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: **Daunorubicin**

This assessment does not include Liposomal Daunorubicin presentations.

Requirements for shelf life

Ideally seven days shelf-life in clinically significant concentrations stored at 2 – 8°C in Sodium Chloride 0.9% or Glucose 5%,.

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

There is a BP (Ph Eur) monograph for the starting material but no monograph for Daunorubicin Injection. The starting material monograph includes the content of active between 95 – 102% of stated content (anhydrous substance) and the following related substances limits

Impurity A (daunorubicinone): not more than 0.5%
Impurity B (daunorubicinol): not more than 1.5%
Impurity D (doxorubicin): not more than 0.5%
Other impurities: not more than 0.5% each
Total other impurities: not more than 2.5%

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
Zentiva PL 17780/0310	After reconstitution Daunorubicin should be stored at 2 - 8°C, protected from light. After reconstitution Daunorubicin should be used within 24 hours.	Powder for I.V. Injection. Mannitol	N/A	Seven days in the concentration range 0.4 – 3.0mg/ml in both Sodium Chloride 0.9% and Glucose 5% protected from light and stored at 2 - 8^0C.	See below, up to fourteen days in the concentration range 0.4 – 3.0mg/ml in both Sodium Chloride 0.9% and Glucose 5% protected from light and stored at 2 - 8^0C.

Published studies

A stability-indicating, ion-pairing, reversed-phase liquid chromatography method for studies of daunorubicin degradation in i.v. infusion fluids: J Pharm Biomed Anal ; 83 : 164-170. 2013; Respaud R, Quenum L, Plichon C, Tournamille J.F, Gyan E, Antier D, Viaud-Massuard M.C.

A new stability-indicating method based on high-performance liquid chromatography coupled to ultraviolet and evaporative light scattering detection (HPLC-UV-ELSD) was developed for the quantification of daunorubicin. Good resolution was achieved between daunorubicin, related products and all degradation products. The study covers the concentration range 0.4 – 3.0mg/ml stored at 2 - 8^0C and 21 - 25°C in both Sodium Chloride 0.9% and Glucose 5%, all samples were protected from light. A novel HPLC-UV-ELSD method was used and this was validated as able to detect the main degradation product Daunosamine (not detected by UV alone) as well as separation of other degradation products produced by forced degradation studies including daunorubicinone (Impurity A). The study reports no major degradation products were recorded (although no data is supplied), there was also no significant loss of active at either temperature over the fourteen-day study period. There was no sub-visible particle analysis carried out but turbidity measurements were included and showed no issues.

Discussion / conclusions

In the UK Daunorubicin is now marketed by Zentiva although still part of the Sanofi family which produced the originator product Cerubidin and the same formulation. There are many other older papers on the stability of Daunorubicin but none of them contain sufficient data on which to interpret a shelf life for the ready to administer presentations, neither do any raise significant concerns that the drug is particularly unstable in solution. The one study referenced covers the concentration range 0.4 – 3.0mg/ml (including intermediate at 1.5mg/ml) stored at 2 - 8^0C and 21 - 25°C in both Sodium Chloride 0.9% and Glucose 5%, all samples were protected from light.

In conclusion Daunorubicin (Zentiva) can be safely assigned a shelf life of at least seven days in the concentration range 0.4 – 3.0mg/ml in both Sodium Chloride 0.9% and Glucose 5% protected from light and stored at 2 - 8^{0}C. The Wood paper[3], although not carried out to modern standards, does support syringe compatibility and hence this recommendation can be extrapolated to cover storage in polypropylene syringes as well as in bags. Licensed units should be safe to apply a fourteen-day shelf-life although it would be useful to back this up with some end of shelf-life sub-visible particle counts.

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. A stability-indicating, ion-pairing, reversed-phase liquid chromatography method for studies of daunorubicin degradation in i.v. infusion fluids: J Pharm Biomed Anal ; 83 : 164-170. 2013; Respaud R, Quenum L, Plichon C, Tournamille J.F, Gyan E, Antier D, Viaud-Massuard M.C.
3. Stability of doxorubicin, daunorubicin and epirubicin in plastic syringes and minibags: J Clin Pharm Ther ; 15: 279-289. 1990: Wood MJ, Irwin WJ, Scott DK. SmPC accessed on-line 2nd November 2020