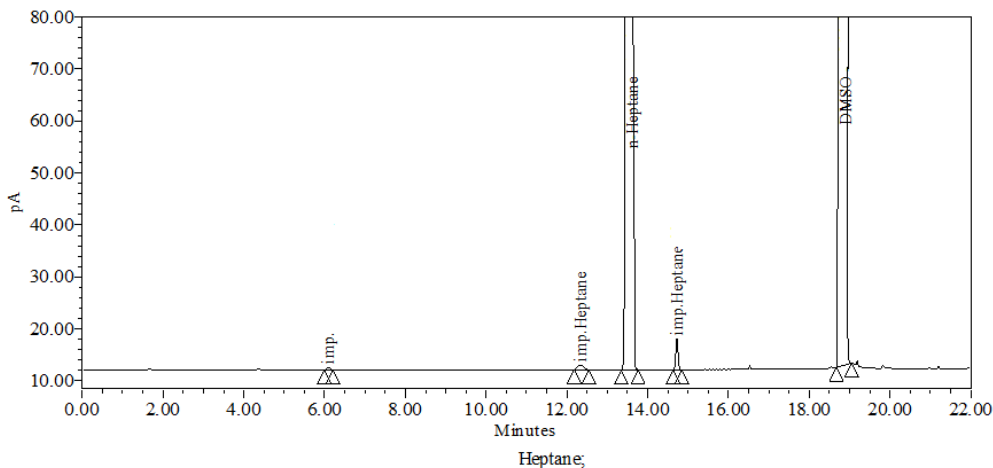
4.1. Specificity

4.1.1. Specificity of Ethanol



Resolution between Ethanol and impurity from DMSO (blank) is 14.2.

4.1.2. Specificity of Heptane

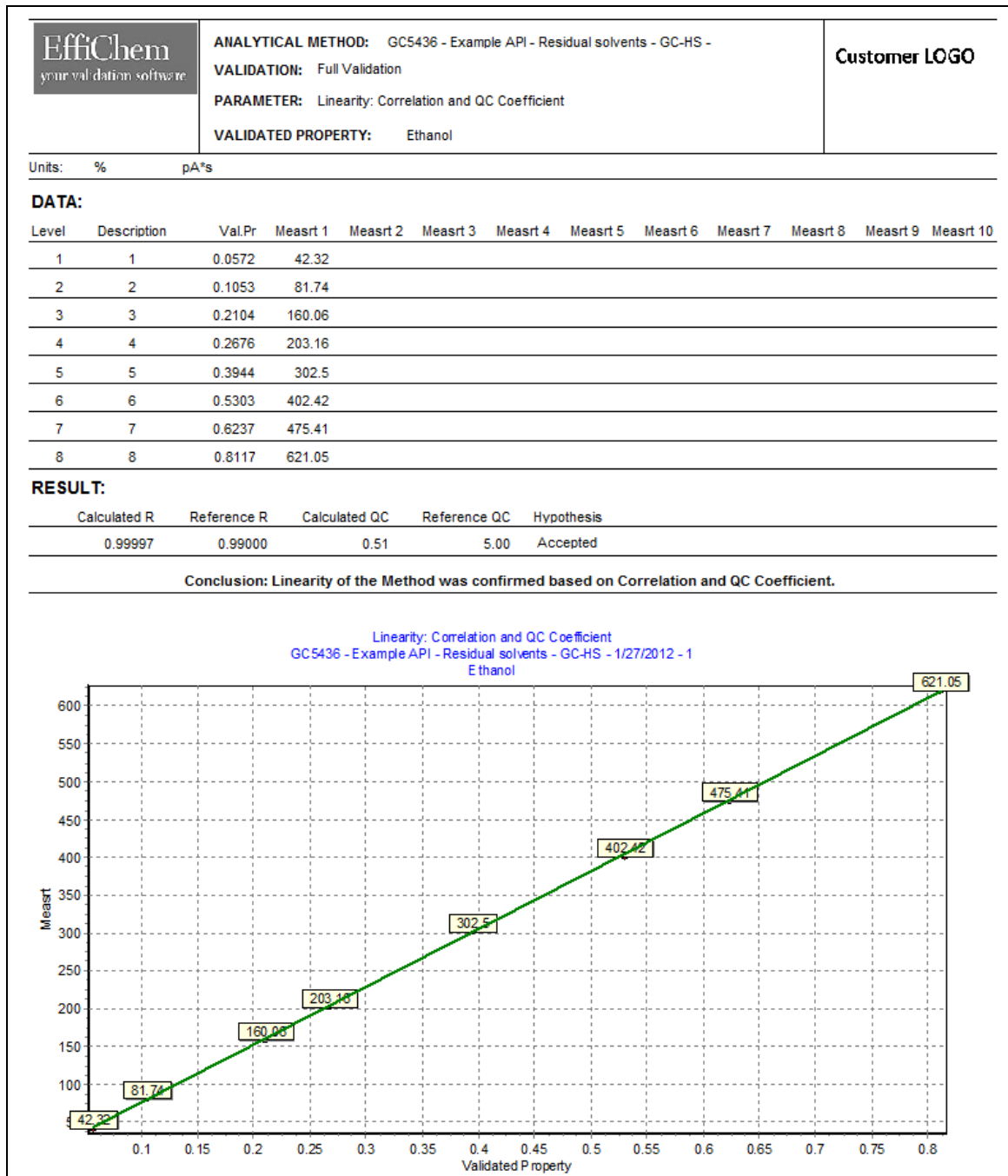


Resolution between heptanes and its nearest impurity is 5.4.

Conclusion: Peak resolution for Ethanol and Heptane is > 1.5 . There is no interference with the peaks from the blank. The method is considered sufficiently specific for the Ethanol and Heptane determination.

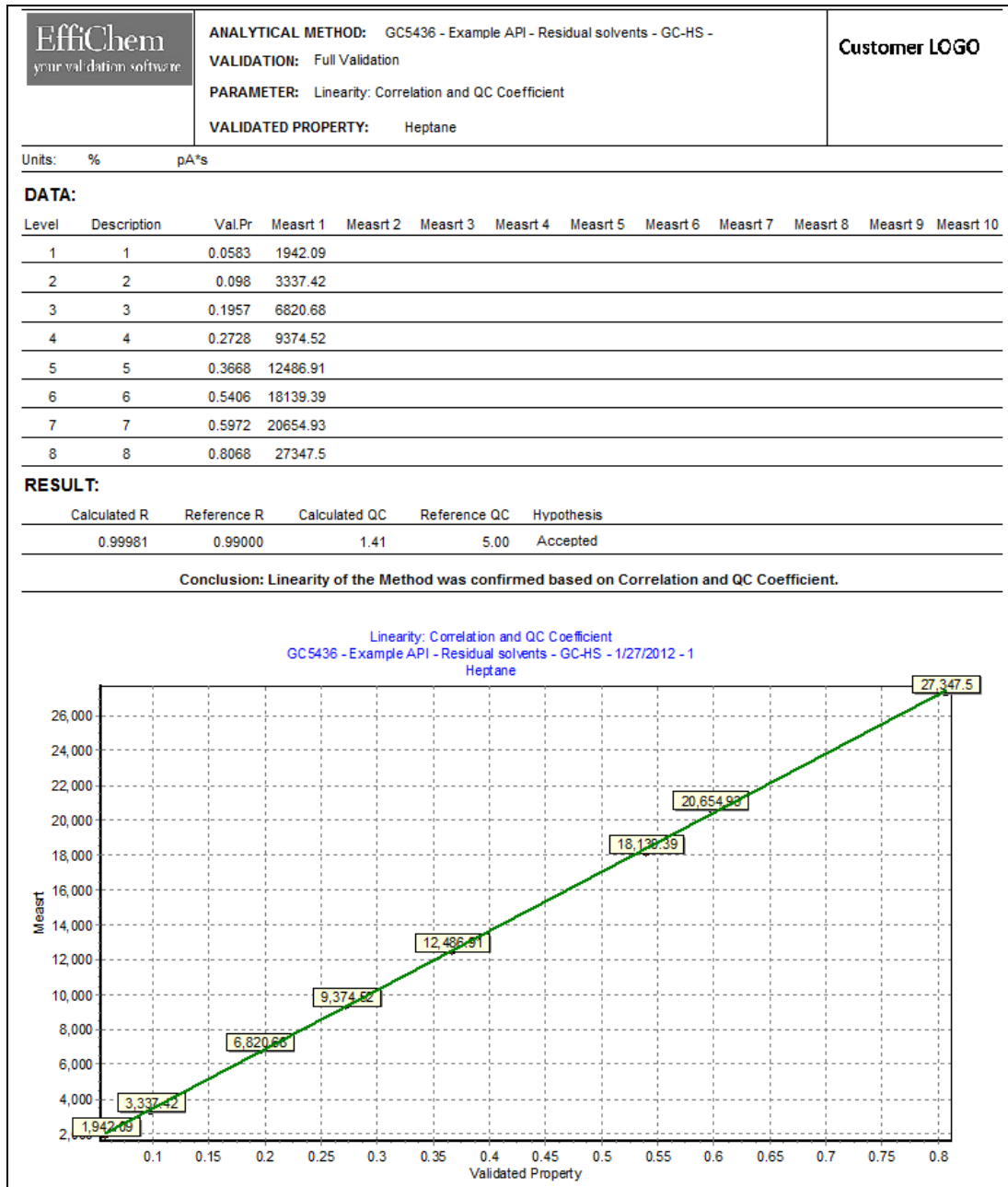
4.2. Linearity

4.2.1. Linearity of Ethanol



Conclusion: All linearity acceptance criteria for Ethanol were met.

4.2.2. Linearity of Heptane

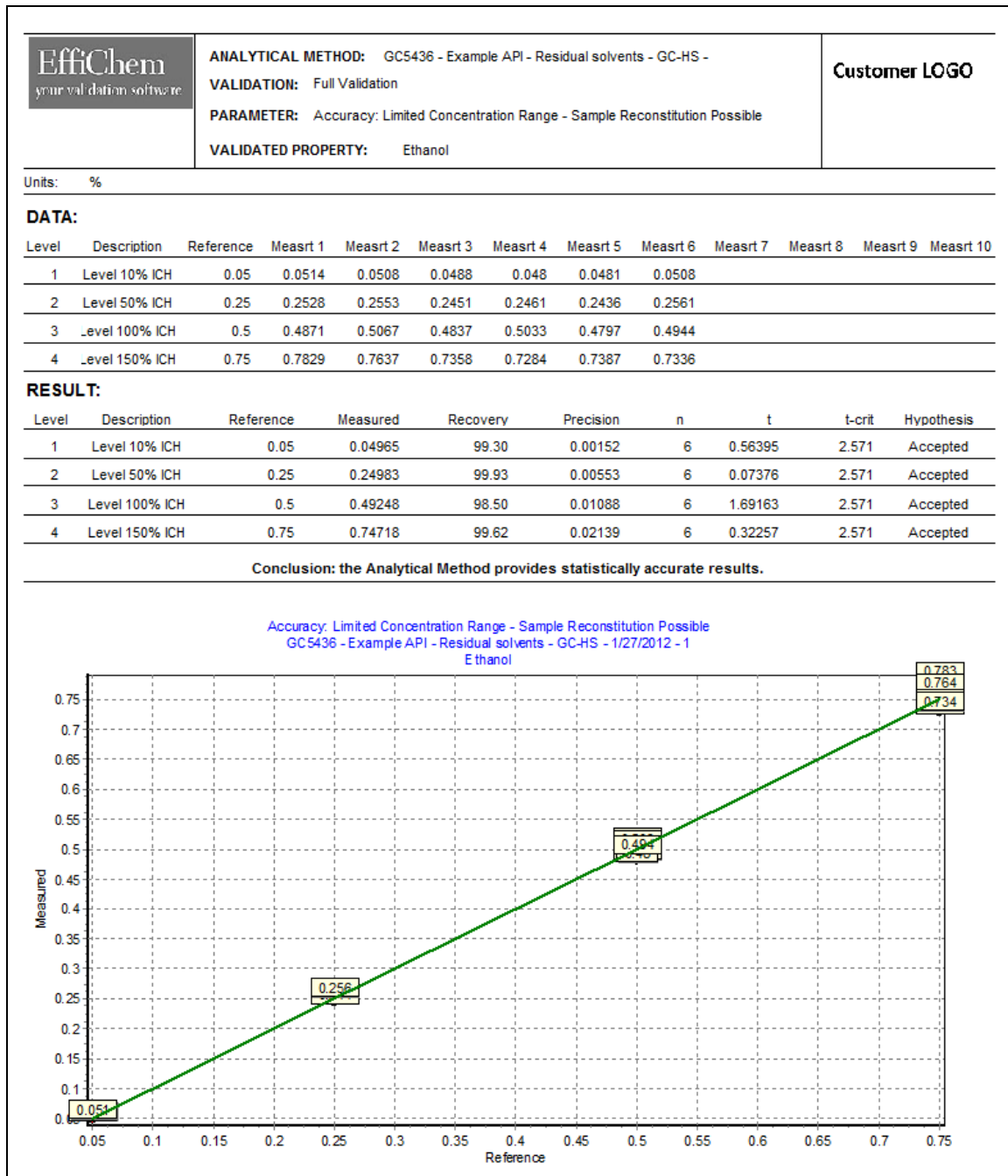


Conclusion: All linearity acceptance criteria for Heptane were met.

Conclusion: The given method has been proven to be sufficiently linear for the Ethanol and Heptane determination.

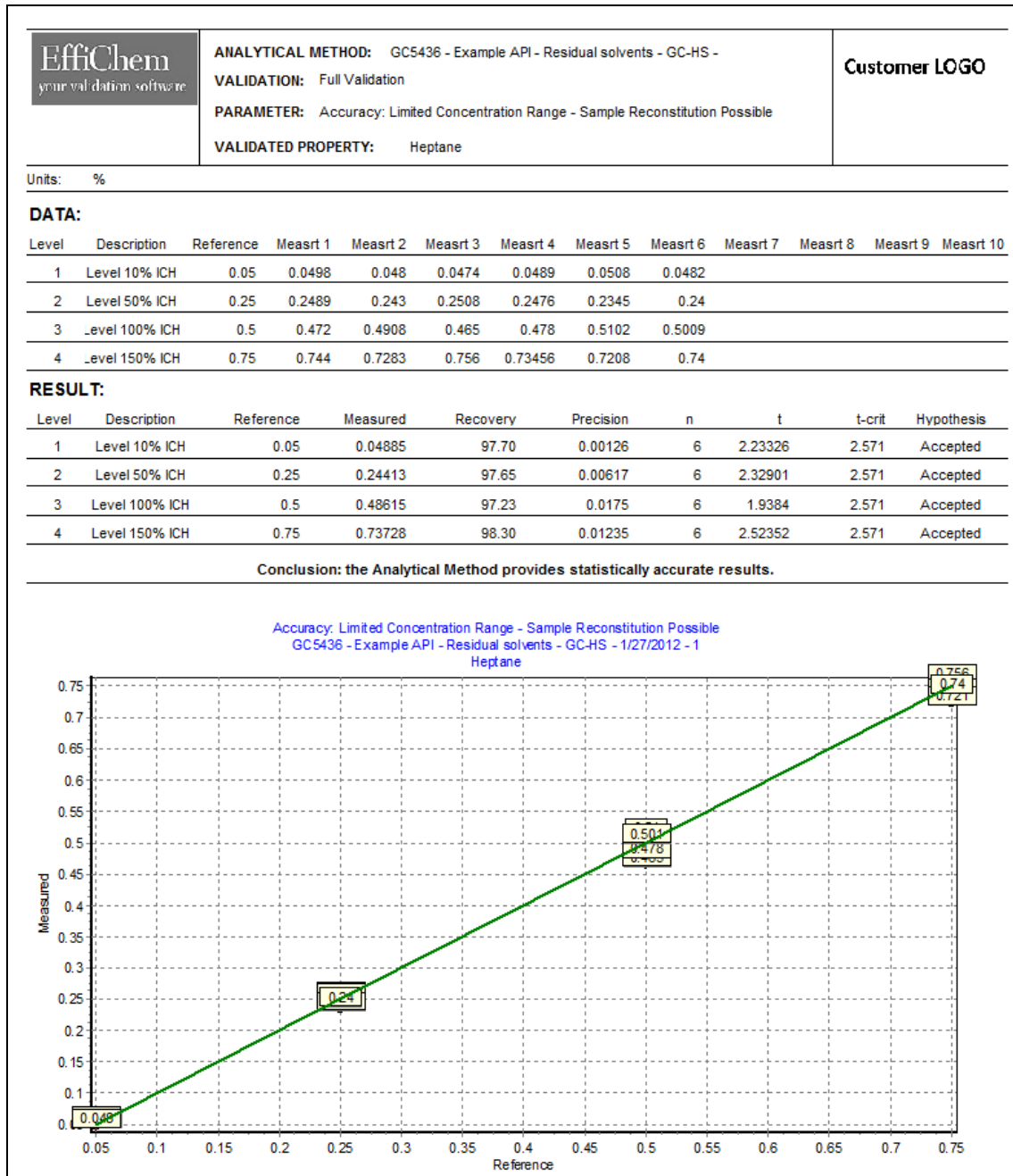
4.3. Accuracy

4.3.1. Accuracy of Ethanol



Conclusion: Accuracy of the Ethanol determination was confirmed using a t-test. The obtained Recovery met the acceptance criterion $80\% < \text{Recovery} < 120\%$.

4.3.2. Accuracy of Heptane

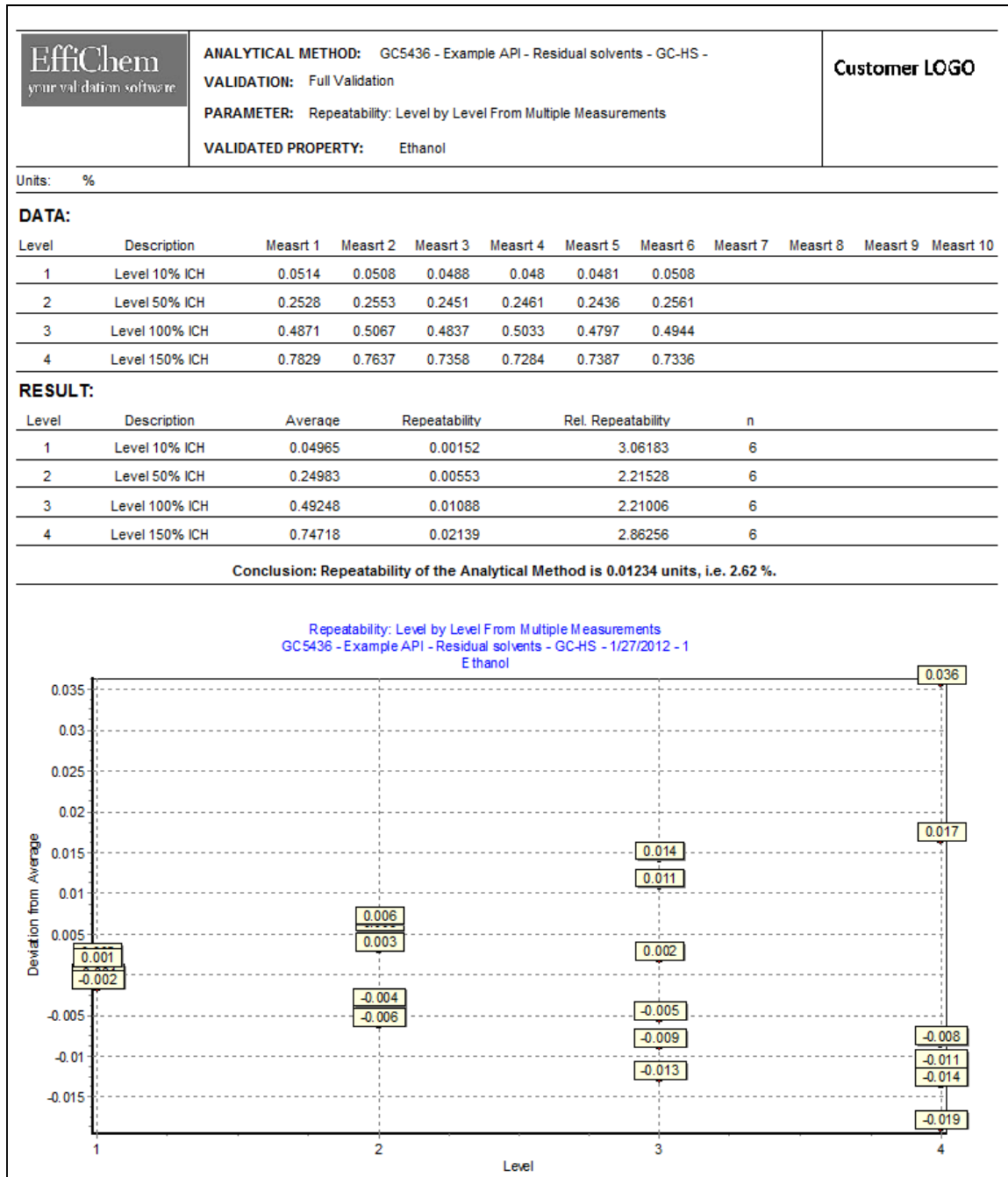


Conclusion: Accuracy of the Heptane determination was confirmed using a t-test. The obtained Recovery met the acceptance criterion $80\% < \text{Recovery} < 120\%$.

Conclusion: The method is sufficiently accurate for the Ethanol and Heptane determination.

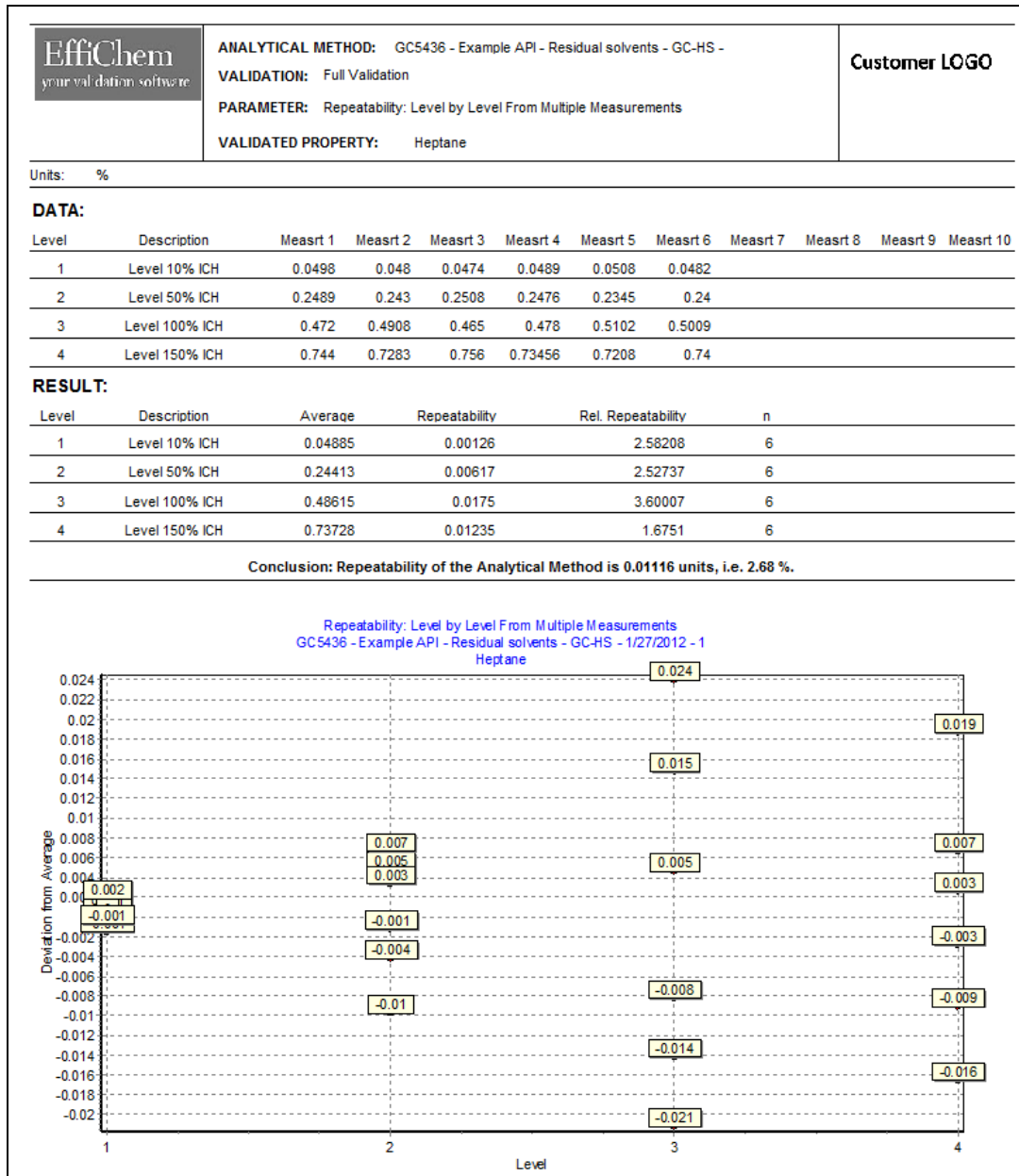
4.4. Repeatability

4.4.1. Repeatability of Ethanol



Conclusion: Repeatability of the Ethanol determination is 2.6%. This result meets the acceptance criterion for Repeatability < 15%.

4.4.2. Repeatability of Heptane



Conclusion: Repeatability of the Heptane determination is 2.7%. This result meets the acceptance criterion for Repeatability < 15%.

Conclusion: The method is sufficiently precise for the Ethanol and Heptane determination.

4.5. Range

4.5.1. Ethanol Range

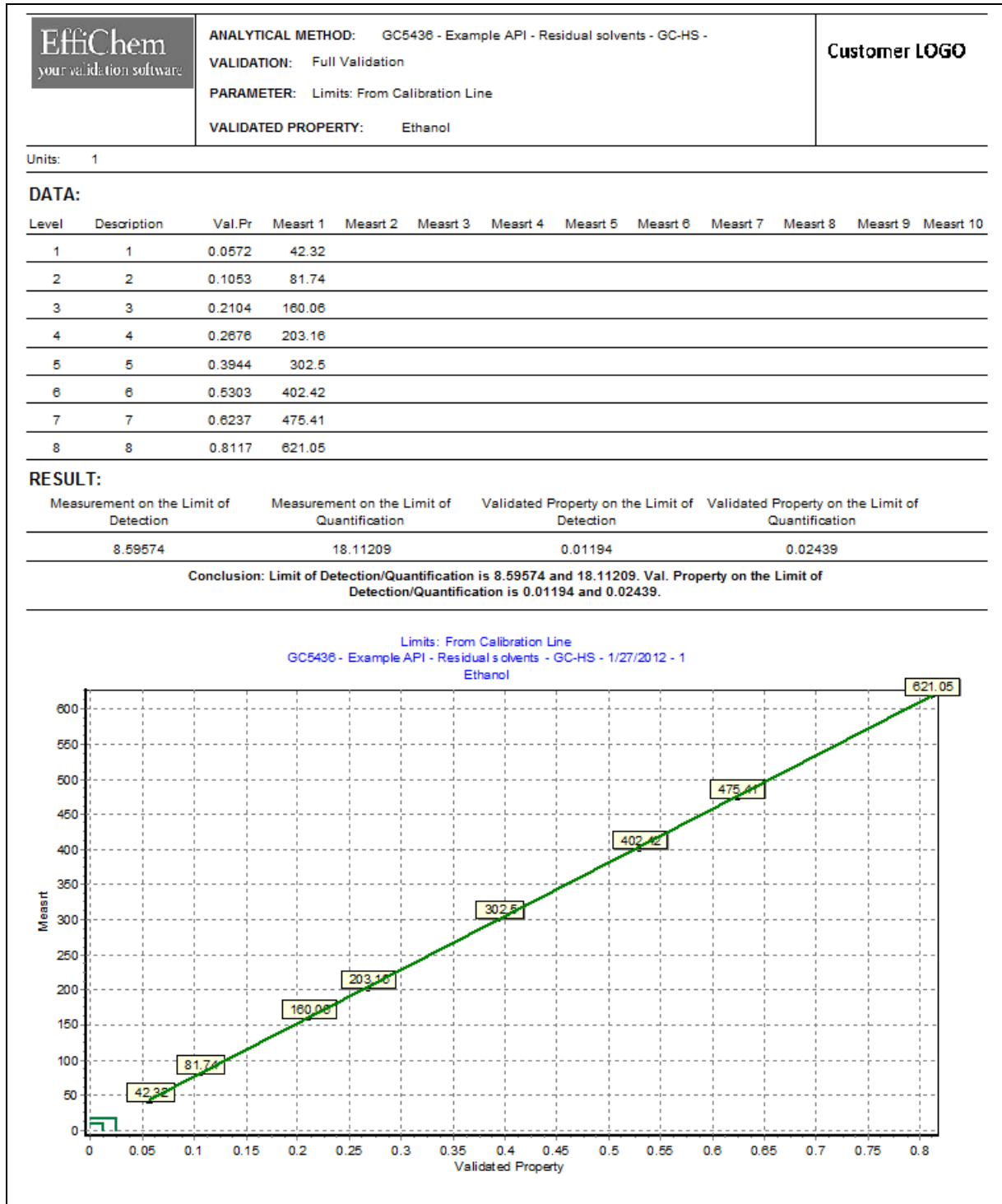
Based on the Linearity, Accuracy and Precision results it can be concluded the method can be safely used for the Ethanol determination from 0.05% to 0.75%. The target value of 0.5% is well within this range.

4.5.2. Heptane Range

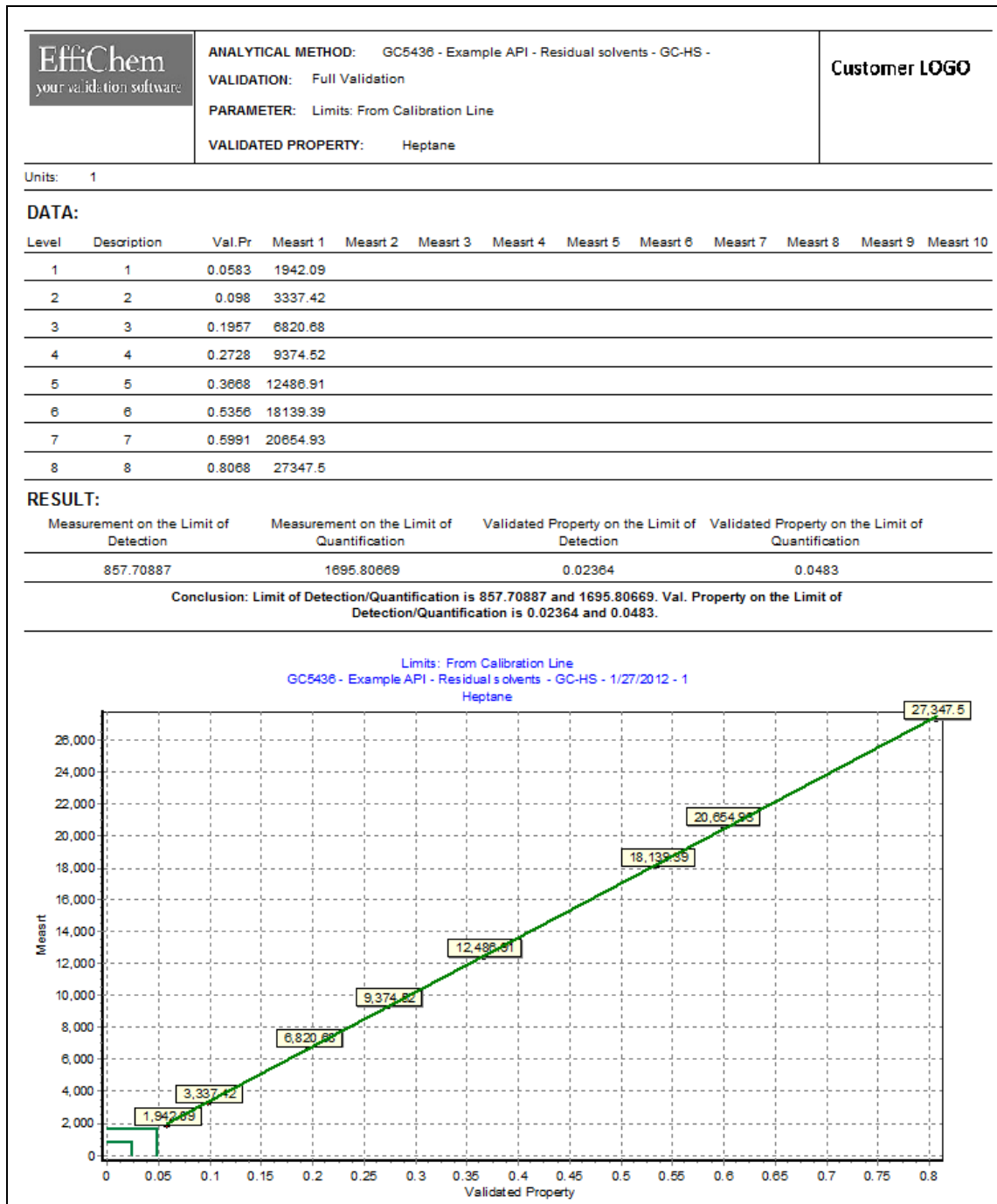
Based on the Linearity, Accuracy and Precision results it can be concluded the method can be safely used for the Heptane determination from 0.05% to 0.75%. The target value of 0.5% is well within this range.

4.6. Limit of Detection and Limit of Quantitation

4.6.1. Limit of Detection and Limit of Quantitation Ethanol



4.6.2. Limit of Detection and Limit of Quantitation Heptane

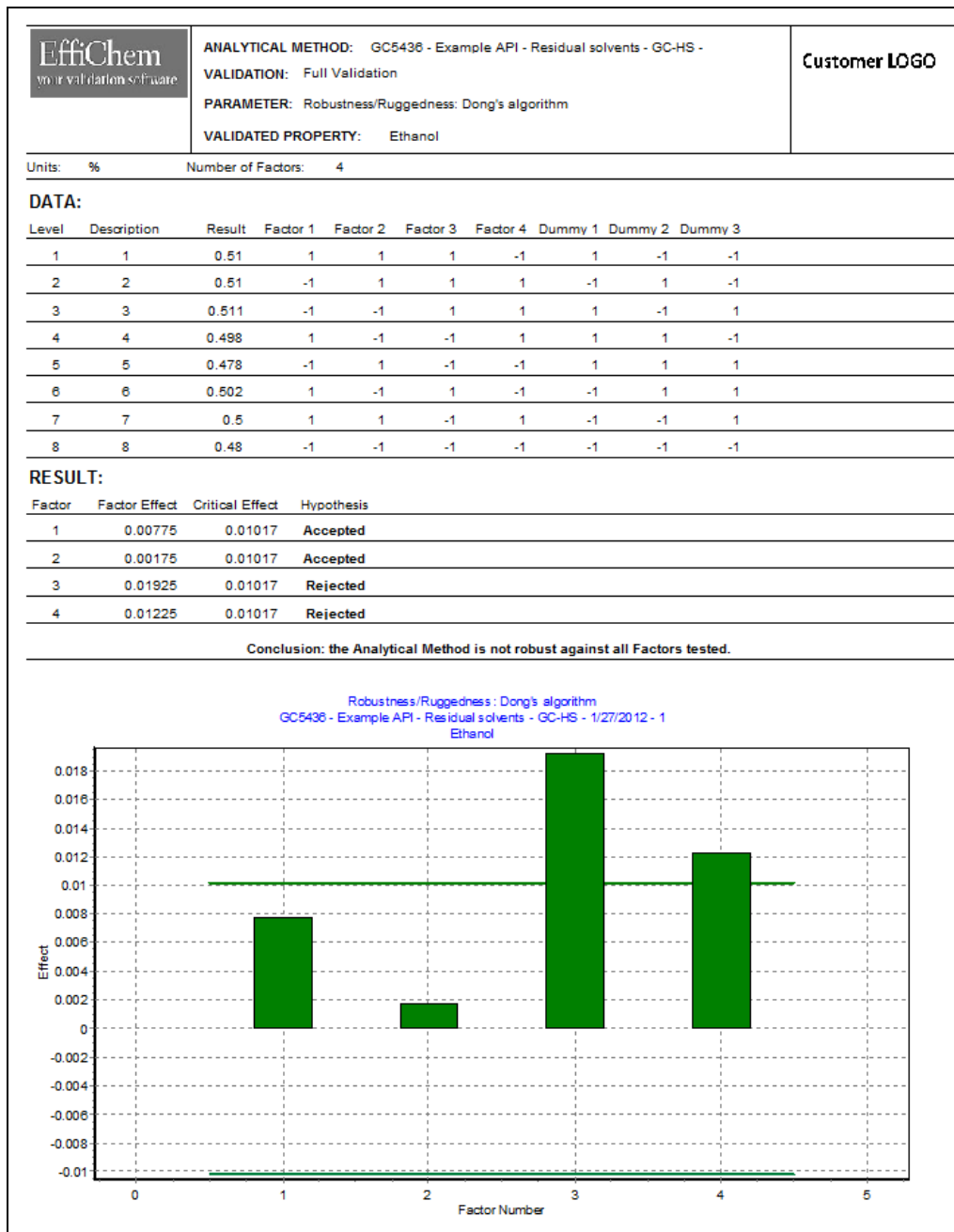


Conclusion: Limit of Quantitation for both Ethanol and Heptane is below 0.05% which is suitable for this determination with the target value of 0.5%.

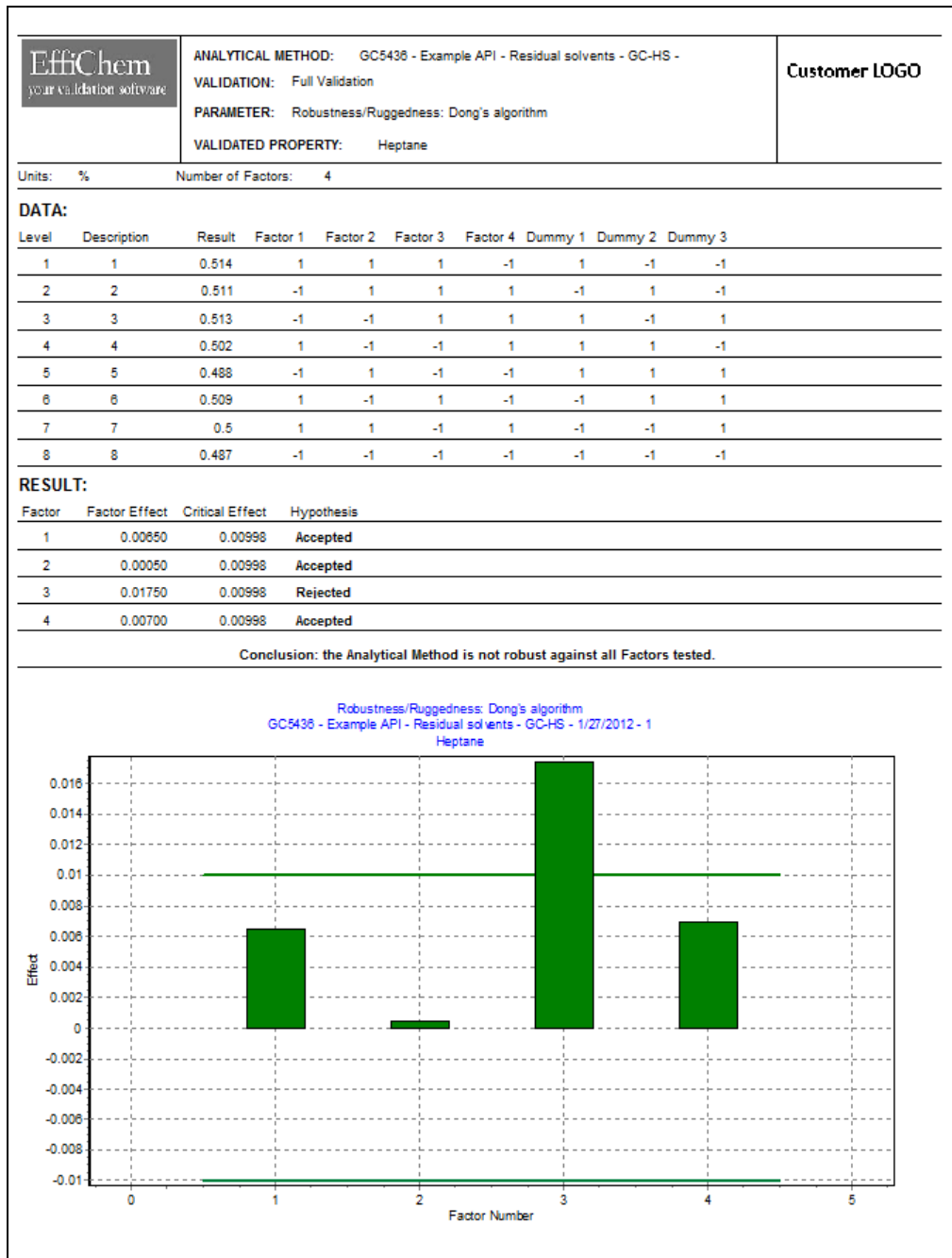
4.7. Robustness

Influence of 4 factors was tested: Factor 1: oven temperature, Factor 2: column pressure, Factor 3: incubation temperature and Factor 4: incubation time

4.7.1. Robustness of Ethanol




4.7.2. Robustness of Heptane




Conclusion: Influence of Factor number 3, incubation temperature, on both Ethanol and Heptane, and Factor number 4, incubation time, on Ethanol are significant. It is therefore necessary to maintain those factors close to their nominal levels.

4.8. System Suitability Test

4.8.1. Plate Number of Ethanol


 your validation software	ANALYTICAL METHOD: GC5436 - Example API - Residual solvents - GC-MS -	Customer LOGO	
	VALIDATION: HPLC_FDA		
	PARAMETER: Theoretical Plate Number - FDA		
	VALIDATED PROPERTY: Ethanol		
Units: min. min.			
DATA:			
Level	Description	Ret. Time	Peak Width at
1	Injection 1	3.85	0.198
2	Injection 2	3.83	0.195
3	Injection 3	3.86	0.197
4	Injection 4	3.85	0.196
5	Injection 5	3.84	0.197
RESULT:			
Level	Description	Theoretical Plate Number	
1	Injection 1	6049	
2	Injection 2	6172	
3	Injection 3	6143	
4	Injection 4	6173	
5	Injection 5	6079	
Conclusion: Theoretical Plate Number is 6,123. This meets the Requirement N > 2000.			

4.8.2. Plate Number of Heptane


 your validation software	ANALYTICAL METHOD: GC5436 - Example API - Residual solvents - GC-MS -	Customer LOGO	
	VALIDATION: HPLC_FDA		
	PARAMETER: Theoretical Plate Number - FDA		
	VALIDATED PROPERTY: Heptane		
Units: min. min.			
DATA:			
Level	Description	Ret. Time	Peak Width at
1	Injection 1	13.51	0.154
2	Injection 2	13.54	0.159
3	Injection 3	13.55	0.162
4	Injection 4	13.55	0.154
5	Injection 5	13.53	0.159
RESULT:			
Level	Description	Theoretical Plate Number	
1	Injection 1	123137	
2	Injection 2	116028	
3	Injection 3	11193€	
4	Injection 4	123867	
5	Injection 5	115857	
Conclusion: Theoretical Plate Number is 118,165. This meets the Requirement N > 2000.			

Conclusion: Plate number for Ethanol and Heptane meets the acceptance criterion > 2000.

4.8.3. Tailing Factor of Ethanol

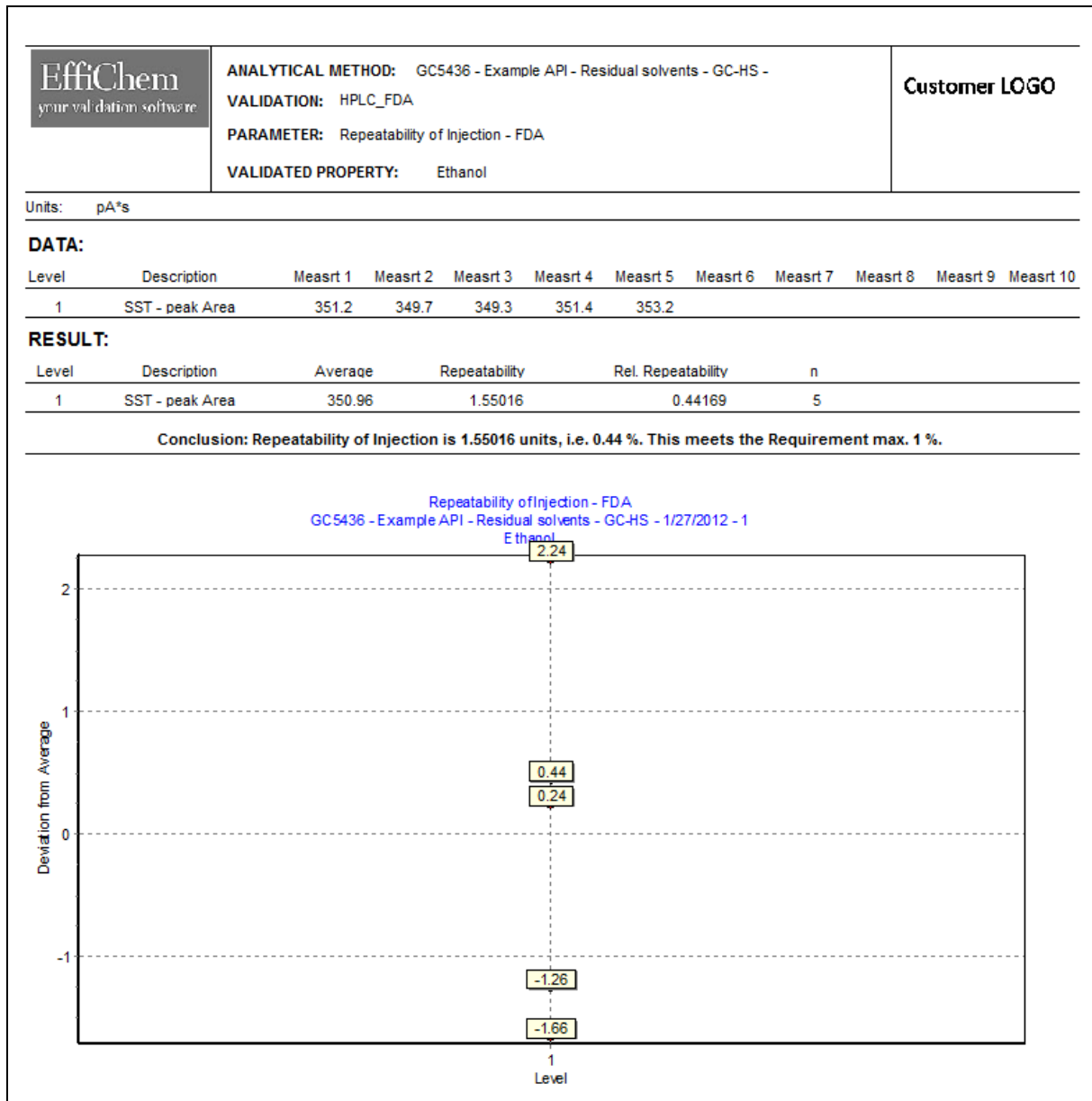
 your validation software	ANALYTICAL METHOD: GC5436 - Example API - Residual solvents - GC-HS -	Customer LOGO
	VALIDATION: HPLC_FDA	
	PARAMETER: Tailing Factor - FDA	
	VALIDATED PROPERTY: Ethanol	
Units: min. min.		
DATA:		
Level	Description	Peak Difference Width at Max.-Start
1	Injection 1	0.383 0.207
2	Injection 2	0.419 0.209
3	Injection 3	0.394 0.204
4	Injection 4	0.403 0.205
5	Injection 5	0.399 0.205
RESULT:		
Level	Description	Tailing
1	Injection 1	1.03642
2	Injection 2	1.01592
3	Injection 3	1.04545
4	Injection 4	0.99686
5	Injection 5	0.97205
Conclusion: Tailing is 1.01334, which meets the Requirement for Tailing max. < 2.		

4.8.3. Tailing Factor of Heptane

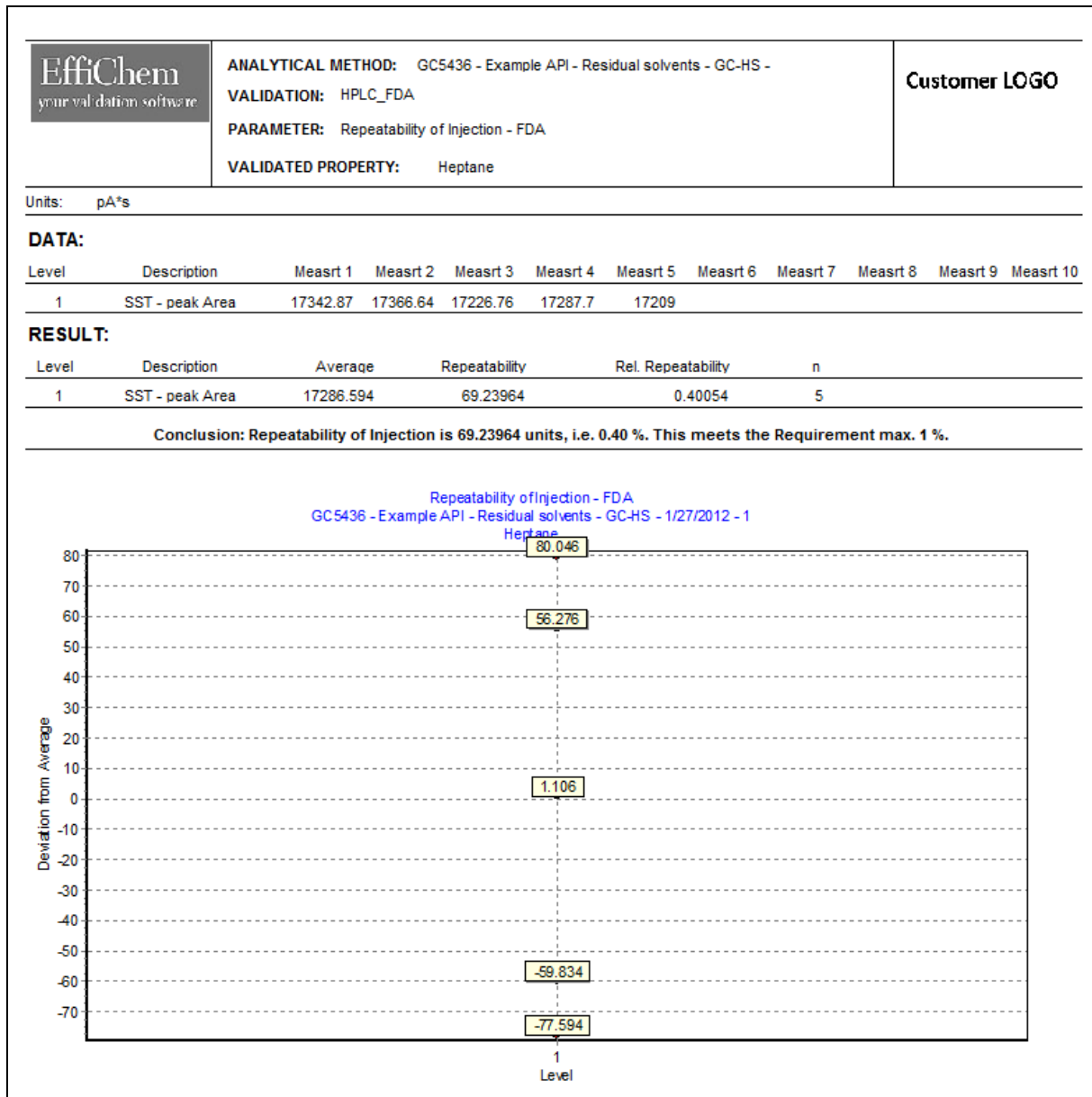
 your validation software	ANALYTICAL METHOD: GC5436 - Example API - Residual solvents - GC-HS -	Customer LOGO
	VALIDATION: HPLC_FDA	
	PARAMETER: Tailing Factor - FDA	
	VALIDATED PROPERTY: Heptane	
Units: min. min.		
DATA:		
Level	Description	Peak Difference Width at Max.-Start
1	Injection 1	0.313 0.151
2	Injection 2	0.319 0.157
3	Injection 3	0.322 0.154
4	Injection 4	0.317 0.159
5	Injection 5	0.313 0.161
RESULT:		
Level	Description	Tailing
1	Injection 1	1.03642
2	Injection 2	1.01592
3	Injection 3	1.04545
4	Injection 4	0.99686
5	Injection 5	0.97205
Conclusion: Tailing is 1.01334, which meets the Requirement for Tailing max. < 2.		

Conclusion: Tailing factor for Ethanol and Heptanes meets the acceptance criterion < 2.

4.8.5. Repeatability of injection (Peak Area) of Ethanol



4.8.6. Repeatability of injection (Peak Area) of Heptane



Conclusion: Repeatability of injection for Ethanol and Heptane is < 1.0%.

5. Conclusions

Evaluation of the validation parameters is summarized in the table below.

Validation parameter	Requirements for Ethanol and Heptane
Specificity	Sufficient separation of Ethanol and Heptane from each other; no interference with the peaks from the Blank. Peak resolution > 1.5
Linearity	R > 0.99 QC coefficient > 5.0%
Accuracy	t-test criteria met. 80% < Recovery < 120%
Repeatability	Repeatability < 15%
Range	Method Range established from 0.05% to 0.75%
Limit of Detection and Limit of Quantitation	Limit of Detection and limit of Quantitation were determined. For both solvents Limit of Quantitation is < 0.05%
Robustness	The tested changes in oven temperature and column pressure have no effect on Ethanol and Heptane results. On the other hand, the incubation temperature and time can have a significant effect. They must be well controlled to prevent biased results.
System suitability testing	The determined plate number, tailing factor and repeatability of injection met the Pharmacopoeia requirements.

Conclusion: Based on the above presented results the method is considered to be suitable for the intended purpose and fully validated.

Document change history:

Date	Version	Author	Subject
2012-01-30	1.0	EffiChem	Document initiation