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Analytical Method Development and Validation of Faricimab Injection by RP-HPLC

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Abstract: *A robust and reliable Reverse Phase High-Performance Liquid Chromatography (RP-HPLC) method was developed and validated for the quantitative analysis of Faricimab in Vabysmo injections. Faricimab, an IgG1-based bispecific antibody targeting VEGF-A and Ang-2, is used for treating retinal vascular disorders like age-related macular degeneration and diabetic macular edema. The method development involved the use of an Inertsil C18 column (250 x 4.6 mm, 5 µm) with a mobile phase composed of KH2PO4 (pH 4.6) and methanol in a 1:1 ratio, sonicated for 20 minutes.*

The developed method was evaluated for various validation parameters as per ICH guidelines, including linearity, precision, accuracy, and sensitivity. Linearity was demonstrated within the concentration range of 50-150 µg/ml with a correlation coefficient (R^2) of 0.999. The limit of detection (LOD) and limit of quantitation (LOQ) were found to be 0.050 µg/ml and 0.166 µg/ml, respectively, indicating high sensitivity. Precision, expressed as relative standard deviation (RSD), was below 0.1%, confirming the method's reliability.

Accuracy was assessed, with mean assay values ranging between 97-101%, and RSD below 0.2%, indicating the method's precision. Robustness tests confirmed the method's resilience against slight variations in analytical conditions such as acetonitrile ratio, flow rate, detection wavelength, and pH.

Stability studies showed that Faricimab remains stable under various stress conditions, including exposure to 0.1N HCl, 0.1N NaOH, 30% peroxide, heat, and sunlight, with assay values ranging from 88.93% to 94.07%. The optimized RP-HPLC method ensures good peak shape and resolution, making it suitable for routine quality control of Faricimab in pharmaceutical formulations. The validated method adheres to ICH guidelines, ensuring its reliability for consistent and accurate quantification of Faricimab..

Keywords: Reverse Phase High-Performance Liquid Chromatography.

I. INTRODUCTION

Medication is a chemical molecule utilized for diagnosing, curing, alleviating, preventing, or treating ailments in people or animals[1]. Pharmaceuticals are classified based on their pharmacodynamic qualities, which can involve antineoplastic drugs. Pharmacodynamic treatments target specific biological systems to relieve symptoms without addressing the root cause. They are mainly used for non-infectious conditions to restore reduced physiological function. Chemotherapeutic drugs target infections while minimizing harm to the host.

Every jurisdiction sets certain quality standards for bulk drugs and their formulations. Pharmaceutical standards are outlined in many sections and consolidated in a document called a "Pharmacopoeia," which includes IP, USP, BP, and Martindale Extra Pharmacopoeia (MEP)[2].

Analysis is a systematic and creative approach used to determine the makeup of materials by studying the elements or compounds present in them. Instrumental analysis is the evaluation of a sample's physical properties to determine its chemical makeup[3]. Pharmaceutical analysis concentrates on methods for identifying, measuring strength, evaluating quality, and determining the purity of therapeutically important pharmaceuticals[4]. Analytical sciences play a vital role in the research, development, and manufacturing of pharmaceuticals. Analytical technology is used in several industries to examine small amounts of complex biological components and guarantee the quality of the final output. The collection comprises pharmaceutical compounds, together with their formulations and precursors[5]. Strict quality

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standards are essential in all products and services, particularly in medicine, as they directly impact human life. Pharmaceuticals must comply with strict quality standards[6].

Quality control is a systematic procedure that ensures the production of perfect products by using strategies to predict and correct errors at different stages of the manufacturing process. Stringent quality control measures are enforced throughout all stages of product development, production, and distribution. Conventional quality control methods guarantee that medications or pharmaceutical products adhere to rigorous quality criteria. The quality assurance department must adhere to "Good Laboratory Practice" to ensure the accuracy and reliability of their generated data.

It is our ethical duty to provide comprehensive oversight to ensure the quality and reliability of pharmaceuticals for individuals requiring medical treatment.

Decisions on product launch or discontinuation are based on one or a mixture of two control systems. Accurate data analysis is essential for assessing the reliability of a product. Typically, the method involves manually combining different potent drugs.

Pharmaceutical items are assessed using standard gravimetric and titrimetric techniques, which are improved by electronic balances and automated titration devices. Pharmaceutical testing methods may necessitate many analytical approaches.

Chromatographic processes, particularly separation techniques, are beneficial for drug analysis. Modern spectrophotometers, featuring microprocessor control and diode array detectors, are essential tools for analysis.

Colorless substances are converted into a vibrant derivative for examination. The color's intensity is measured at a certain wavelength and then compared to a reference substance with a known level of purity. The solvents needed for dilution in UV-Vis spectrophotometric analysis require specific purification processes different from those used for other purposes. Record the initial absorbance levels of the solvent and reagents before starting the tests.

Drug estimation techniques are classified into physical, chemical, physicochemical, and biological methods. The most often used methods are physico-chemical and physical. Physical analysis involves studying the physical properties of a substance.

The inspection includes assessing solubility, transparency, color intensity, specific gravity (for liquids), moisture content, and melting, freezing, and boiling temperatures. Physicochemical research examine the physiological impacts of chemical interactions[7-9].

Key physico-chemical processes involve optical techniques such as refractometry, polarimetry, emission and fluorescence analysis, photometry (including photocolorimetry), and UV-vis and IR spectrophotometry, along with chromatographic methods like column, paper, thin-layer[10], gas-liquid[11], and HPLC[12,13].

DRUG PROFILE

Table No1: FARICIMAB Drug profile

Name of the drug	**FARICIMAB**
Biologic Classification	**Protein Based Therapies Monoclonal antibody (mAb)**
Protein Chemical Formula	$C_{6506}H_{9968}N_{1724}O_{1026}S_{45}$
Protein Average Weight	**146000.0 Da**
Category	**IgG1-derived bispecific antibody**
Dosage form	**IntravitrealInjection, solution.**
Dose	**6 mg / 0.05 mL, 120 mg/ml**
Brand Name	***Vabysmo* Intravitreal *injections***

FARICIMAB is an IgG1-based bispecific antibody that targets VEGF-A and Ang-2 to treat age-related macular degeneration and diabetic macular edema.

Retinal vascular disorders (RVDs) as diabetic macular edema (DME), age-related macular degeneration (AMD), and retinal vein occlusion (RVO) can result from retinal ischemia, leading to neovascularization (NV). VEGF-A plays a crucial role in regulating retinal neovascularization. Aflibercept and ranibizumab are treatments for retinal vascular

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disorders that function by specifically blocking VEGF-A. The Tie/Ang axis, consisting of the transmembrane Tie-2 receptor and its soluble ligands Ang-1 and Ang-2, is essential for increasing VEGF-A-induced NV[13,14,15].

Faricimab is a bispecific antibody derived from IgG1 that can target and eliminate both VEGF-A and Ang-2. It was created to enhance the effectiveness of treatment, particularly in patients who do not respond well to anti-VEGF-A monotherapy[13-18].

Faricimab received FDA approval on January 28, 2022, and is now being sold as VABYSMO by Genentech, Inc[19]. It was later approved for the same uses in Canada in May 2022[20]. The EMA's CHMP recommended granting marketing authorization for faricimab in July 2022 for the treatment of neovascular age-related macular degeneration and diabetic macular edema[21].

II. MATERIAL AND METHOD

MATERIALS:

- KH_2PO_4
- Peroxide
- Methanol
- Sodium hydroxide
- Phosphoric acid
- Hydrochloric acid

DRUG:

- FARICIMAB (FRC)

INECTION:

- Brand name: Vabysmo injections
- Claimed content: FRC –100 µg/ml
- Manufacture by: Genentech, Inc

APPARATUS:

- HPLC system: make company - Waters alliance
- Photodiode array detector: make company - Waters alliance
- Dissolution Apparatus: make company – Lab India

MOBILE PHASE:`

- Combine 136.09g of KH_2PO_4 (1M) with 1000ml of HPLC water in a beaker to get a pH of 4.6 with OPA.
- Mix 500ml of the KH_2PO_4 solution with 500ml of Methanol in the mobile phase. Subject the mixture to sonication for 20 minutes.

Diluent:

- A diluent is a mixture of solvents used to reduce the concentration of the mobile phase.

III. ASSAYING CONDITIONS FOR LIQUID CHROMATOGRAPHIC DETERMINATION OF FRC:

Stock FRC solution:

A stock solution of FRC at a concentration of 100 µg/ml was prepared by dissolving 100 mg of FRC in 100 ml of the selected diluent.

Working FRC solutions:

A working solution of FRC at a concentration of 100 µg/ml was generated by diluting 1 ml of a stock FRC solution (1000 µg/ml) in 10 ml of a chosen diluent.

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Linearity FRC solutions:

- To make a solution with a concentration of 50 µg/ml, 0.5 ml of a stock FRC solution (100 µg/ml) was mixed with 9.5 ml of the selected diluent.
- A 75 µg/ml solution was created by combining 0.75 ml of a 100 µg/ml stock FRC solution with 9.25 ml of a specified diluent.
- To make a solution with a concentration of 100 µg/ml, 1.0 ml of a stock FRC solution (100 µg/ml) was mixed with 9.0 ml of the selected diluent.
- A 125 µg/ml solution was created by combining 1.25 ml of a 100 µg/ml concentrated FRC solution with 8.75 ml of a specified diluent.
- A solution was made by combining 1.50 ml of a 100 µg/ml concentrated FRC solution with 8.50 ml of a specified diluent, resulting in a final concentration of 150 µg/ml.

VALIDATION EVALUATION OF DEVELOPED METHOD:

The analytical procedure for quantifying FRC in Vabysmo injections was evaluated for estimating all validation parameters using international conference on harmonization guidelines for validation.

CONTENT ASSAY OF FRC IN VABYSMO INJECTION:

150 mg of FARICIMAB was combined with Vabysmo injectable concentrate in a 100 ml clean and dry volumetric flask. The mixture was sonicated until completely dissolved, and then the volume was modified. Following filtering, 1 mL of the solution was transferred into a 10 mL volumetric flask. A diluent was added to achieve a total volume of 10 mL.

A chromatographic solution was prepared by diluting 10 ml of a 1500 µg/ml stock FRC solution with 100 ml of a specified diluent to get a final concentration of 150 µg/ml.

Analyzed a 10 µL sample at high pressure using an Inertsil C18 column that is 250*4.6 mm with a particle size of 5 µm. We examined the FRC components in Vabysmo injection according to the given parameters in the chromatographic analysis of FRC.

FRC STABILITY EVALUATION:

The stability of FRC was tested by subjecting it to the conditions listed below.:

S. No.	Name of the sample	Period of exposure	Physical appearance
1	Mother / control (as such sample)	-	Clear , No change
2	Solution in 2N HCl at 60 °C	Refluxed for 30 min	Clear , No change
3	Solution in 2N NaOH at 60 °C	Refluxed for 30 min	Clear , No change
4	Solution in water at 60 °C	6 hours	Clear , No change
5	Solution in 20 % H_2O_2 at 60 °C	Refluxed for 30 min	Clear , No change
6	Solution under dry heat, 105 °C	6 hours	Clear , No change
7	UV exposed sample	200 Watt hours/m^2 1.2 million lax hrs	Clear , No change

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Stability of FRC in 0.1N HCL:

After 30 minutes of ultrasonication in a 100-ml flask, 10 ml of a stock injection solution with a concentration of 100µg/ml was dissolved in 10 ml of 0.1N HCl. After 30 minutes, a enough quantity of appropriate diluent was added to achieve a total volume of 100 ml in the flask. An injectable solution of 10 microliters was introduced into Inertsil C18 after being treated with 0.1N HCl. Examined the elements of an FRC injection solution made with 0.1N HCl following the instructions provided in the "FRC ASSAYING CONDITIONS" section.

Stability of FRC in 0.1N NaoH:

A 10ml stock solution with a concentration of 100 µg/ml of FRC was mixed with 10 ml of 0.1N NaOH in a 100-ml flask using ultrasonication for 30 minutes. After 30 minutes, pour 100 ml of a suitable diluent into the flask to get a total volume of 100 ml. 10 liters of the injection fluid were treated with 0.1N NaOH before being put to an Inertsil C18 column. Evaluated the FRC concentration in the FRC injection solution made with 0.1N NaOH based on the criteria specified in the "FRC TESTING CONDITIONS" section.

Stability of FRC in 30% peroxide:

We utilized 30 minutes of ultrasonication to dissolve the FRC injectable solution (10ml) in a 30% peroxide solution. After 30 minutes, dilute it to a volume of 100 ml. 10 milliliters of a 30% hydrogen peroxide solution was introduced into Inertsil C18. Examined a 30% hydrogen peroxide injection solution for the presence of Free Radical Chlorine according to the specified criteria in the "FRC ASSAYING CONDITIONS" section.

Stability of FRC in sun light:

The FRC injection solution, with a concentration of 100µg/ml, was exposed to direct sunlight during six hours. There were 100 milliliters left in the bottle after the specified time elapsed.

A ten-milliliter injection solution was loaded into an Inertsil C18 column after being exposed to sunlight for six hours. The FRC concentration of the injectable fluid treated with 30% peroxide was tested according to the standards outlined in the "FRC ASSAYING CONDITIONS."

Stability of FRC at 105^0 C:

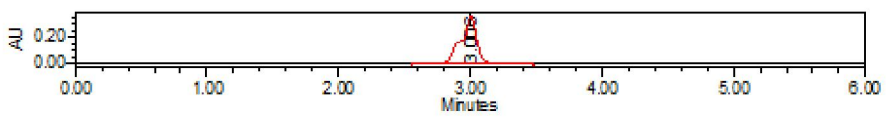
The FRC injection solution (FRC – 100µg/ml) was left in direct sunlight for six hours. There remained 100 ml in the bottle after the specified time had passed.

A 10 mL fluid sample was irradiated with sunlight for six hours and subsequently introduced onto an Inertsil C18 column. The FRC content of an injectable solution treated with 30% peroxide was assessed based on the criteria specified in the "FRC ASSAYING CONDITIONS."

IV. METHOD DEVELOPMENT

Trial-1

Mobile Phase	**: KH_2PO_4: Acetonitrile (50:50)**
Column	**: Thermo, C18, 250X4.6mm, 5µm**
Flow Rate	**: 0.8ml/Min**
Column Temperature	**: 25°C**
Sample Temperature	**: 25°C**
Volume	**: 10µl**
Run time	**: 6min**
Detector	**: PDA**



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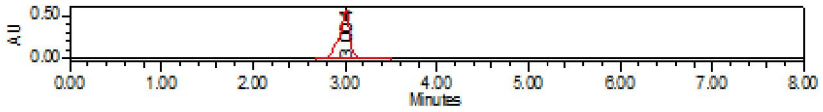
Conclusion: Peak shape is not good, so we perform another trial.

Trial-2

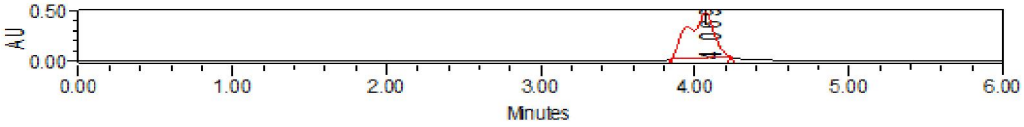
Mobile Phase : KH_2PO_4: Acetonitrile (60:40)
Column : Thermo, C18, 250X4.6mm, 5µm
Flow Rate : 1 ml/Min
Column Temperature : 25˚C
Sample Temperature : 25˚C
Volume : 10µl
Run time : 6min
Detector : PDA



Conclusion: Peak shape is not good, so we perform another trial.

Trial-3

Mobile Phase : KH_2PO_4: Acetonitrile (60:40)
Column : PHENOMENAX, C18, 250X4.6mm, 5µm
Flow Rate : 1ml/Min
Column Temperature: 25˚C
Sample Temperature: 25˚C
Volume : 10µl
Run time : 6min
Detector : PDA



Conclusion: Peak shape is not good, so we perform another trial.

Trial-4

Mobile Phase : KH_2PO_4: Acetonitrile (60:40)
Column : PHENOMENAX, C18, 150X4.6mm, 5µm
Flow Rate : 0.8 ml/Min
Column Temperature : 25˚C
Sample Temperature : 25˚C
Volume : 10µl
Run time : 6min
Detector : PDA

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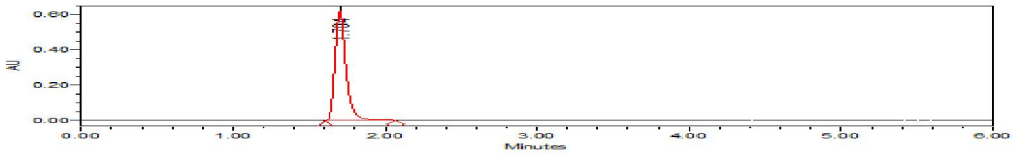
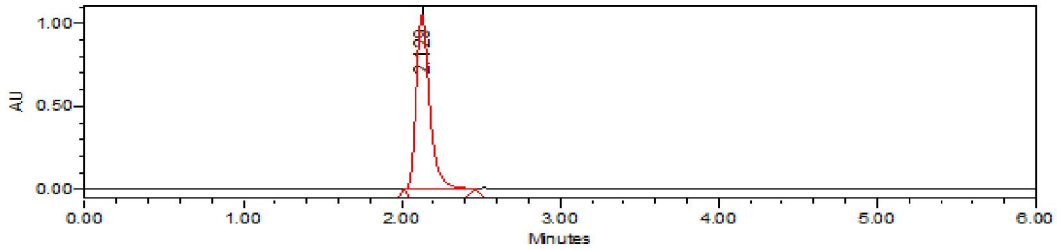


Trial – 5 (Final and Optimized Trial)

Mobile Phase : KH_2PO_4: Acetonitrile (60:40)
Column : PHENOMENAX, C18, 150X4.6mm, 5µm
Flow Rate : 1 ml/Min
Column Temperature : 25˚C
Sample Temperature : 25˚C
Volume : 10µl
Run time : 6min
Detector : PDA



Conclusion: Theoretical Plate and Tailing Factor observed within acceptance criteria, also the peak shape is good, hence method found satisfactory, here with need to go for method validation.

V. RESULTS AND DISCUSSION

VALIDATION OF DEVELOPED METHOD BY UTILISING ICH:

Linearity:

- To achieve linearity, a 50 µg/ml concentration of FMC was generated by mixing 0.5 ml of a 100 µg/ml FMC stock solution with 9.5 ml of the chosen diluent.
- A 75µg/ml solution was prepared by combining 0.75 ml of a 100 µg/ml concentrated FMC stock solution with 9.25 ml of a selected diluent.
- To achieve a solution with a concentration of 100 µg/ml, 1.0 ml of an FMC stock solution (100 µg/ml) was mixed with 9.0 ml of the necessary diluent.
- By mixing 1.25 ml of an FMC stock solution (100 µg/ml) with 8.75 ml of a diluent, a concentration of 125 µg/ml was achieved, indicating a strong relationship.
- To find a solution, 1.50 ml of a concentrated solution with a concentration of 100µg/ml of FMC was mixed with 8.50 ml of the required diluent.
- The gathered data shows a significant level of linearity in the FMC analysis

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Table 2: FARMICIMAB response peak area and concentration

FARMICIMAB	
Response peak area	**µg/ml amount**
3549080	50
5309778	75.00
7111384	100.00
8900177	125
10705271	150

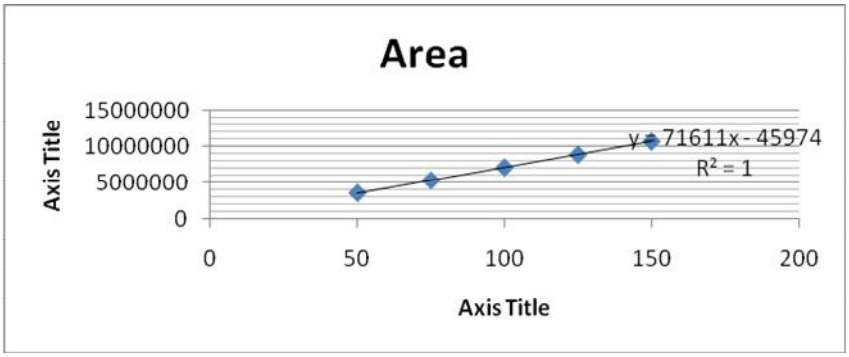

Figure 1: FARMICIMAB calibration curves

Limit of detection:

Determined using technique of standard deviation with formula:

Limit of detection = 3.3 × deviation of drug response peak area/slope of drug calibration curve

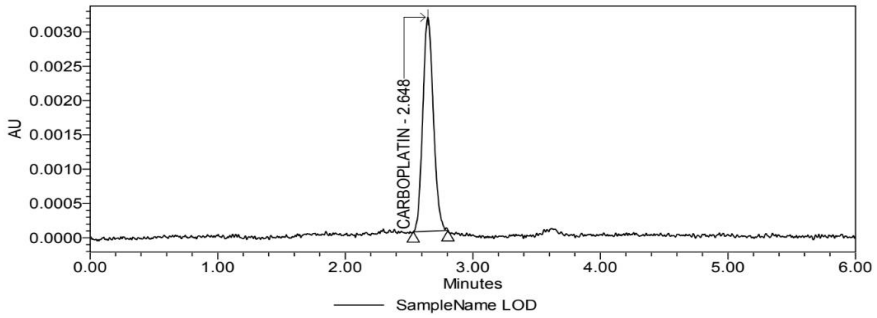

Figure 2: Reading FMC chromatogram – sensitivity – limit of detection

Limit of detection for FMC: 0.050 µg/ml

Signal / noise ratio for FMC at µg/ml is 6014.5

Limit of quantitation:

Determined using technique of standard deviation with formula:

Limit of quantitation = 10 × deviation of drug response peak area/slope of drug calibration curve

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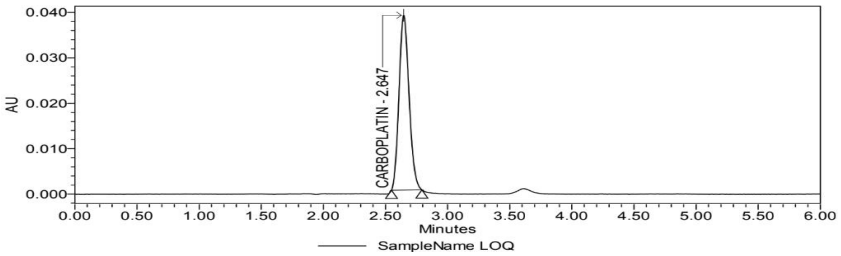

Figure 3: Reading FMC chromatogram – sensitivity – limit of quantitation

Limit of quantitation for FMC: 0.166 µg/ml

Ratio of signal to noise for FMC at µg/ml is 6014.5

The data gathered proved method have enough sensitivity for FMC analysis.

Precision:

Six injections of an FMC solution, each with 10 microliters at a concentration of 100 micrograms per milliliter, were applied to a C18 column of 150 x 4.6 mm and with a particle size of 3.5 micrometers. The data was analyzed based on the settings specified in the "FMC ANALYSIS CONDITIONS" section. The highest point of the FMC answers was determined. Standard deviation and relative percent standard deviation were computed for the FMC response peak in six regions. The gathered data confirmed the accuracy of the methodology for FMC analysis.

Table 3: Precision investigation readings for FARMICIMAB

µg/ml amount considered	µg/ml amount quantified	Assay percent	
FARMICIMAB			
49.500	49.21	99	
49.500	47.94	97	**Mean percent assay**
49.500	47.88	97	99.5
99.000	99.72	101	**Standard assay Deviation**
99.000	99.50	101	0.2
99.000	99.67	101	**RSD**
148.500	148.69	100	0.2
148.500	150.02	101	
148.500	148.79	100	

Accuracy:

Six injections of a 10 µL solution of FMC (100 µg/mL) were made on a C18 column measuring 150 x 4.6 mm with a particle size of 3.5 µm. The data was analyzed based on the parameters specified in the "FMC ANALYSIS CONDITIONS" section. The FMC assay results were quantified as percentages. Statistical characteristics such as mean, standard deviation, and relative percent standard deviation were calculated for six FMC injections. The results confirmed the accuracy of the current FMC analytical approach.

Table 4: Accuracy investigation readings for FARMICIMAB

Response peak area	
FARMICIMAB	
7115984	**Mean response peak area**
7108454	7114319
7114903	**Standard response Deviation**
7111819	4423.0
7113172	**RSD** 0.1

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Robustness:

The evaluation criteria for the FMC solution at a concentration of 100 µg/ml were slightly modified under the "FMC ASSAYING CONDITIONS" section. The device settings were considered appropriate for FMC. The data acquisition validated the efficacy of FMC analytical methods.

Modification one:

Acetonitrile ratio optimized was 40% volume

Modified values were 50% (comp 1) and 30% (comp 2)

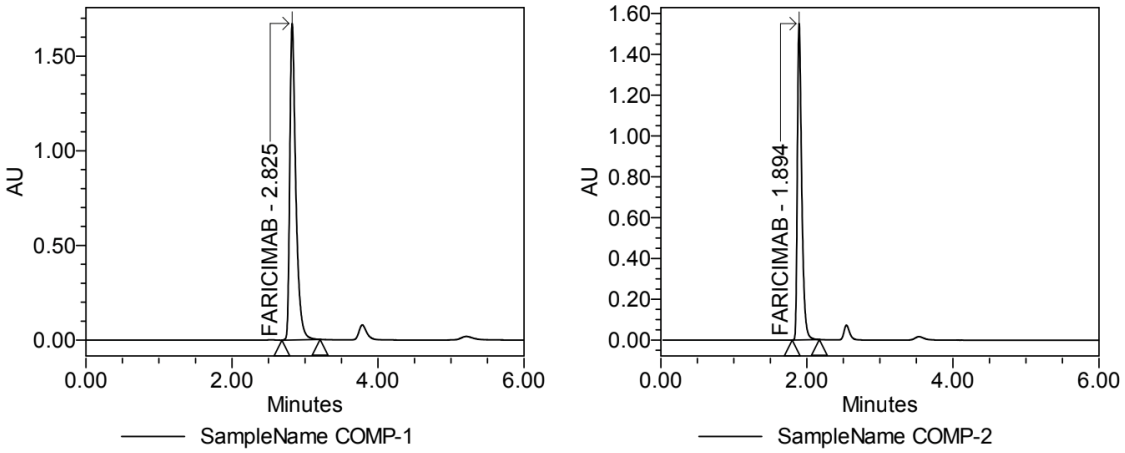

Figure 4: Readings of suitability testing and chromatograms of robustness (Acetonitrile modification)

Modification two:

Flow optimized : 1.0ml/Min

Modified values were 0.9 (flow 1) and 1.1 (flow 2)

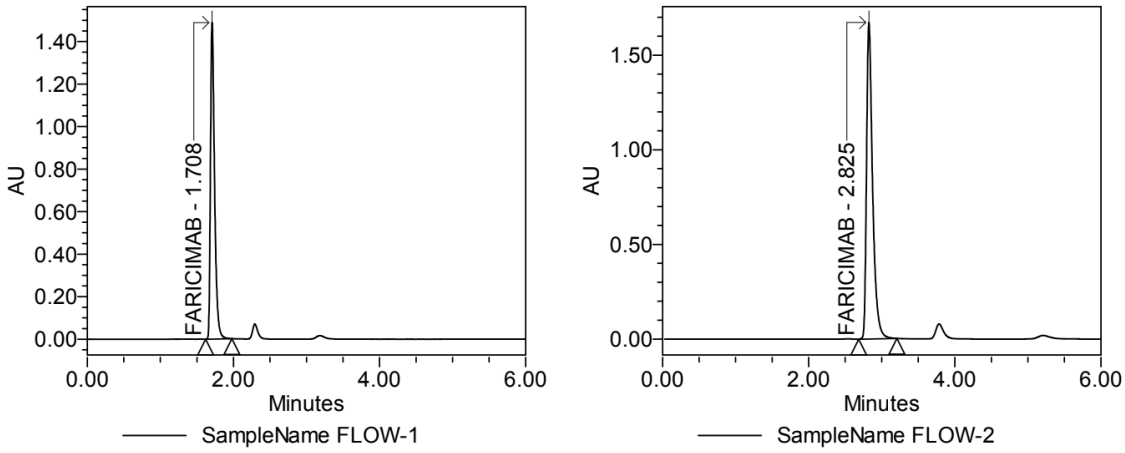

Figure 5: Readings of suitability testing and chromatograms of robustness (flow modification)

Modification three:

nm optimized was 226

Modified values were 221 (nm 1) and 231 (nm 2)

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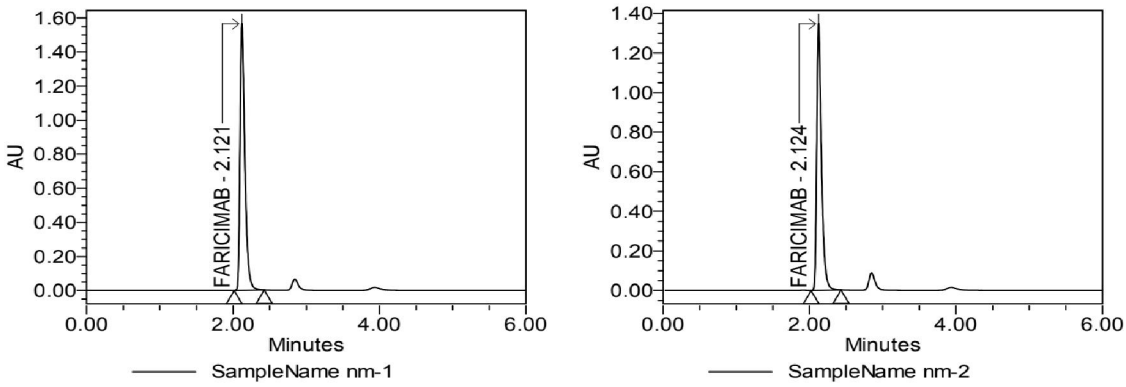

Figure 6: Readings of suitability testing and chromatograms of robustness (nm modification)

Modification four:
pH optimized was 4.6
Modified values were 4.4 (pH 1) and 4.8 (pH 2)

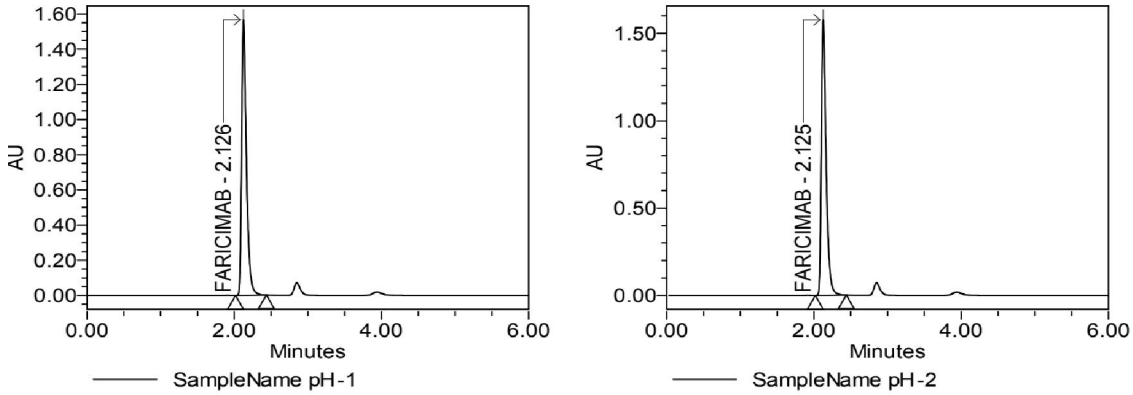

Figure 7: Readings of suitability testing and chromatograms of robustness (pH modification)

Stability of FMC :

FMC stability reports after investigated through exposing to 0.1 N HCl, 0.1N NaOH, peroxide, sun light and 105oC given as below table.

Table 5: Stability of FMC

	FMC	
Drug exposed	**Response Area**	**% Assay**
Acid	**422925**	**88.93**
Base	**440297**	**92.58**
Peroxide	**442820**	**93.11**
Heat	**423250**	**89.00**
Sunlight	**447370**	**94.07**
Untreated	**466567**	**98.11**

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FMC stability direction:
Acid>Heat >Base >Peroxide >Sunlight

Stability indicating nature and specificity:

The FMC stability reports display chromatograms generated by exposing the samples to different circumstances including 0.1 N HCl, 0.1 N NaOH, peroxide, sunshine, and a temperature of 105°C. The collaboration with FMC is outstanding and ideal for impaired compounds. The results demonstrated that the method was dependable and accurate in conducting FMC evaluations.

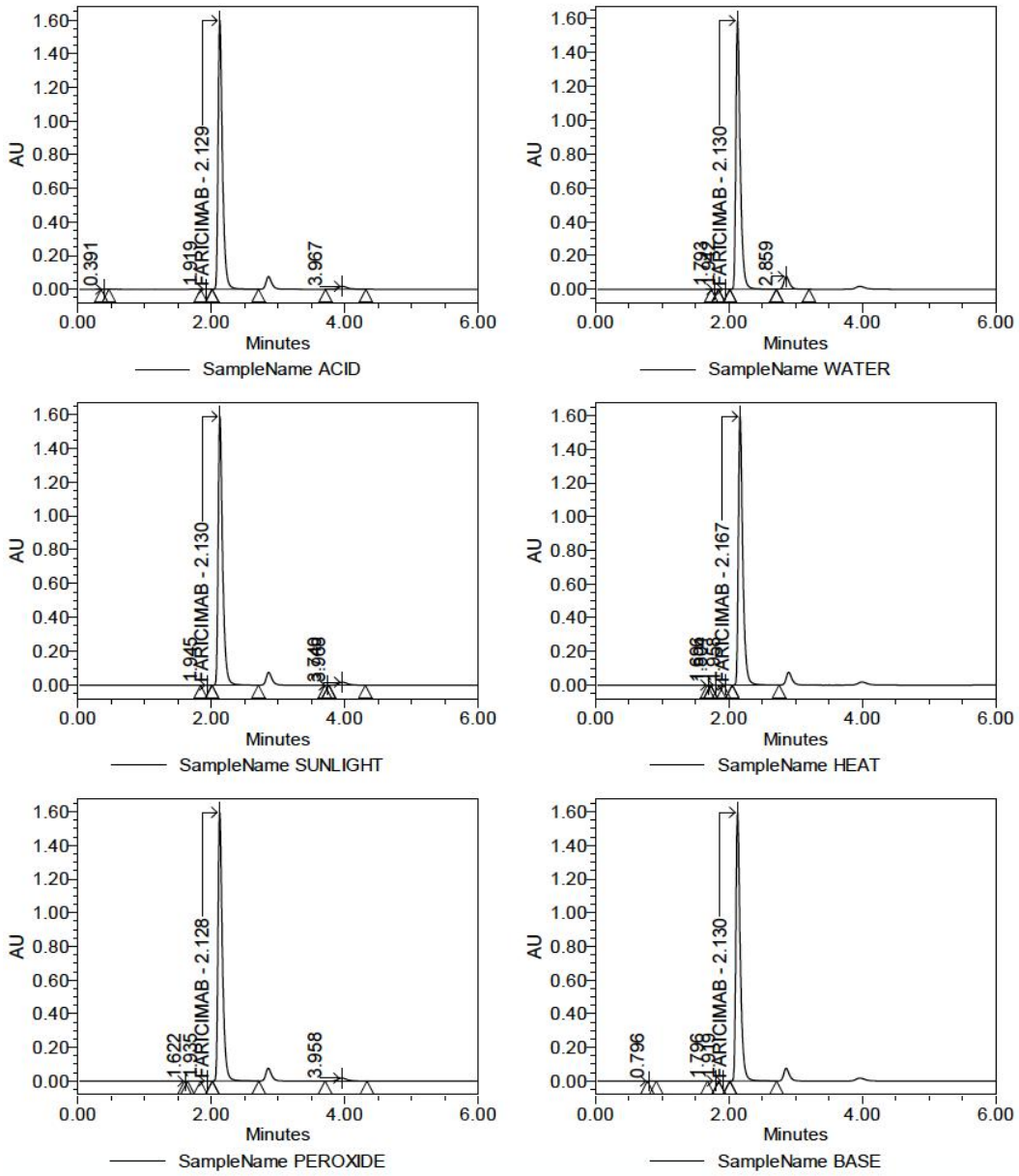

Figure 8: Readings of chromatograms of stability nature and specificity

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VI. CONCLUSION

A robust and reliable RP-HPLC method was successfully developed and validated for the analysis of Faricimab in Vabysmo injections. The method demonstrated excellent linearity, precision, accuracy, and sensitivity. The stability studies confirmed that Faricimab remained stable under various stress conditions, including exposure to acid, base, peroxide, heat, and sunlight. The optimized chromatographic conditions ensured good peak shape and resolution, confirming the method's suitability for routine quality control of Faricimab injections in pharmaceutical formulations. The validated method adheres to ICH guidelines, ensuring its reliability for consistent and accurate quantification of Faricimab.

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