**Change to the shelf life of ready-to-administer cyclophosphamide injection and infusion aseptically prepared in Specials units**

**Background**

Baxter Healthcare (Manufacturing Authorisation (MIA) holder for Cyclophosphamide Injection) has revisited the stability data for the ready-to-administer product in syringes and infusion bags. A new study was carried out to the standards outlined in ’A Standard Protocol for Deriving and Assessment of Stability Part 1 – Aseptic Preparations (Small molecules)’¹. Aligned with this protocol, the study also included analysis that degradation product levels remained within the limits of the Marketing Authorisation for the licensed dry powder product.

One of these degradation products exceeded the acceptable limits before 5% of the active ingredient was lost in this study and hence has become the shelf life limiting factor for the ready-to-administer product. Following discussions between Baxter and the MHRA, this has led to a reduction in the shelf life for ready-to-administer cyclophosphamide injection from up to 84 days to:

**25 days (2-8°C) followed by 6 hours at room temperature to allow for administration,**

or

**21 days (2-8°C) followed by 12 hours at room temperature.**

**Q&As**

**Is there any evidence that the degradation products detected are hazardous?**

There is no evidence from a review of pharmacovigilance data that any harm has come to patients over the many years that cyclophosphamide has been used with extended shelf life (Some suppliers had previously assigned 120 days to ready-to-administer product). There is also no evidence that the degradation products themselves are toxic, although of course cyclophosphamide itself is a highly toxic drug.
Will the shelf life reduction apply to all ready-to-administer cyclophosphamide regardless of the brand of starting material used?

Yes, this will impact on all NHS and commercial specials units currently manufacturing cyclophosphamide, the information that limits the shelf life is part of the specification for the MIA and is not within the Pharmacopoeial specification for cyclophosphamide injection. The stability of the molecule is independent of concentration, container and also brand of starting material and therefore the MHRA will be writing to manufacturers of cyclophosphamide ready-to-administer products to inform them of the shelf life restriction regardless of brand used.

Can I still use the ready-to-administer cyclophosphamide in stock with a longer shelf life?

Yes, there is no need to recall stock already in the supply chain with the extended expiry date nor does this need to be relabelled with a shorter expiry date. These have been deemed safe to use following the review of toxicology and pharmacovigilance data. Please do use the older stock first rather than using new stock with a shorter shelf life. Please also try to resist the temptation to stockpile existing product with an extended shelf life.

So why has the shelf life been shortened significantly if there is no risk to patients?

The specifications for products apply throughout the shelf life and hence a product which is non-compliant with that specification should not be made available. The exceeding of a limit for a degradation product does, therefore, limit the shelf life of that product. For the specification to be changed, significant toxicological data will be required for the degradation products and this will need to be submitted via a licence variation.

Will the shelf life for other ready-to-administer products be shortened?

The issue found is specific for cyclophosphamide, however, companies should constantly review their stability data and shelf life assignment and any new stability studies should be compliant with NHS standards.\(^1\)\(^2\) Hence, this may see shortening of shelf lives for some other products

What should happen if my NHS unit is manufacturing this product with an extended shelf life under a Specials Licence?

The shelf life should not exceed the 25 days outlined in this advice note even if you have other information which would appear to contradict this.

Any comments or clarifications required should be addressed to Mark Santillo, Regional QA Officer (South West England) mark.santillo@nhs.net