Background

Following the review of stability for cytotoxic drugs for the NHS tender, these monographs are designed to capture the information in a format that is useful for NHS aseptic units, particularly those working under Section 10 exemption with restricted shelf lives for products. There is also, where applicable, a view on the extended data beyond the maximum seven days that can be assigned under Section 10 exemption. This may be of use to licensed NHS aseptic units and also to procurement staff in terms of assessing the shelf lives assigned by commercial aseptic compounding units.

The studies provided have been reviewed against the standards of the NHS standards for stability testing of small molecule drug aseptic products[1].

Drug: Vinblastine Injection

CMU requirements for shelf life (taken from Wave 12 tender)

7 days shelf life at 0.1-0.3mg/ml in sodium chloride 0.9% stored in a refrigerator at 2 – 8°C

British Pharmacopoeia specification for product. General BP requirements (e.g. Parenteral Preparations Monograph) also apply

BP monograph for Vinblastine sulfate powder for injection and for Vinblastine sulfate solution for injection (same limits apply)

Content of vinblastine sulfate 92.5 to 107.5% of the stated amount of anhydrous vinblastine sulfate.

Related substances test, any secondary peak <2%, sum of secondary peaks <5% of principal peak

Assessment:

Manufacturer	SmPC shelf life	Excipients / formulation details	Assessment of Extended studies submitted	Shelf-life recommendation (section 10 units)	Comments on further shelf life extension
Pfizer (Hospira UK Ltd)	No information given regarded shelf life of the diluted product.	Solution for Injection Sodium chloride Water for injections	Additional study report at 0.25 – 0.5mg/ml[2] in syringes, study not compliant with yellow cover standards, no sub-visible particles, poor quality report. Only three data points although good number of replicates. Includes degradation product analysis with data compliant over 14 days. However, also references issues with visible particulates.	See below	See below

<u>Conclusions based on submitted data</u>

The study supplied by Pfizer (Hospira) was not compliant with the standards in the yellow cover document[1] in that there were few data points and no sub-visible particle counts, there was also commentary on visible particles being an issue at day 14 which is a concern, although a lack of detail on this matter. There is little in the way of quality published reports for diluted Vinblastine although the drug itself seems to be chemically fairly stable looking at all the evidence. Physical instability is only really suggested by the Pfizer submitted paper[2] but caution should be taken to ensure bags which are prepared in advance are checked for visible particulates prior to use.

Considering the published papers below and the data supplied by Pfizer (Hospira) the drug itself does look to be relatively stable, it is deemed safe to assign a 7 days shelf life to Vinblastine diluted in sodium chloride 0.9% stored in a refrigerator in the concentration range of 0.02 to 1mg/ml. It should be noted, however, that the quality of data is not in line with the yellow cover standards[1] and the drug should be a priority for commissioning a compliant study.

Published papers

No published papers of great quality appear to exist for Vinblastine injection.

Stability of vinblastine sulphate containing infusions. Pharmazie ; 54: 625-626. 1999: Mittner A, Vincze Z, Jemnitz K.[3]

The paper looks at Vinblastine sulfate 0.05mg/ml in Sodium chloride 0.9% in glass and indicates stability for 21 days at room temperature (21 – 25°C) and refrigerated (2 – 8°C). There was no visual inspection reported, which bearing in mind the report from Pfizer is a concern. Degradation products are detected but not quantified. Bearing in mind this is in glass it does not add anything to the above.

Stability of vinca alkaloid anticancer drugs in three commonly used infusion fluids; J Parenter Sci Technol ; 43: 84-87. 1989: Beijnen JH, Vendrig DEMM, Underberg WJM.[4]

This study looked at the stability of Vinblastine 0.02mg/ml in 0.9% sodium chloride, 5% dextrose, and Ringer's Lactate injection in polypropylene containers at 4°C and 25°C and showed less than 5% loss over 21 days at 4°C. The study did not report physical appearance, sub-visible particles or degradation product profile and was only for the single concentration. The solution was on the low side and didn't show up any adsorption issues within the specific containers used.

Chemical stability of cytarabine and vinblastine injections; Br J Pharm Pract ; 12: 53-54, 60. 1990; Weir PJ, Ireland DS.[5]

This study covered Vinblastine 1mg/ml in sodium chloride 0.9% in polypropylene syringes for up to 30 days at 6 – 9°C and 21°C protected from light, but again did not report on physical appearance, sub-visible particles or degradation product profile.

Stability of vinblastine sulphate in 0.9% sodium chloride in polypropylene syringes; Boll Chim Farm. Jul-Aug 1996;135(7):413-4; V Girona, J Prat, M Pujol, M Muñoz

This study also covered Vinblastine 1mg/ml in sodium chloride 0.9% in polypropylene syringes for up to 30 days at 25°C. It reported stability for 30 days based on assay of the active ingredient only.

Assessment carried out and report written by

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References

1. A Standard Protocol for Deriving and Assessment of Stability Part 1 – Aseptic Preparations (Small molecules) Edition 5, September 2019 (NHS PQA Committee)
2. 14 days stability study for 0.25mg/ml and 0.5mg/ml Vinblastine sulphate when diluted in saline and stored in BD Plastipak syringes at refrigeration temperatures, Report number 4159,
3. Stability of vinblastine sulphate containing infusions. Pharmazie ; 54: 625-626. 1999: Mittner A, Vincze Z, Jemnitz K.
4. Stability of vinca alkaloid anticancer drugs in three commonly used infusion fluids; J Parenter Sci Technol ; 43: 84-87. 1989: Beijnen JH, Vendrig DEMM, Underberg WJM.
5. Chemical stability of cytarabine and vinblastine injections; Br J Pharm Pract ; 12: 53-54, 60. 1990; Weir PJ, Ireland DS.