



Stability study of a biosimilar of Bevacizumab in vials and after dilution in 0.9% NaCl in polyolefin IV bags

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INTRODUCTION

Bevacizumab was first marketed in 2005. Since then, its stability has been extensively studied. The arrival of numerous biosimilars on the market has called into question these stabilities and organisation within reconstitution units.

OBJECTIVES

To study the stability of the Bevacizumab biosimilar Alymsys® marketed by Zentiva Laboratory in ready-to-use vials at a concentration of 25 mg/mL and following dilution to obtain final concentrations of 1.4 and 16.5 mg/mL and storage in polyolefin IV bags at 4°C as well as in vials after opening at 4°C. In parallel, the impact of an excursion of the storage temperature to 25°C for 3 days for the bags and for a storage of the vial before opening at room temperature was studied.

MATERIAL & METHODE

The vials were supplied by Zentiva Laboratory. The vials (three batches) were diluted to the final concentrations of 1.4 mg/mL or 16.5 mg/mL in NaCl.

The IV bags and vials were stored at 4°C and at room temperature during the duration of the study.



The physico-chemical stability was tested using the following methods: turbidimetry, UV spectrometry and fluorescence, dynamic light scattering, ion exchange and steric exclusion chromatography, pH, osmolality and density.

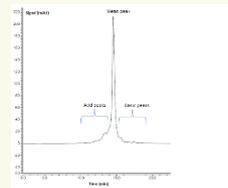
RESULTS - DISCUSSION

DLS (Dynamic Light Scattering)

Mean Diameter (nm)	D0 (C1)	D0 (C2)	D90 (C1)	D90 (C2)	D90+72h (C1)	D90+72h (C2)
Bags (n=3)	11,74± 0,1102	14,45± 0,0865	12,20± 0,3147	14,53± 0,1068	11,22± 0,1531	13,71± 0,0304
Mean Diameter (nm)	D0		D45		D60	
Vials 4°C (n=3)	16,21± 0,0259		16,28± 0,1214		16,32± 0,1201	
Vials 25°C (n=1)	16,23		17,01		NA	

- No change in mean hydrodynamic diameter measured by DLS
- No influence of storage duration and temperature on hydrodynamic diameter (no formation of sub-micron or micron sized aggregates and particules)

CEX (Exchange Chromatography)

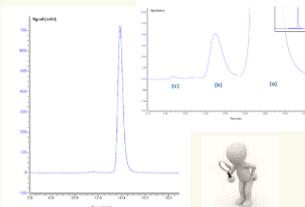


Calculation of percentages of acid variants, main variant and basic variants.

For the study concerning the bags, no new peaks were observed, in either the acid or basic parts of the chromatogram, → no change in the distribution of the variants

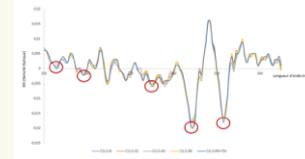
- No change in the isoform percentages, even after 90 days of storage at 4°C followed by 72 hours at 25°C (No degradation by hydrolysis and isomerisation).
- For vials, no change in the distribution of variants was observed for those stored for up to 60 days at 4°C after opening.

SEC (Steric exclusion chromatography)

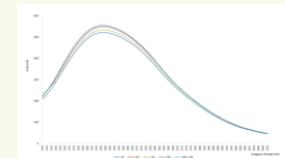


- Presence of 3 peaks: the monomer (a), a dimer (b) and a high molecular weight peak (c).
- No additional peaks appeared, irrespective of the temperature and storage duration tested, demonstrating the absence of oligomer formation and of changes in the drug that would have led to fragmentations.

Spectrophotometric analyses



- Absence of any change in the 250-270 nm region → preservation of the tertiary structure



- The fluorescence emission spectra demonstrate an identical profile, with emission maxima that do not differ on the basis of temperature and storage duration

For pH, osmolality and density, regardless of the storage conditions, the values remained within the defined specifications.

The sterility test performed after 3 months of storage at +4°C followed by 72 hours at 25°C did not reveal microbial contamination.

CONCLUSION

- ➡ The Bevacizumab biosimilar Alymsys in vials at 25 mg/ml can be stored 60 days between +2°C and +8°C after opening, protected from light and after dilution in sterile conditions with 0.9% NaCl in polyolefin IV bags, at the usual concentrations of 1.4 mg/mL and 16.5 mg/mL, during three months between +2°C and +8°C protected from light without any noticeable loss of stability.
- ➡ After a three-day temperature excursion at +25°C for the bags followed by a return to temperature between 2°C and 8°C, stability data remained unchanged. Before opening, vials (25mg/ml) are stable 15 days at 25°C, protected from light.