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: **Oxaliplatin Solution for Infusion**

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

0.2 -0.7mg/ml in Glucose 5% at 2-8°C shelf-life of seven days in infusion bags (non-PVC)

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

Monograph is for the active substance only and not for the injection. General monograph requirements apply to the injection. Active substance monograph includes specific limits for Impurity C, unspecified impurities and the sum of impurities. Note that the Pfizer product contains tartaric acid and hence has limits for Tartaroplatin impurity additionally.

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 Healthcare PL20075/0112	After dilution in 5% glucose, chemical and physical in-use stability has been demonstrated for up to 48 hours at +2°C to +8°C and for 24 hours at +25°C	Water for injections	Study 0.1 - 1.2mg/ml and 5mg/ml for 35 days. No replicates (although protected from light and not protected from light), no sub-visible particles, no degradant product analysis	Satisfactory for seven days shelf life assignment at 0.1 – 1.2mg/ml in Glucose 5% at +2°C to +8°C	Study well short of compliance with NHS standards[1].
Fresenius Kabi PL18727/0012	After dilution in glucose 5% solution, chemical and physical in-use stability has been demonstrated for 24 hours at 2°C to 8°C and 6 hours at 15°C to 25°C.	water for injections, succinic acid and sodium hydroxide	Study supplied which is largely compliant with the YCD (although had acceptance criterion of 10% loss). Diluted in concentrations between 0.1 mg/mL and 0.7 mg/mL in 5% w/v glucose solution for injection in Freeflex and KabiPac container, is stable for 84 days at 2-8°C under light protection and at room temperature under light protection for 28 days. This statement is supported based on 5% loss.	Satisfactory for seven days shelf life assignment at 0.1 – 0.7mg/ml in Glucose 5% at +2°C to +8°C	Study is largely compliant with the NHS standards[1], hence can be used for extended shelf life as long as the data is held on file

Manufacturer	SmPC shelf life	Excipients / formulation details	Assessment of Extended studies submitted	Shelf-life recommendation (section 10 units)	Comments on further shelf life extension
Medac PL11587/0086	After dilution in 5 % glucose, chemical and physical in-use stability has been demonstrated for 48 hours at +2 °C to +8 °C and for 6 hours at +25 °C.	Water for injection	Supporting data for the SmPC supplied but nothing further.	No data supplied, SmPC shelf life 48 hours at 2°C to 8°C should be followed	SmPC shelf life 48 hours at 2°C to 8°C should be followed. However, formulation identical to Accord and Sun Pharma.
Pfizer PL04515/0215	After dilution in 5% glucose, chemical and physical in-use stability has been demonstrated for 24 hours at +2°C - +8°C and for 6 hours at +25°C.	Water for Injections Tartaric acid Sodium Hydroxide	Study supplied retrospectively, only covers 24 hours at room temperature and 48 hours refrigerated. Study only has two data points at each storage condition and concentration but is detailed for related substances.	Shelf life should not be beyond 48 hours at 2°C to 8°C (or 24 hours at room temperature). Note different excipients to other suppliers and potential for different related substance profile.	Shelf life should not be beyond 48 hours at 2°C to 8°C (or 24 hours at room temperature). Note different excipients to other suppliers and potential for different related substance profile.
Sun Pharma (Ranbaxy UK) PL31750/0048	After dilution in 5% glucose, chemical and physical in-use stability has been demonstrated for 24 hours at room temperature (15-25°C) or for 48 hours under refrigeration (2°C-8°C)	Water for injection	Study 0.2 - 0.7mg/ml in a variety of infusion bags. Poor presentation of data and it is difficult to trend, no statistical analysis and day 7 data is an outlier across all samples, no explanation is offered for this. No sub-visible particles, no degradant product analysis. Acceptance criterion just set at not below 95% which means some very high results have been accepted.	Satisfactory for seven days shelf life assignment at 0.2 – 0.7mg/ml in Glucose 5% at +2°C to +8°C	Study well short of compliance with NHS standards[1].

Manufacturer	SmPC shelf life	Excipients / formulation details	Assessment of Extended studies submitted	Shelf-life recommendation (section 10 units)	Comments on further shelf life extension
Tillomed (QILU PHARMA) PL44570/0002	After dilution in 5% glucose, chemical and physical in-use stability has been demonstrated for 48 hours at 2°C to 8°C and for 24 hours at 25°C.	Water for injections	No further data submitted	No data supplied, SmPC shelf life 48 hours at 2°C to 8°C should be followed	SmPC shelf life 48 hours at 2°C to 8°C should be followed. However, formulation identical to Accord and Sun Pharma.

Conclusions (based on the data provided)

The extended study provided by Fresenius Kabi was of a good standard. Their formulation is different to other suppliers and therefore this data cannot be extrapolated. The studies from Accord and Sun Pharma are well short of NHS standards although do supply sufficient data for a seven day shelf life assignment. Medac and Tillomed supplied no further data beyond their SmPC but their formulation appears identical to Accord and Sun Pharma. Pfizer provided data to cover only 48 hours refrigerated and 24 hours at room temperature and their formulation is different to other suppliers with a potential for a different degradation profile (including potential for formation of tartaroplatin).

Published and other relevant reports for Oxaliplatin

The abstracts available did not specify brand although the pre-2010 papers are likely to have used Eloxatin (Sanofi) original studies should be accessed and reviewed before using the data.

Physicochemical stability of oxaliplatin in 5% dextrose injection stored in polyvinyl chloride, polyethylene, and polypropylene infusion bags, American Journal of Health-System Pharmacy, Volume 66, Issue 21, 1[6]

Solutions of oxaliplatin 0.2 and 1.3 mg/mL in 5% dextrose injection were stable in the three container types for at least 14 days at both 4 °C and 20 °C without regard to light exposure.

Stability of oxaliplatin in infusion bags containing 5% dextrose injection, American Journal of Health-System Pharmacy, Volume 64, Issue 18, 15[7]

Oxaliplatin 0.7 mg/mL in infusion bags containing 5% dextrose injection was chemically stable for at least 30 days at both 3–7 °C and 20–24 °C without regard to light exposure (although acceptance criteria >90% of initial)

Long-term stability of Oxaliplatin-beta-infusion concentrate and diluted infusion solutions, Krankenhauspharmazie 2017;38:334–40. (Stabilis rated A+)[8] (published in German with English abstract)

Covers 0.2 – 1mg/ml in Dextrose 5% over 28 days protected from light at room temperature or refrigerated tested by HPLC, visual inspection, particle counting of sub-visual particles and pH measurement. Study showed that product remained, independent from the concentration, physically and chemically stable over a storage period of 28 days

Assessment carried out and report written by

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2. Physical and chemical stability of Oxaliplatin 5mg/ml concentrate for solution for infusion Accord 25/05/2012 provided 25/06/2019
3. Stability Statement of Oxaliplatin 5 mg/mL Concentrate for solution for infusion (Fresenius Kabi) report SU 920/12 provided 03/10/2019
4. Oxaliplatin Injection infusion study 880-REG-023 (Hospira Australia) provided 07/04/2020
5. Stability study on Oxaliplatin bags, Stockton NHS QC Laboratory (not dated) provided 25/06/2019
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8. Long-term stability of Oxaliplatin-beta-infusion concentrate and diluted infusion solutions, Krankenhauspharmazie 2017;38:334–40, Irene Krämer, Iman Sarakbi, Judith Thiesen SmPCs accessed on-line or sent as part of the tender between June and October 2019