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: **Azacitidine**

CMU requirements for shelf life (taken from originator product shelf life)

When Vidaza is reconstituted using refrigerated (2 °C to 8 °C) water for injections, the chemical and physical in-use stability of the reconstituted medicinal product has been demonstrated at 2 °C to 8 °C for 22 hours.

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

No monographs for injection or active substance

EU Reference product specification

Content of Azacitidine 95 – 105%
Impurity C <2.5%
N-(formyl amidino)-N'-β-D-ribofuranosylurea <4.0%
Other related substances <0.2%
Total related substances (excluding N-(formyl amidino)-N'-β-D-ribofuranosylurea) <3.0%

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
Accord EU/1/19/1413/001	When Azacitidine Accord is reconstituted using water for injections that has not been refrigerated, chemical and physical in-use stability of the reconstituted medicinal product has been demonstrated at 25 °C for 60 minutes and at 2 °C to 8 °C for 8 hours. The shelf life of the reconstituted medicinal product can be extended by reconstituting with refrigerated (2 °C to 8 °C) water for injections. When Azacitidine Accord is reconstituted using refrigerated (2 °C to 8 °C) water for injections, the chemical and physical in-use stability of the reconstituted medicinal product has been demonstrated at 2 °C to 8 °C for 22 hours.	Mannitol	Looks at the frozen product compared to the originator (Celgene) product only. Not a stability study just one time point given and no T=0 for comparison nor acceptance criteria for degradation products.[2]	When reconstituted using refrigerated (2 °C to 8 °C) water for injections, shelf life can be assigned as 22 hours at 2 °C to 8 °C.	See below
Celgene EU/1/08/488/001	When Vidaza is reconstituted using water for injections that has not been refrigerated, chemical and physical in-use stability of the reconstituted medicinal product has been demonstrated at 25 °C for 45 minutes and at 2 °C to 8 °C for 8 hours. The shelf life of the reconstituted medicinal product can be extended by reconstituting with refrigerated (2 °C to 8 °C) water for injections. When Vidaza is reconstituted using refrigerated (2 °C to 8 °C) water for injections, the chemical and physical in-use stability of the reconstituted medicinal product has been demonstrated at 2 °C to 8 °C for 22 hours.	Mannitol	N/A	When reconstituted using refrigerated (2 °C to 8 °C) water for injections, shelf life can be assigned as 22 hours at 2 °C to 8 °C.	See below

Manufacturer	SmPC shelf life	Excipients / formulation details	Assessment of Extended studies submitted	Shelf-life recommendation (section 10 units)	Comments on further shelf life extension
Dr Reddy's	When Azacitidine betapharm is reconstituted using water for injections that has not been refrigerated, chemical and physical in-use stability of the reconstituted medicinal product has been demonstrated at 25 °C for 45 minutes and at 2 °C to 8 °C for 8 hours. The shelf life of the reconstituted medicinal product can be extended by reconstituting with refrigerated (2 °C to 8 °C) water for injections. When Azacitidine betapharm is reconstituted using refrigerated (2 °C to 8 °C) water for injections, the chemical and physical in-use stability of the reconstituted medicinal product has been demonstrated at 2 °C to 8 °C for 22 hours.	Mannitol	Additional study includes a 48 hour time point post reconstitution but this does not have the plus 30 minutes for warming which is included for the 22 hour data. For one batch total impurities slightly exceeds the specification above at 48 hours (although no acceptance criteria set in the paper submitted)	When reconstituted using refrigerated (2 °C to 8 °C) water for injections, shelf life can be assigned as 22 hours at 2 °C to 8 °C.	See below
Seacross	When reconstituting using water for injections that has not been refrigerated, the reconstituted suspension must be placed in a refrigerator (2 °C to 8 °C) immediately after reconstitution, and kept in the refrigerator for a maximum of 8 hours. When reconstituting using refrigerated (2 °C to 8 °C) water for injections, the reconstituted suspension must be placed in a refrigerator (2 °C to 8 °C) immediately after reconstitution, and kept in a refrigerator for a maximum of 22 hours. (from PIL and SmPC not available)	Mannitol	Detailed report submitted although only data to support the SmPC shelf life in syringes (slightly longer for the reconstituted solution in the vial)[4]	When reconstituted using refrigerated (2 °C to 8 °C) water for injections, shelf life can be assigned as 22 hours at 2 °C to 8 °C.	See below

Conclusions (based on the data supplied)

All preparations are lyophilised drug powder with mannitol, all SmPCs have the same statement regarding stability and the possibility to extend this to 22 hours in the refrigerator provided that refrigerated water (2 – 8°C) is used for reconstitution and the product is refrigerated as quickly as possible after reconstitution. It is clear from room temperature shelf life (45 minutes) and the data submitted that the product is very unstable at room temperature. The data from Dr Reddy's extends to 48 hours but this did not include a period of warming ahead of administration and the total impurities exceeded the specification above (although only marginally).

The Accord paper looked at the impact of freezing the product but was not a full stability study and only included the analysis post storage (i.e. no T=0 time point for comparison), furthermore, using the specification above the product and the frozen Celgene product used as a comparator were out of specification for both Impurity C and for total impurities at the tested time point (note that no acceptance criteria were set for these within the report).

It should also be noted that freezing of products in syringes is not recommended due to concerns about the integrity of the syringes particularly during the freezing and thawing cycles when the various components could expand and contract at different rates. To date there has been no validation to show that during these critical phases that integrity is maintained. Furthermore, the expansion of the liquid on freezing means that the syringe plunger will be pushed further down the barrel, meaning an area previously outside of the rubber grommet (and hence not necessarily still sterile) can become within the drug storage compartment. There is also the risk of leakage of the product to consider, which has been reported. Syringes are not intended as medicines storage devices and variation within syringes (inter batch and intra batch) can be significant and hence any validation will only apply to the syringes tested. Further information can be found in the PhQAC statement 'The supply of frozen Azacitidine in plastic disposable syringes'[5].

Hence it is recommended that the shelf life specified within the various SmPCs is not exceeded, namely when reconstituted using refrigerated (2 °C to 8 °C) water for injections, shelf life can be assigned as 22 hours at 2 °C to 8 °C, otherwise it is 8 hours at 2 °C to 8 °C. The use of product frozen in syringes is not recommended[5].

Published studies

Stability of 25 mg/mL 5-azacitidine suspension kept in fridge after freezing. Pharmaceutical Technology in Hospital Pharmacy ;2, 1:11-16. 2017, Balouzet C, Chanat C, Jobard M, Brandely-Piat M-L, Chast F.[6]

This study did look at the chemical and physical stability of Azacytidine including frozen (but see above recommendations), the study included physical examination of the suspension including using optical microscopy and turbidity measurements plus determination of the content, and ribosylguanylurea

and N-formyl ribosylguanylurea degradation products. Phase separation was seen after freezing and thawing although this could be redistributed by shaking. Crystal sizes did increase during the post freezing refrigerated storage period. During 30 days frozen storage the drug concentration fell very slightly the levels of ribosylguanylurea did increase noticeably. Once removed from the freezer and stored in the refrigerator the levels of active drug fell significantly and the levels of ribosylguanylurea increased rapidly. The paper does conclude that freezing followed by three days refrigerated is acceptable but insufficient evidence is provided within the paper to fully support this (particularly actual levels of degradation products seen).

Stability of Azacitidine in Sterile Water for Injection, Can J Hosp Pharm ; 65, 5: 352-359 2012, Walker S.E, Charbonneau L.F, Law S, Earle C.[7]

Solutions of azacitidine (10 or 25 mg/mL) were stored in polypropylene syringes and glass vials at room temperature (23°C), 4°C, or −20°C. For reconstitution, the temperature of the diluent was 4°C for samples to be stored at 4°C or −20°C and room temperature for samples to be stored at 23°C. The concentration of azacitidine was determined by a validated, stability-indicating liquid chromatographic method, degradation products were not analysed and neither was a visual inspection of solutions reported. Azacitidine degradation was very sensitive to temperature but not storage container (glass vial or polypropylene syringe). Reconstitution with cold sterile water reduced degradation. At 23°C, 15% of the initial concentration was lost after 9.6 hours; at 4°C, 32% was lost after 4 days; and at −20°C, less than 5% was lost after 23 days. The conclusion is based on allowing 10% loss which would take the product outside of the above specification but it is clear from the data that the SmPC recommended shelf life is probably the best that can be obtained to maintain product within specification.

Stability of Azacitidine Suspensions. Ann Pharmacotherapy ;45, 4:546. 2011, Duriez A, Vigneron J.H, Zenier H.A, May I, Demoré B.M.[8]

Study looked at freezing for up to 8 days followed by 8 hours storage at 2 – 8^{o}C, degradation products were measured but not identified, one degradation product increased over time (likely to be N-(formyl amidino)-N'-β-D-ribofuranosylurea) . After 8 days, syringes retained a concentration higher than 95 % of initial azacitidine concentration (maximum difference 4.5 %).

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5. The supply of frozen Azacitidine in plastic disposable syringes, NHS Pharmaceutical Quality Assurance Committee Advice Note, August 2020, https://www.sps.nhs.uk/?post_type=articles&p=44722&preview=true
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