Farmacia Hospitalaria 50 (2026) 265–268

Farmacia HOSPITALARIA
Órgano oficial de expresión científica de la Sociedad Española de Farmacia Hospitalaria
www.elsevier.es/farmaciahospitalaria

Brief report

Sterility of repackaged faricimab for intravitreal administration

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ARTICLE INFO

Article history:
Received 29 April 2025
Accepted 9 October 2025
Available online 6 January 2026

Keywords:
Faricimab
Anti-vascular endothelial growth factor
Sterility
Repackaging
Intravitreal injection

SUMMARY

Objectives: New drugs such as faricimab have been developed to treat ophthalmic neovascular diseases. While these drugs increase treatment success, they also increase costs. Repackaging drugs strikes a balance between technical requirements and treatment flexibility. The aim of this study was to evaluate the microbiological stability of repackaged faricimab under controlled conditions in order its already demonstrated chemical, biological, and microbiological stability.
Methods: This was a prospective, controlled experimental study. The contents of four vials of faricimab were repackaged into 16 silicone oil-free syringes with a low dead space volume. A bubble adaptor was used to ensure the maximum efficiency from fractioning. All samples were stored at 2–8 °C. Four of the syringes were cultivated on blood and Sabouraud agar at set time points (9 days, 16 days, 23 days, and 30 days). The endpoint of the study was positive microbiological growth in any of the samples. Negative and positive controls were cultivated alongside the test samples.
Results: None of the 16 samples or the negative controls exhibited microbiological growth at any stage of the culturing process. All positive controls showed microbiological growth.
Conclusions: When repackaged in silicone oil-free syringes, faricimab retains microbiological stability for up to 30 days when it is prepared and stored under controlled conditions.
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Estabilidad microbiológica de faricimab fraccionado para administración intravitrea

Palabras clave:
Faricimab
Factor de crecimiento endotelial antivascular
Esterilidad
Reenvasado
Inyección intravítrea

RESUMEN

Objetivos: Nuevos fármacos como faricimab se han desarrollado para las enfermedades neovasculares oftálmicas, aumentando el éxito de los tratamientos, así como sus costes. El fraccionamiento aúna el equilibrio entre los requisitos técnicos y la flexibilidad del tratamiento. El objetivo de este estudio fue evaluar la estabilidad microbiológica de faricimab fraccionado en condiciones controladas para confirmar la estabilidad química, biológica y microbiológica ya demostrada.
Métodos: Se realizó un estudio experimental prospectivo y controlado. Se procedió al fraccionamiento y reacondicionamiento de cuatro viales de faricimab en 16 jeringas libres de silicona con bajo espacio muerto. Se utilizó un adaptador tipo burbuja para garantizar la máxima eficiencia del fraccionamiento. Todas las muestras se almacenaron a 2–8 °C. Cuatro jeringas se cultivaron en agar sangre y Sabouraud a los 9, 16, 23 y 30 días. Se busco el crecimiento microbiológico positivo en cualquiera de las muestras. Se utilizaron controles negativos y positivos junto las muestras.
Resultados: Ninguna de las 16 muestras ni de los controles negativos mostró crecimiento microbiológico. Todos los controles positivos mostraron crecimiento microbiológico.
Conclusiones: Cuando faricimab se fracciona en jeringas sin aceite de silicona, conserva su estabilidad microbiológica hasta 30 días si se prepara y almacena en condiciones controladas.
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https://doi.org/10.1016/j.farma.2025.10.016
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Background

The introduction of vascular endothelial growth factor (VEGF) inhibitors has revolutionized the treatment of neovascular age-related macular degeneration (nAMD) and diabetic macular edema (DME). Due to their high costs, compounding techniques are used to repackage these treatments into single-dose syringes, increasing flexibility and efficiency.[1] However, this practice presents several challenges, such as preventing microbial contamination and the risk of infectious endophthalmitis. Best practices include working in a laminar flow hood with personnel using validated aseptic technique with specific materials.[2]

Dead space in syringes can lead to medication wastage and underdosing of patients, while certain syringes may release silicone oil droplets or other particles into the eye, which can cause complications.[3,4]

According to the *Spanish Good Practices Guide for Medication Preparation in Pharmacy Services* (*Spanish acronym GBPP*)[5] and the *Consensus on intraocular drug preparations*,[6] compounding anti-VEGF is categorized as a sterile medium-risk preparation with a default stability period of 9 days when preserved at 2 and 8 °C. Several studies demonstrated the long-term chemical stability and biological activity of various VEGF inhibitors (including bevacizumab, aflibercept, ziv-aflibercept, and faricimab), meeting the standards of the US and European Pharmacopoeias for extended periods of up to 28–45 days.[7–9] Additionally, microbiological stability studies have been confirmed for up to 28 days using blood agar and Sabouraud agar cultures for 5 days at 35 °C to detect bacterial growth.[10,11] Recent findings for faricimab[12] (Vabysmo®, Roche, Switzerland) have demonstrated that repackaged syringes stored at 4 °C maintain their structure and binding properties for up to 37 days[8] with microbiological stability demonstrated for up to 28 days (stored at 2–8 °C).[13]

Employing a sterile bubble adapter (Zero Residual™ Bubble Adapter) between the drug vial and the syringes allows for air-free prefilling, thus enhancing the efficiency of the repackaging process. Consequently, it is necessary to validate our current practice.

Objective

The purpose of this study was to evaluate the microbiological stability of repackaged faricimab syringes when prepared via our specific compounding technique.

Materials and methods

Sample size

As in our real clinical setting, the number of total preparations was less than 25 repackaged syringes, and according to the European Pharmacopeia (Ph. Eur.)[14] and *Annex 6 of the International Council for Harmonization (ICH) Topic Q4B*,[15] the number of samples required for the sterility test was determined to be 4 at each control time point.

Materials

We used 4 vials of 120 mg/ml faricimab (each with 28.8 mg/0.24 ml, which guarantees the administration of a dose of 6 mg/0.05 ml), purchased from the supplier laboratory Roche© (batch number B1535B25, expiration date 06/2026). We also employed silicone oil-free syringes (Zero Residual©, reference ZSR12103C; batch number 231225, expiration date 12/2026) and 30G × 3/8″ needles (reference ZRN3009; batch number 230812, expiration date 08/2028) as final packaging. For compounding, we used the bubble-type adapter from the manufacturer Zero Residual© (reference ZRB04LL-LS; batch number 240630, expiration date 06/2027). All Zero Residual© material was purchased through the authorized supplier in Spain, Dextromedica S.L.

Preparation and repackaging

We followed the general procedure for sterile medications set out in *GBPP*.[5] Four vials of faricimab were opened in a laminar flow hood (clean room level A) under aseptic conditions. The entire content was extracted via an 18G loading needle with a built-in 5-µm filter, attached to the bubble adapter with a sterile 10-ml syringe. The entire volume of the drug was collected, approximately 0.96 ml, so at no time did the liquid come into contact with the syringe. The bubble was then left to rest for a few minutes to remove any foam that could have formed. The 10-ml syringe used for aspiration was removed, and the bubble was attached to the 1 ml sterile syringes used for final packaging. As the syringes had minimal dead space, as did the needles, 16 fractions were obtained in total, each of which was 0.06 ml, then labeled and sealed in a sterile plastic package and stored at 2–8 °C, matching the conditions described by Jørstad et al.[8]

Sterility test

Sterility tests were performed after 9, 16, 23, and 30 days of storage. At each time point, 4 repackaged syringes were tested (16 in total). The cultures of the whole aliquots were done in a qualitative manner, with a 10-µl calibrated loop, in Petri dishes with blood agar media and Sabouraud agar for fungi (8 cultures per testing day, as summarized in Table 1). The culture was carried out using the triple streak plate isolation procedure technique in a controlled environment. The samples were then incubated for 5 days at 35 ± 2 °C for subsequent qualitative reading. A positive culture was defined as the presence of any number of colony-forming units (CFUs), which would imply a loss of sterility of the sample, whereas a negative culture was defined as when no growth being detected.

To ensure the validity of the results, positive and negative controls were cultivated alongside the test samples. The commercial ATCC 25922 *E. coli* strain was selected as a positive control, while sterile water was used as the negative control.

Results

The sterility of all the samples was maintained throughout the study at storage temperatures ranging from 2 to 8 °C. All the cultured aliquots presented no colony-forming units (CFUs) at any time point under the incubation conditions.

All the negative controls used were confirmed to have negative growth, as all the positive controls were cataloged as positive.

Discussion

The fractioning of high-cost drugs for use in treating several patients with high-prevalence diseases appears to be an attractive option as it enables precise dosing while reducing waste and costs. The possibility of keeping these repackaged aliquots stored between 2 and 8 °C allows better organization of ophthalmology departments and better use of resources, resulting in better care for patients and increasing the sustainability of the healthcare system.

Table 1
Description of cultures.

	Culture 1				Culture 2				Culture 3				Culture 4			
Days from repackaging	9				16				23				30			
Blood agar	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Sabouraud	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Syringe number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16

Together with physicochemical stability and efficacy tests, microbiological stability tests provide assurance that drugs are being used in accordance with the pharmacopeial and clinical guidelines. The repackaged drug should be prepared by appropriately trained personnel in controlled, clean room facilities using aseptic technique.

For this study, a standard culture method was used underconditions similar to those employed in the physicochemical stability studies carried out by Jørstad et al.[8] and Taschauer et al.[12] Once it was confirmed that compounding and storage did not significantly affect the stability of faricimab, our results reinforce existing evidence in line with standard clinical practices in our setting.

The introduction of an additional device in the manufacturing process, such as a bubble adapter, should be accompanied by a microbiological study that supports this practice.

The limitations of this study are as follows. Firstly, this was a single-center study that did not involve other centers; thus, there may be slight differences in the compounding technique used. Secondly, the low number of samples used, *since these are adapted to the assistance practice and ICH requirements*, may not be comparable with other centers that assist a much larger population and therefore require the repackaging of more than 25 samples. This practice would imply carrying out quality controls for each batch manufactured according to the guidelines for *GBPP*. Thirdly, we did not test for the presence of bacterial endotoxins during the storage period, which also play an important role in the emergence of intraocular inflammation after the administration of anti-VEGF therapy. And finally, *the fact that the referenced paper of Taschauer A et al.* may overlap with the objectives of this study, but as we have justified, it is necessary to add data that support the evidence in our environment.

Conclusion

The present study demonstrates the safety of the compounding process, with no bacterial growth occurred in fractionated and repackaged faricimab silicone oil-free syringes after stored for 30 days at controlled temperatures between 2 and 8 °C. Therefore, in addition to the published studies on physicochemical and microbiological stability, we can use 0.06 ml of faricimab to repackaged samples for 30 days under these conditions while maintaining cost-effectiveness for intravitreal injections.

Contribution to the scientific literature

The chemical stability and biological activity of Faricimab in repackaged syringes is guaranteed for up to 37 days. Microbiological stability when samples are taken directly from punctured vials is up to 28 days, stored under light protection at 2–8 °C, in only one recently published study. Using a bubble adapter in our different repackaging conditions adds robustness to faricimab microbiological stability which is set up at 30 days when stored under light protection at 2–8 °C.

This study allows for increasing the efficiency of Faricimab pre-filled syringes, while ensuring patient safety and allowing for more efficient use of resources in the healthcare environment.

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Availability of data and materials

All data supporting the findings are included in this published article. The culture photographs are available from the corresponding author on reasonable request.

CRediT authorship contribution statement

Antonio Raymundo: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Methodology, Investigation, Conceptualization. **Lourdes Cervera:** Methodology, Investigation. **Francisco Crespillo:** Writing – original draft, Validation, Methodology, Investigation. **Sara Esplá:** Writing – original draft, Supervision. **Mariola Sirvent:** Writing – review & editing, Writing – original draft, Supervision, Project administration, Methodology, Investigation, Conceptualization.

Consent for publication

Not applicable

Ethics approval and consent to participate

Not applicable

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

Conflicts of interest

The authors declare that they have no competing interests.

Acknowledgements

Not applicable.

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