Therapeutic Goods Administration
Office of Scientific Evaluation
Pharmaceutical Chemistry Evaluation Section

Evaluation of Quality Data
(Chemical Drug Substance)

New chemical entity
(type of application)

Cabazitaxel (as acetone solvate)
(drug substance)

JEVTANA®
CABAZITAXEL WINTHROP
CABAZITAXEL SANOFI
(brand name)

Injection, Concentrated
40 mg/mL presented as a 60 mg/1.5 mL vial with a 4.5 mL diluent vial
(dose form and strengths)

Sanofi-Aventis Australia Pty Ltd
(sponsor)

25 August 2010
(date of application)

PM-2010-02565-3-4
(application number)

2010/014252
(DSEB Chem/Biol File Number)

2010/011351
(associated DMF files and dates)

Evaluator: s22 [redacted]

I. Introduction

Sanofi-Aventis Australia Pty Ltd *(hereafter referred to as Sanofi)* has submitted a category 1 application to register cabazitaxel 40 mg/mL concentrate injection, under the trade names of "JEVTANA", "CABAZITAXEL WINTHROP" and "CABAZITAXEL SANOFI". The drug product is presented as a 60 mg/1.5 mL non-aqueous concentrate injection solution vial for use in an infusion only. The applicant has a similar taxane product, Taxotere® docetaxel 80 mg/2 mL concentrate injection + diluent, currently registered on the ARTG (AUST R 53455).

Cabazitaxel (as an acetone solvate) is a new chemical entity proposed for use in combination with prednisone or prednisolone *for the treatment of patients with hormone refractory mestatic prostrate cancer, previously treated with a docetaxel-containing regimen.*

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s22 [redacted] Development of the proposed drug product has been based on the previously registered taxoid parenteral product, *Taxotere® docetaxel 80 mg/2 mL injection vial with diluent vial* (AUST R 53455).

The recommended dose of cabazitaxel is 25 mg/m^2 administered as a 1-hourly intravenous infusion every 3 weeks, in combination with oral prednisone (or prednisolone) 10 mg administered daily throughout the treatment.

No bioavailability data are required as the product is a simple non-aqueous solution, that once diluted, is intended for intravenous infusion.

At the time of submission, similar applications had been submitted in the USA, EU, Canada, Mexico, Brazil, Switzerland, Russia, South Africa and Israel. All applications are currently pending approval with the exception of the USA, as the FDA granted approval on 17 June 2010. ***The applicant should be asked to confirm if the overseas regulatory status has changed since the date of the original submission.***

Note: This evaluation report covers the chemical, manufacture, quality control and stability aspects of the product. Endotoxin and sterility aspects will be evaluated by the Microbiology Section of OLSS.

II. Summary and Assessment of the Data as Originally Submitted

Module 3.2.S: Drug Substance

The manufacture, quality control and stability of the active ingredient, cabazitaxel (as the acetone solvate) are described in the associated Drug Master File from s47G which is the subject of a separate evaluation report s47G

The DMF holder has provided appropriate authorisation for the TGA to refer to the DMF in support of the present application.

Proposed Name

The applicant has provided documentation to support the proposal of *'cabazitaxel'* as an Australian Approved Name (AAN). The documentation supplied in Module 1.2 of the application should be passed on to the AAN Committee for consideration.

Manufacturers

The names, addresses and steps carried out, for each manufacturing and testing site are listed in the application form. Refer to *Module 1 – GMP Status of Manufacturers and Packers* towards the end of this evaluation report.

Specification

The drug product manufacturer, *Aventis Pharma Dagenham, UK*, is affiliated with the drug substance manufacturer, *Sanofi-Aventis recherché & développement, Vitry-sur-Seine, France*. Therefore, the drug substance specification and associated test methods utilised by the drug product manufacturer is identical to that presented in the Drug Master File from *Sanofi Chimie, France* (refer chem/biol. File No. 2010/011351). For reference, a copy of the drug substance specification is provided in **Appendix 1** at the end of this evaluation report.

Module 3.2.P: Drug Product – Injection, Concentrated

3.2.P.1 Description and Composition of the Drug Product

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[redacted]

Drug Product – Injection, Concentrated

3.2.P.2 Pharmaceutical Development

3.2.P.2.1 Components of the Drug Product

The acetone solvate (Form A) of the drug substance, ***cabazitaxel***, was selected on the basis of the manufacturing feasibility and reproducibility, given that distillation is applied during the proposed manufacturing process.

Cabazitaxel is lipophilic with a measured log P of 3.9 and the drug substance is practically insoluble in water (8 µg/mL). Solubility of the drug substance in polysorbate 80 pH 3.5 and ethanol enabled the manufacture of a cabazitaxel concentrate injection (i.e. solubility of 86 mg/mL at 15ºC and 34 mg/mL at 30ºC in 50/50 v/v solution of polysorbate 80 pH 3.5 and ethanol).

The excipients used in the manufacture of the drug product all comply with pharmacopoeial standards as highlighted in the table above, with polysorbate 80 pH 3.5 the exception. They are conventional for the use in the manufacture of parenteral products and are therefore, found to be acceptable. None of the excipients are derived from animals or genetically modified organisms.

Polysorbate 80 is used to solubilise the drug substance. It allows the formation of micellar solutions in the premix and in the infusion solutions, which enable the drug substance to remain in solution.

Ethanol – absolute (or anhydrous ethanol) is used as a co-solvent of the drug substance, given that the viscosity of polysorbate 80 is not compatible with direct dissolution of the drug substance in pure polysorbate. Ethanol is removed during the distillation step of the manufacturing process.

Nitrogen is used as a headspace gas and as a processing aid during the filling stage.

3.2.P.2.2 Drug Product

The formulation of the cabazitaxel concentrate injection solution was established primarily on the basis of previous knowledge and experience gained during the development of other taxoid parenteral products such as *Taxotere® docetaxel 80 mg/2 mL concentrated injection – AUST R 53455*, which met the same intended target product profile (i.e. administration of an infusion solution during 1 hour).

Polysorbate 80 was used on the basis that surfactants are known to form micellar solutions, which increase solubility of drugs like cabazitaxel in aqueous solutions. As for Taxotere®, a cabazitaxel concentrate at 80 mg/2 mL was initially prepared using polysorbate 80 at pH 3.5, along with a diluent formulated as an aqueous solution containing 13% w/w ethanol. Solubility studies at various pHs confirm the satisfactory stability of the JEVTANA® concentrate injection at the targeted pH of 3.5.

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An 22% overfill is employed to compensate for liquid losses during preparation of the premix solution. The minimum target fill volume is 1.83 mL to ensure the label volume of 1.5 mL is available for withdrawal. This is acceptable.

No excipient overages are used in the manufacture of the JEVTANA® concentrate injection formulation.

The pharmaceutical development investigations presented are considered thorough and are acceptable.

3.2.P.2.3 Manufacturing Process Development

The manufacturing methods utilised are conventional manufacturing processes commonly used to produce parenteral drug products. Solution compounding, pH adjustment, filtration, compatibility with sterilising filters, filling and hold times were all satisfactorily investigated in order to optimise the manufacturing process.

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The equipment and procedures used to manufacture clinical and stability batches and those proposed for use in to manufacturing commercial scale batches, have the same operating principles with differences only to scale of manufacture. The data presented to document any differences between the clinical and pivotal primary stability batches is acceptable.

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3.2.P.2.4 Container Closure System

The drug product is to be packaged in clear, glass Type I vials with polymer coated elastomeric rubber stoppers and flip-off aluminium/plastic overseals, which are conventional for the dosage form. Details of the container/closure system are described in Section 3.2.P.7 of this evaluation report.

Extractables/leechables studies were not carried out on the proposed drug product, as these studies were carried out and assessed for the Taxotere® docetaxel 80 mg/2 mL concentrate injection solution (AUST R 53455). Given that the excipients used in JEVTANA® and Taxotere® formulations are the same, the rubber closures are the same and the drug substance molecules themselves are similar, the evaluator believes that this approach is acceptable.

3.2.P.2.5 Microbiological Attributes

Microbiological aspects of the product should be assessed by the TGA Office of Laboratories and Scientific Services (OLSS) and have not been discussed in this evaluation report.

3.2.P.2.6 Compatibility

Prior to administration, the premix solution of the JEVTANA® cabazitaxel concentrate injection requires dilution with large volume parenteral (LVP) diluents followed by intravenous infusion into patients. The following diluents are recommended in the JEVTANA® Product Information; 0.9% Sodium Chloride injection solution and 5% Glucose injection solution.

Compatibility of the drug product with the recommended diluents was assessed via three studies:

- A chemical compatibility study with infusion containers (bags and bottles);
- A physical compatibility study with infusion containers (bags and bottles); and
- An in-use stability study mimicking infusion conditions.

The four different infusion containers selected for assessment were, glass bottles; multilayer polyolefin bags made of polypropylene as the external layer and polyethylene in contact with the drug product; LDPE bags; and di-(2-ethylhexyl)phthalate (DEHP) containing polyvinyl (PVC) bags.

The four different infusion sets selected for assessment were made from, PVC/DEHP; PCV DEHP-free; polyolefin (PVC lined with polyethylene); and polyurethane.

Two (2) hours was selected for the infusion time to represent the worst-case scenario compared to the recommended 1-hour infusion time. The JEVTANA® concentrate was diluted to concentrations of 0.10 mg/mL and 0.26 mg/mL to represent the in-use potential dilution range. Prepared infusion solutions using both 0.9% Sodium Chloride injection solution and 5% Glucose injection solution were stored up to 48 hours at 5ºC and 30ºC in terms of *visual appearance*, *pH*, *assay* and *impurities* by HPLC, and *DEHP content* specifically for the PVC infusion bags.

Analysis confirmed that cabazitaxel infusion solutions stored in either glass bottles, LDPE or polyolefin bags were chemically compatible for 48 hours of storage at 5ºC and 30ºC, whatever the infusion diluent.

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However, significant losses in the assay content and an increase in DEHP up to 120 ppm were observed at 48 hours storage at 30ºC for the PVC bags containing DEHP. **Therefore, PVC/DEHP bags are not recommended for use with JEVTANA® cabazitaxel concentrated injection solution or its diluted solutions.**

An appropriate statement has been included in the package insert leaflet, which is placed inside the carton.

Visual inspection of the different infusion containers was undertaken at both 24 and 48 hours and examined for crystallisation. No crystallisation was observed at 5ºC after 48 hours storage, in any infusion container or diluent. However, crystallisation was observed after 48 hours in LDPE bags containing sodium chloride 0.9% and in PVC/DEHP bags containing 5% glucose, when stored at 30ºC. Therefore, the applicant has recommended that any infusion solution stored at ambient conditions be limited to 8 hours only, to ensure that there is no risk of crystallisation. This is acceptable.

Based on the in-use stability generated, it was confirmed that a 2-hour infusion time at ambient temperatures with polyethylene, PVC DEHP-free and PVC/DEHP sets and either infusion diluent is supported over the range of 0.10 to 0.26 mg/mL. However, the assay of solutions through the polyurethane sets revealed unacceptable decreases in assay values to below 94%. **As such, the use of polyurethane infusion sets is not recommended for use with JEVTANA® cabazitaxel concentrated injection solution or its diluted solutions.** Again, an appropriate statement has been included in the package insert leaflet.

3.2.P.3 Manufacture

3.2.P.3.1 Manufacturers

The names, addresses and steps carried out for each manufacturing, packing and testing site are listed in the application form. *Refer to Module 1 – GMP Status of Manufacturers and Packers* later in this evaluation report for assessment of these details.

3.2.P.3.2 Batch Formula

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[redacted]

Drug Product – Injection, Concentrated

3.2.P.3.3 Description of Manufacturing Process and Process Controls

A copy of the manufacturing process flow chart is provided in **Appendix 2** at the end of this evaluation report. The manufacturing process is a simple one and conventional for the dosage form. No reprocessing procedures are proposed at this point in time.

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Sterility aspects of the manufacturing process should be referred to the Microbiology Section of OLSS for assessment.

3.2.P.3.4 Controls of Critical Steps and Intermediates

Critical steps

The applicant has identified the following in-process controls for the manufacturing process as tabulated below. The critical chemical in-process controls and their acceptance criteria are acceptable. The Microbiology Section of OLSS should comment on the acceptability of any microbiological aspects.

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Intermediate products

Not applicable. No intermediate products are isolated during the manufacture of the JEVTANA® cabazitaxel 60 mg/1.5 mL concentrated injection.

3.2.P.3.5 Process Validation and/or Evaluation

With respect to the chemical validation of the manufacturing process, the applicant has provided process validation data for three consecutive primary stability batches and for the first validation batch. The batch sizes correspond to the proposed commercial batch size (20 L) nominated in Section 3.2.P.3.2. Details of the batches presented and tested are provided overleaf.

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All batches met all in-process and finished product controls. The applicant has provided the commitment to manufacture an additional two production scale batches to complete the validation process. The assurance is acceptable.

Sterile process validation and evaluation of the aseptic manufacturing process for JEVTANA® is provided and should be assessed by the Microbiology Section of OLSS.

3.2.P.4 Control of Excipients

The excipients used in the manufacture of the drug product, namely; *ethanol (absolute)*, *and nitrogen* are conventional and both comply with the harmonised Ph. Eur./USP/JP monographs relevant to each excipient.

C*itric acid monohydrate* is used to adjust the pH of the polysorbate 80 excipient to pH 3.5. ***The applicant should confirm that the quality control of citric acid monhydrate is ensured through compliance with the relevant pharmacopoeial monograph.***

The quality of the excipient, *polysorbate 80*, is controlled by an in-house specification, which has been based upon the relevant Ph. Eur./USP-NF/JP monographs with some modifications. Polysorbate 80 is considered non-compendial as it does not meet the Ph.Eur./USP-NF limits for acid value, due to the pH of the excipient undergoing adjustment to pH 3.5 (range 3.3 to 3.8) by the addition of citric acid. Modifications to the pharmacopoeial monographs are summarised overleaf.

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The evaluator believes that the in-house specification for polysorbate 80 is satisfactory.

No excipient of human or animal origin has been used in the manufacture of the drug product.

3.2.P.5 Control of Drug Product

3.2.P.5.1 Specifications

The applicant has provided a combined in-house release and expiry specification for JEVTANA®, a copy of which is provided in **Appendix 3** at the end of this evaluation report. The frequency with which the drug product manufacturer will perform each test at release has not been stated. ***The applicant should be asked to confirm that each test will be performed on every batch, or justify otherwise.***

Differences between the release and expiry specifications are summarised below.

Test	Release Specification	Expiry Specification
Assay	57.0 to 63.0 mg/1.5 mL (95.0 to 105.0%)	56.4 to 63.0 mg/1.5 mL (94.0 to 105.0%)
Degradation Products RPR202670 Total degradation products	 ≤ 0.20% ≤ 0.50%	 ≤ 0.50% ≤ 1.0%

3.2.P.5.2 Analytical Procedures

The proposed analytical procedures for the assessment of *appearance of solution (clarity and colour)*, *pH*, *uniformity of dosage units*, *particulate contamination* and *water content* (volumetric and coulometric Karl Fischer) are based upon Ph. Eur. pharmacopoeial monographs. No validation reports have been provided for the pharmacopoeial methods and this is acceptable.

The analytical procedures for the assessment of *sterility* and *bacterial endotoxins* also reference Ph. Eur. pharmacopoeial methods, however, microbial aspects of the drug product should be referred to the Microbiology Section of OLSS for assessment.

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An in-house TLC *identification* test is used as a secondary identification method (Method No. CMC-PA-2009-19800). The main spot in the sample chromatogram should have the same colour and Rf value (approx. 0.66) as the cabazitaxel spot in the reference chromatogram.

An in-house gradient HPLC test method (Method No. CMC-PA-2009-23953) is used for the assessment of *assay content*, *identification* and determination of levels of *degradation products* (not including drug substance process impurities or impurities arising from the polysorbate 80 excipient). The chromatographic conditions used in the in-house HPLC method are summarised below.

Parameter	**In-house method**			
Column	Symmetry C18, 550 mm x 4.6 mm, 5 µm or equivalent			
Column temperature	30ºC			
Mobile phase (A)	Acetonitrile/Methanol/Water at pH 4.0 (35:25:40 v/v)			
Mobile phase (B)	Acetonitrile/Methanol/Water at pH 4.0 (50:25:25 v/v)			
	Acetonitrile/Anhydrous ethanol (80:20 v/v)			
Gradient program	**Time (mins)**	**A**	**B**	**C**
	0	100	0	0
	20	0	100	0
	42	0	100	0
	42.1	0	0	100
	48	0	0	100
	48.1	100	0	0
	58	100	0	0
Flow rate	0.9 mL/min			
Detection wavelength	UV at 230 nm			
Injection volume	25 µL			
Run time / RT	45 minutes / 19 mins RT for cabazitaxel			

Identification of cabazitaxel is confirmed by ensuring the retention time of the principle peak in the sample chromatogram corresponds to that of the principle peak in the reference standard chromatogram.

Known process impurities and degradation products are identified by their relative retention times. Quantification is by comparison against the peak area of a cabazitaxel standard and relative response factors are applied. Adequate system suitability criteria are included in the test method.

3.2.P.5.3 Validation of Analytical Procedures

Identification by TLC (Method No. CMC-PA-2009-19800)

The analytical procedure has been satisfactorily validated. Specificity has been demonstrated with respect to polysorbate 80 as well as regarding the identification of two related taxanes (larotaxel and docetaxel), which are used in manufacture at the Dagenham site.

Identification by HPLC, Assay and Degradation Products (Method No. CMC-PA-2009-23953)

The method has been satisfactorily validated in terms of specificity, linearity, accuracy, precision (system and method) and intermediate precision. Robustness of the method was demonstrated by changes to the method such as column temperature (28-32ºC), mobile phase composition and adjustments to pH of acidified water in the mobile phase (3.8-4.2). The sample and standard solutions were shown to be stable at least 4 days at 10ºC and 4 weeks at 5ºC. The system suitability criteria are considered acceptable.

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With regard to the related substances validation, the LOD was determined to be 0.02 ng/mL (corresponding to 0.02% of the nominal cabazitaxel concentration) and the LOQ was determined to be 0.07 ng/mL (corresponding to 0.06% of the nominal cabazitaxel concentration).

Microbiological tests

Microbiological aspects of the drug product should be referred to the Microbiology Section of OLSS for assessment.

3.2.P.5.4 Batch Analyses

Batch analysis data were provided for the three primary stability batches, one validation batch and one clinical batch, manufactured at the 20 L commercial scale at the proposed manufacturing site. Details of the batches are specified below.

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[redacted]

The results, which comply with the proposed specifications, are summarised below.

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[redacted]

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The applicant should be requested to provide an explanation for the noted differences in results.

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Batch analysis data were also provided for a further four batches representative of the initial development presentation of 80 mg/2 mL, which were used in clinical studies.

3.2.P.5.5 Characterisation of Impurities

No impurities or degradants have been observed in the finished product have not been observed in the drug substance, cabazitaxel. Please refer to the DMF evaluation report (refer chem/biol. File No. 2010/011351).

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3.2.P.5.6 Justification of Specifications

Identification

The HPLC and TLC identification tests for cabazitazel are included in both the release and expiry specifications are considered acceptable.

Assay

The proposed release assay limit of 95.0 – 105.0% of the label claim content is considered acceptable.

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Degradation products

The applicant has proposed release and expiry limits as summarised below.

Impurities	Release Specification	Expiry Specification
RPR202670	NMT 0.20%	NMT 0.50%
No. of unspecified degradation products above 0.20%	0	0
Total degradation products	NMT 0.50%	NMT 1.0%

The limit of 0.20% for **any unspecified degradation products** has been based upon the identification threshold limit of 0.2%, based on a maximum daily dose of 25 mg/m^2 i.e. 40 mg/day of cabazitaxel. The limit is acceptable.

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[redacted]

Other dose-form specific tests

The proposed **water content** limit at release and expiry is NMT 1.0% w/w and has been based upon the theoretical content of the excipients with an extra margin for safety. No increase in water content was observed in the stability data provided (highest value recorded was 0.4%) and as such, the evaluator believes that the proposed limits are not supported by the release and stability data provided in the application. ***The applicant should be requested to provide tighter limits based upon batch analysis and stability data generated to date, or justify otherwise.***

The proposed limit for **particulate contamination** complies with Ph Eur. 2.9.19 (Method 1 – Light Obscuration Particle Count Test) and is acceptable.

The proposed limit for **uniformity of dosage units** (by mass variation) complies with Ph. Eur. 2.9.40 and is considered acceptable.

The proposed limit for **pH** (3.0 to 4.0) has been based upon batch data generated to date and is considered acceptable.

With regards to **extractable volume,** the applicant has not proposed a limit for routine testing in the drug product specification. Although the fill volume is monitored by means of fill weight determination as an in-process control, the evaluator believes that an appropriate test and limit should be applied to the parenteral drug product. ***The applicant should be requested to propose an appropriate limit, or justify otherwise.***

Given that the JEVTANA® concentrated injection is further diluted with an aqueous solution containing 13% w/w ethanol, the evaluator supports the applicant's justification to control the level of ethanol in the drug product as an in-process control after the distillation process.

The acetone component of the cabazitaxel acetate solvate drug substance is removed during the distillation step of the proposed drug product manufacturing process to levels less than 10% of the permitted level of 50 mg/day allowed by ICH residual solvent guidelines for Class 3 solvents. Therefore, the justification for the exclusion of acetone testing is considered acceptable.

Microbiological aspects

The drug product manufacturer has included limits for *sterility* and *bacterial endotoxins* in the release and expiry specifications. Microbiological aspects of the product should be assessed by the Microbiology Section of OLSS and have not been discussed in this evaluation report.

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3.2.P.6 Reference Standards or Materials

The same reference standard is used in the testing of the drug product, as that used in the testing the drug substance. No data has been presented in this Module of the application, but it is acceptable in this case.

3.2.P.7 Container Closure System

The packaging component details are summarised below.

Component		Description	Supplier
Primary packaging component	Vial	15 mL Type I clear, colourless glass vial with a 20 mm outer neck diameter.	?
	Stopper	20 mm grey chlorobutyl chlorobutyl rubber stopper coated with a ethylenetetrafluoroethylene (ETFE) polymer film of approx. 0.1 mm on the product contact side.	?
Secondary packaging component	Overseal	20 mm aluminium overseal with a light green plastic Flip-Off® cap.	?

The vials containing JEVTANA® cabazitaxel concentrated injection are to be marketed in cartons as single units co-packaged with a single vial of 4.5 mL diluent.

No specifications, batch analysis data or Certificates of Analysis have been provided for any of the packaging components. However, the applicant has provided acceptable assurances that the vials and rubber stoppers comply with relevant Ph. Eur and USP packaging monographs.

The applicant should be asked to provide the supplier(s) name, address and product codes applicable to the rubber stopper component of the packaging in order to assist with the evaluation of the container closure system.

3.2.P.8 Stability

3.2.P.8.1 Stability Summary and Conclusion

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The proposed shelf life for the unopened product is 24 months (2 years) when stored below 30 °C. The additional storage condition of "Do not refrigerate" is also proposed.

The proposed Product Information (PI) makes the following stability-related statements;

- After initial dilution of JEVTANNA® cabazitaxel 60 mg/1.5 mL concentrate with the diluent, the resulting diluent mixture (pre-mix) is stable for 1 hour if stored below 30ºC;
- After final dilution in the infusion bag/bottle, the infusion solution may be stored up to 8 hours below 30ºC (including the 1 hour infusion);
- The chemical and physical stability of the infusion solution has been demonstrated for 48 hours under refrigerated conditions (below 5ºC).

Results of the compatibility studies conducted by the drug product manufacturer are discussed in Section 3.2.P.2.6 of this evaluation report.

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3.2.P.8.2 Post-approval Stability Protocol and Stability Commitment

The applicant has completed accelerated (40°C/75%RH) and long-term (25°C/60%RH) stability studies up to 6 months and 12 months respectively for the three stability batches, DI-01567, DI-01568 and DI-01569. No further testing will be carried out on these batches at the above-mentioned storage temperatures.

To date, the applicant has completed long-term (30°C/65%RH) and refrigerated (5°C) stability studies up to 12 months respectively for the three stability batches, DI-01567, DI-01568 and DI-01569. The applicant has provided the commitment to continue testing up to and including 36 months, for both of these storage temperatures for all three stability batches as per the submitted stability protocol. The assurance is acceptable.

The applicant has provided an assurance stating the remaining full scale process validation batches will be placed onto the stability program at 30ºC/65%RH and 40ºC/75%RH to be tested throughout the shelf life as per the stability testing protocol up to and including 36 months and 6 months, respectively. The assurance is acceptable.

Furthermore, the applicant has also committed that thereafter, at least one batch per year (unless none is produced that year) will be placed on the stability program for testing after storage at 30°C/65%RH up to and including 36 months. The commitment is acceptable.

3.2.P.8.3 Stability Data

Stability of the unopened product

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The following parameters were monitored during the stability studies; *appearance and colour*, *appearance of solution S*, *pH*, *water content*, *assay*, *degradation products*, *particulate contamination*, *container closure integrity*, *sterility* and *bacterial endotoxins*. Testing was not performed at every time point for *container closure integrity*, *sterility* and *bacterial endotoxins*. This is acceptable.

With regard to the stability batches, the following observations were made;

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- The pH and water content results remained stable under all storage conditions over time.

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- Levels of the degradant, RPR202670 and the total impurities remained constant over time under all storage conditions

Stability in use

The physical and chemical stability of the product after dilution with the infusion fluids; 5% Glucose injection and 0.9% Sodium Chloride injection was investigated and is discussed further in Section 3.2.P.2.6 of this evaluation report. It was confirmed that a 2-hour infusion time at ambient temperatures with polyethylene, PVC DEHP-free and PVC/DEHP sets and either infusion diluent is supported over the range of 0.10 to 0.26 mg/mL. However, the assay of solutions through the polyurethane sets revealed unacceptable decreases in assay values to below 94%. As such, the use of polyurethane infusion sets is not recommended for use with JEVTANA® cabazitaxel concentrated injection solution or its diluted solutions.

Photostability

The applicant has conducted a photostability study on one batch of JEVTANA® cabazitaxel concentrated injection solution (60 mg/1.5 mL), batch DI-01567, as per ICH guideline CPMP/ICH/279/95. Following exposure to the light, samples were analysed for *appearance and colour, appearance of solution (clarity and degree of colouration), assay, degradation products, pH, water content* and *particulate contamination*.

All results met the expiry specification limits for the test parameters, suggesting that the drug product when packaged in the proposed commercial packaging is not sensitive to light and does not require secondary protection from light. The stability data presented are acceptable.

Freeze/thaw study

A freeze/thaw study was conducted on the two batches (DI-01522 and DI-01569). The study was conducted over three days using vials stored in both inverted and upright orientations. Samples were stored at -20°C for 3 days followed by storage at 30°C/65%RH for 4 days. The cycle was repeated three times. No significant changes or trends were observed during the study. The stability data presented are acceptable.

Conclusions regarding the proposed shelf life

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Furthermore, based on the results of the additional in-use and compatibility testing conducted by the applicant, the following statements in the PI are considered justified.

- After initial dilution of JEVTANNA® cabazitaxel 60 mg/1.5 mL concentrate with the diluent, the resulting diluent mixture (pre-mix) is stable for 1 hour if stored below 30ºC;
- After final dilution in the infusion bag/bottle, the infusion solution may be stored up to 8 hours below 30ºC (including the 1 hour infusion);

- The chemical and physical stability of the infusion solution has been demonstrated for 48 hours under refrigerated conditions (below 5ºC).

Module 3.2.P: Drug Product – Diluent

3.2.P.1 Description and Composition of the Drug Product

The diluent for JEVTANA® cabazitaxel 60 mg/1.5 mL concentrated injection is a single-use, preservative-free, sterile, aqueous solution containing 13 %w/w solution of ethanol (96%) presented as a 4.5 mL volume.

The diluent is a clear colourless liquid and is packaged in a 15 mL Type I clear glass vial, closed with a grey chlorobutyl rubber closure coated with a transparent ETFE coating and capped with a gold-coloured aluminium cap covered with a colourless plastic flip-off cap.

Each diluent vial is to be packaged as a single unit into a carton accompanied by one vial of JEVTANA® cabazitaxel 60 mg/1.5 mL concentrated injection. The chemistry, manufacturing and quality control data relating to the JEVTANA® drug product has been evaluated and is presented earlier in *Module 3.2.P, Drug Product (Injection, Concentrated).*

Formulation details for the diluent are tabulated below.

Ingredient	Quantity per vial (mg or mL)	Quantity (%)	Standard	Function
Ethanol (96%)	573.3 mg	13 % w/w#	Ph.Eur./USP-NF	Solvent
Water for injection	q.s. to 4.5 mL	q.s. to 100%	Ph. Eur./USP/JP	Solvent

Corresponds to a solution at 12 %w/w ethanol-absolute.

Of note, a 26% overfilling of the diluent vials is intended to allow removal of an accurate dose of pre-mix at 10 mg/mL after addition of the JEVTANA® concentrate. The target fill volume is 5.67mL, equivalent to a corresponding target fill weight of 5.557 g.

3.2.P.2 Pharmaceutical Development

The JEVTANA® cabazitaxel 60 mg/1.5mL concentrate injection is to viscous to be added directly to an infusion solution and therefore a diluent was required to prepare a premix solution at 10 mg/mL. The diluent was based on the solvent for dilution supplied with the marketed Taxotere® docetaxel 80 mg/2 mL concentrate injection vial + diluent vial (AUST R 53455).

The two diluent formulations have the same qualitative composition and concentration of ethanol as indicated below.

Components	Composition for solvent for cabazitaxel 60 mg/1.5 mL (Per vial)	Composition for solvent for Taxotere® 80mg/2mL (Per vial)
Alcohol (a)	573.3 mg	764.4 mg
Water for Injection qs(b)	4.5 mL	6 mL
Concentration in ethanol	13 % w/w (c)	13 % w/w (c)

(a): USP standard term corresponding to ethanol 96 % Ph. Eur.
(b): sufficient quantity
(c): corresponding to a solution at 12 % w/w ethanol 100 % v/v

No ingredients derived from animal origin or genetically modified organisms are used in the manufacture of the diluent.

There is no manufacturing overage for the diluent.

Drug Product – Diluent

The diluent is packaged in the same packaging components as those used to package the accompanying diluent for the Taxotere® docetaxel 80 mg/2 mL concentrate injection drug product. Given this, the applicant has chosen not to conduct any further extractables/leechables studies and this is acceptable, given the similar nature of the respective taxane drug substances.

Compatibility studies have been discussed in Section 3.2.P.2.6 for the Injection Concentrate.

The Microbiology Section of OLSS should be requested to assess sterility and other microbiological aspects of the drug product development.

3.2.P.3 Manufacture

3.2.P.3.1 Manufacturers

s47G [redacted]

s47G [redacted] Please *refer to Module 1 – GMP Status of Manufacturers and Packers* later in this evaluation report for an assessment of the proposed manufacturing site.

3.2.P.3.2 Batch Formula

The proposed maximum commercial batch size for the manufacture of the JEVTANA® diluent vial presentation is 90 kg, equivalent to approximately 16,000 vials, assuming a target fill volume of 5.67 mL (corresponding to 5.557 g). Details of the batch formula are presented in the table below. No overages are used in the formulation of the proposed drug product.

Components	Amount per 90 kg batch
Ethanol	11.7 kg
Water for injection	q.s. to 90 kg

3.2.P.3.3 Description of Manufacturing Process and Process Controls

A copy of the manufacturing process flow chart is provided in **Appendix 4** at the end of this evaluation report. The manufacturing process is a simple one and conventional for the dosage form (i.e. mixing, filtration of the bulk solution using a sterilised 0.2µm hydrophilic filter, and terminal sterilisation [steam/autoclave for NLT 121°C for a minimum of 15 minutes]).

Sterility aspects of the manufacturing process should be referred to the Microbiology Section of OLSS for assessment.

3.2.P.3.4 Controls of Critical Steps and Intermediates

A bioburden limit of NMT 50 cfu/mL is applied prior to sterile filtration of the aqueous solution containing 13% ethanol, through sterilised 0.2µm hydrophilic filters. The theoretical target fill weight is 5.557 ± 4% with fill weight check conducted during the filling process.

No intermediate products are isolated during the manufacture of the JEVTANA® diluent.

Drug Product – Diluent

3.2.P.3.5 Process Validation and/or Evaluation

Sterile process validation and evaluation of the aseptic manufacturing process for the JEVTANA® diluent is provided and should be assessed by the Microbiology Section of OLSS.

With respect to the chemical validation of the manufacturing process, the applicant has provided process validation data for three consecutive primary stability batches as described below. The batch sizes correspond to the proposed commercial batch size (90 kg) nominated in Section 3.2.P.3.2.

Batch number	DI-01572 D8C613	DI-01573 D8C614	DI-01574 D8C615
Batch type	Stability	Stability	Stability
Presentation	4.5 mL		
Solution batch size	90 kg	90 kg	90 kg
Number of vials filled per batch	10,384 (a)	10,416 (a)	10,320 (a)
Manufacturing site	Dagenham	Dagenham	Dagenham
Manufacturing date	Oct 2008	Oct 2008	Oct 2008
Ethanol batch number	D803463	D803373	D803625

(a): a part of the 90 kg was used corresponding to manufacturing of clinical supply and stability needs

All batches met the specified in-process and finished product controls, thus demonstrating consistent quality from batch to batch. The data presented is acceptable.

3.2.P.4 Control of Excipients

The two excipients, *ethanol* and *water for injections*, are conventional and both comply with the harmonised Ph. Eur./USP-NF/JP monographs applicable to each excipient. The applicant will be requested to confirm that water for injections is manufactured by distillation and not by reverse osmosis. The applicant provided no certificates of analysis, specifications or test methods, but as these are monographed excipients, this is considered acceptable.

No excipient of human or animal origin has been used in the manufacture of the drug product.

3.2.P.5 Control of Drug Product

3.2.P.5.1 Specifications

The applicant has provided a combined in-house release and expiry specification for the JEVTANA® diluent, a copy of which is provided in **Appendix 5** at the end of this evaluation report.

The proposed release and expiry limits for all test parameters are equivalent.

The frequency with which the drug product manufacturer will perform each test at release has not been stated. ***The applicant should be asked to confirm that each test will be performed on every batch, or justify otherwise.***

Drug Product – Diluent

3.2.P.5.2 Analytical Procedures

The proposed analytical procedures for the assessment of *appearance of solution (clarity and degree of colour)*, *identification of ethanol* via GC, *uniformity of dosage units* and *particulate contamination* are based upon Ph. Eur. pharmacopoeial monographs. No validation reports have been provided for the pharmacopoeial methods and this is acceptable.

The analytical procedures for the assessment of *sterility* and *bacterial endotoxins* also reference Ph. Eur. pharmacopoeial methods, however, microbial aspects of the drug product should be referred to the Microbiology Section of OLSS for assessment.

An in-house GC analytical method is used for the *identification* and determination of the *content* of ethanol (Method No. CMC-PA-2009-19799). Capillary GC determines the levels of ethanol with a flame ionisation detector. 1-propanol is used as the internal standard.

3.2.P.5.3 Validation of Analytical Procedures

Identification and Assay content of Ethanol by GC (Method No. CMC-PA-2009-19799)

The method has been satisfactorily validated in terms of specificity, linearity, accuracy, precision and robustness. The validation data are acceptable.

Microbiological tests

Microbiological aspects of the drug product should be referred to the Microbiology Section of OLSS for assessment.

3.2.P.5.4 Batch Analyses

Batch analysis data were provided for the three stability batches and an additional batch (DI-01529), the results of which are summarised below. All four batches were manufactured at the 20 L commercial scale and at the proposed manufacturing site. Details of the three stability batches are specified in Section 3.2.P.3.5 (Diluent) of this evaluation report.

The results, which comply with the proposed specifications, are summarised below.

Test	Specification	Range of Results
Ethanol content	11.4 – 12.6 %w/w (95.0 – 105.0%)	11.8 – 12.2% (98.3 – 101.7%)
Particulate contamination No. of particles per container ≥ 10 µm No. of particles per container ≥ 25 µm	 ≤ 6000 ≤ 600	 5 – 10 0 - 2
Fill volume[#]	5.39 – 5.95 mL (mean = 5.67mL)	5.68 – 5.70 mL

[#] Not proposed in the release and expiry specification

3.2.P.5.5 Characterisation of Impurities

There are no impurities that require identification.

3.2.P.5.6 Justification of Specifications

Identification tests

The GC identification test for ethanol and the identification of ethanol through the reaction with iodine (as per Ph. Eur. monograph for ethanol anhydrous, Identity test D) are acceptable.

Drug Product – Diluent

Assay - Ethanol

The proposed release and expiry assay limit of 95.0 – 105.0% of the nominal concentration of ethanol in the diluent is considered acceptable.

Particulate contamination

The proposed limit complies with the Ph. Eur. monograph 2.9.19 and the USP <788> for solutions for parenteral infusion or solution for injection supplied in containers with a nominal content of less than 100 mL. The proposed limit is acceptable.

Uniformity of Dosage Units

The proposed limit for uniformity of dosage units (by mass variation) complies with Ph. Eur. 2.9.40 and is considered acceptable.

Extractable volume/Fill volume

With regards to **extractable volume,** the applicant has not proposed a limit for routine testing in the drug product specification. Although the fill volume is monitored by means of fill weight determination as an in-process control, the evaluator believes that an appropriate test and limit should be applied to the parenteral drug product. ***The applicant should be requested to propose an appropriate limit, or justify otherwise.***

Microbiological aspects

The drug product manufacturer has included limits for *sterility* and *bacterial endotoxins* in the release and expiry specifications. Microbiological aspects of the product should be assessed by the Microbiology Section of OLSS and have not been discussed in this evaluation report.

3.2.P.6 Reference Standards or Materials

Ethanol anhydrous Ph. Eur. is used as a reference standard in the testing of the JEVTANA® diluent.

3.2.P.7 Container Closure System

The packaging component details are identical to those proposed for packaging the JEVTANA® cabazitaxel 60 mg/1.5 mL concentrated injection. Please refer to Section 3.2.P.7 – Container Closure System (Injection, Concentrated) earlier in this evaluation report for any comments.

3.2.P.8 Stability

3.2.P.8.1 Stability Summary and Conclusion

The stability of the product under accelerated (40ºC/75%RH), long term (30ºC/65%RH and 25ºC/60%RH) and refrigerated (5ºC) storage conditions has been investigated as summarised below in Section 3.2.P.8.3. Vials have been stored in the upright and inverted orientations.

The proposed shelf life for the unopened diluent vial is 36 months (3 years) when stored below 30 °C. No additional storage conditions are proposed.

Results of the compatibility studies conducted by the drug product manufacturer are discussed in Section 3.2.P.2.6 (Injection, Concentrated) of this evaluation report.

Drug Product – Diluent

3.2.P.8.2 Post-approval Stability Protocol and Stability Commitment

The applicant has completed accelerated (40°C/75%RH) and long-term (25°C/60%RH) stability studies up to 6 months and 12 months respectively for the three primary stability batches, DI-01572, DI-01573and DI-01574. No further testing will be carried out on these batches at the above-mentioned storage temperatures.

To date, the applicant has completed long-term (30°C/65%RH) and refrigerated (5°C) stability studies up to 12 months respectively for the three stability batches, DI-01572, DI-01573 and DI-01574. The applicant has provided the commitment to continue testing up to and including 36 months, for both of these storage temperatures for all three stability batches as per the submitted stability protocol. The assurance is acceptable.

The applicant has provided an assurance stating the full scale process validation batches will be placed onto the stability program at 30ºC/65%RH to be tested throughout the shelf life as per the stability testing protocol up to and including 36 months. The assurance is acceptable.

Furthermore, the applicant has also committed that thereafter, at least one batch per year (unless none is produced that year) will be placed on the stability program for testing after storage at 30°C/65%RH up to and including 36 months. The commitment is acceptable.

3.2.P.8.3 Stability Data

Stability of the unopened product

Stability data have been provided for three **'primary'** batches of product (DI-01567, DI-01568 and DI-01569) manufactured at a 90 kg production scale by the proposed drug product manufacturing site, *Aventis Pharma Dagenham, UK*. These batches have been stored for 12 months at 5ºC, 25°C/60%RH and 30°C/65%RH and for 6 months at 40ºC/75%RH. The batches have been packaged in packaging equivalent to that proposed for marketing in Australia.

The applicant has also provided **'supportive'** stability data for three batches of Taxotere® diluent (J0530, J0531 and J0556). The Taxotere® diluent formulation has the same percentage composition as the JEVTANA® diluent (13 %w/w) and only the filling volumes differ (6.0 mL vs. 4.5mL). The supportive stability batches have been manufactured at a commercial batch size (90 kg) and at the same manufacturing site as that proposed for the JEVTANA® diluent, namely, Aventis Pharma Dagenham, Essex, UK. These batches have been stored under 4-8ºC, 25ºC and 45ºC conditions in both upright and inverted positions. The evaluator believes that the supportive stability data is relevant to the chemical and physical stability of the proposed JEVTANA® diluent drug product.

The following parameters were monitored during the stability studies; *appearance, degree of coloration and of opulescence, ethanol content, particulate contamination, container closure integrity, sterility* and *bacterial endotoxins*. Testing was not performed at every time point for *container closure integrity, sterility* and *bacterial endotoxins.* This is acceptable.

With regard to the **'primary'** stability batches, the following observations were made;

- No significant differences were observed in the stability results generated for vials stored in the upright and inverted positions.

Drug Product – Diluent

- All results for all three batches stored under 5ºC, 25°C/60%RH, and 30°C/65%RH conditions for 12 months and 40ºC/75%RH for 6 months, met the proposed expiry specification.

With regard to the **'supportive'** stability batches, the following observations were made;

- No significant differences were observed in the stability results generated for vials stored in the upright and inverted positions.
- All results for all three batches stored under 4-8ºC, 25°C, and 45°C conditions for 36 months met the proposed expiry specification.

Stability in use

Refer to Section 3.2.P.8.3 (Injection, Concentrated) for relevant information.

Photostability

The applicant has conducted a photostability study on one batch of JEVTANA® diluent, batch DI-01572, as per ICH guideline CPMP/ICH/279/95. Following exposure to the light, samples were analysed for *appearance*, *degree of coloration and of opalescence*, *ethanol content*, and *particulate contamination*.

All results met the expiry specification limits for the test parameters, suggesting that the diluent when packaged in the proposed commercial packaging is not sensitive to light and does not require secondary protection from light. The stability data presented are acceptable.

Conclusions regarding the proposed shelf life

Based on the chemical and physical data generated to date, the evaluator believes that a shelf life of 36 months when stored below 30°C is justified.

Module 1: Administrative and Product Usage Information

GMP Status of Manufacturers and Packers

The following sites of manufacture and packaging are proposed.

1. s47G [redacted]

   GMP: At the time of submission, GMP clearance of this site by the TGA Office of Manufacturing Quality (OMQ) was pending although no application number was provided in the application. ***The applicant should advise as to the current status of this matter and provide a copy of any GMP clearance letter since issued by the OMQ.***

2. s47G [redacted]

   GMP: Acceptable, but the GMP clearance expired on 16/01/2011. A copy of the GMP clearance letter was provided in Module 1.7 of the submission.
   The applicant should advise as to the current status of this matter, and provide a copy of any GMP clearance letter since issued by the TGA Office of Manufacturing Quality (OMQ).

3. s47G [redacted]

   GMP: GMP evidence is acceptable. The GMP clearance remains current until 27/08/2012.

4. s47G [redacted]

5. s47G [redacted]

6. s47G [redacted]

7. s47G [redacted]

8. s47G [redacted]

Provisional ARTG Record (PAR)

The applicant did not provide a Provisional Record (PAR) for review. However, at a later date, the draft PAR, updated as appropriate from the evaluations, will be sent to the applicant for verification.

Labelling

The applicant has submitted colour mock-up labels for the proposed JEVTANA® carton and vial, and DILUENT vial in Module 1.3.4 for consideration.

Although no text or mock-up labels were provided for "CABAZITAXEL WINTHROP" or "CABAZITAXEL SANOFI", it should be assumed by the applicant that the comments below would be relevant to the labelling for each of the above-mentioned drug products.

The draft labelling complies with the Labelling Order (TGO 69) and the *'Best Practice Guideline on Prescription Medicines Labelling'*, except for the following deficiencies.

The **carton label** should be amended as follows;

- ***Please replace 'ethanol 96%' with 'ethanol' to reflect the Australian Approved Name (AAN) for the excipient.***
- The PI refers to the co-packaged diluent vial containing 13 %w/w ethanol in water for injection as 'DILUENT', but the carton label refers to it as 'solvent'. ***For consistency, please replace 'solvent' with 'diluent'.***
- Although the applicant has identified on the front label that the dosage form of the drug product is a concentrated injection, the evaluator has concerns with the statement "Cabazitaxel 60 mg in 1.5 mL for intravenous injection" which is located prominently beneath the drug substance name. It would be preferable to revise the statement to *"Contains 60 mg of cabazitaxel in a 1.5 mL concentrated injection"*, or something to that effect. ***The applicant should be asked to comment and revise the carton label if necessary.***
- ***For consistency, please use either 'mL' or 'ml' on the carton label, but not both.***
- ***Please adjust the placement of 'anti' so that the word 'antimicrobial' is visualised as one word.***
- The statement *"CYTOTOXIC AGENT. To prepare and administered by trained personnel"* does not read correctly. ***Please revise the statement to read as "To be prepared and administered by trained personnel".***

The **JEVTANA® vial label** should be amended as follows;

- ***As per TGO 69, Clause 3(11)(c), the name or registered trademark of the sponsor or supplier of the proprietary name should be included on the label.***

The **DILUENT vial label** should be amended as follows;

- The PI refers to the co-packaged diluent vial containing 13 %w/w ethanol in water for injection as 'DILUENT', but the vial label refers to it as 'SOLVENT'. ***For consistency, please replace 'SOLVENT with 'DILUENT'.***
- The statement "60 mg/1.5 mL concentrated injection" is considered misleading on the solvent vial as this information is relevant only to the JEVTANA® concentrated injection vial. ***Please remove the statement and increase the prominence of the vial contents i.e "Each vial contains 13 %w/w ethanol in water for injections to 4.5 mL".***
- ***As per TGO 69, Clause 3(11)(c), the name or registered trademark of the sponsor or supplier of the proprietary name should be included on the label.***

The **Package Insert** should be amended as follows;

- The PI refers to the co-packaged diluent vial containing 13 %w/w ethanol in water for injection as 'DILUENT', but the package insert refers to it as 'solvent'. ***For consistency, please replace 'solvent' with 'diluent'.***
- ***For consistency, please use either 'mL' or 'ml' in the package insert, but not both.***
- ***Beneath the Shelf Life and Special Precautions for Storage heading, 5th paragraph, please correct the sentence to read as "….has been demonstrated for 48 hours under ~~refrigerate~~ refrigerated conditions".***

Note:

1. The labelling has not been assessed by this evaluator for compliance with Australian State requirements.
2. The acceptability or otherwise of the proposed brand name is a matter for the clinical evaluator to assess.

Product Information (PI)

A copy of the draft PI was provided in Module 1.3.1 of the application. The chemical and pharmaceutical aspects of the PI are satisfactory apart from the following issues.

Description (Page 1)

- ***Please correct the chemical name of the drug substance, cabazitaxel to "(2α,5β,7β,10β, 13α)-4-(acetyloxy)-13-({(…….".***
- ***Please replace "835.93 (for the diluent free)" to "835.93 (for the solvent free)".***
- ***Please remove "(anhydrous and diluent free)" from the 4th paragraph after cabazitaxel.***

Consumer Medicine Information (CMI)

This evaluator has not reviewed the CMI.

III. Summary of Initial Evaluation

The application and the supporting data relating to the composition, development, manufacture, quality control and stability of the product have been assessed and checked for compliance, as applicable, with Australian legislation and requirements for new medicines and in accordance with pharmacopoeial standards and the technical guidelines adopted by the TGA.

Primary assessment

A number of significant deficiencies in the application data were identified during the initial assessment. Registration approval **is not recommended** until satisfactory responses are provided to the issues identified below.

Drug Product – JEVTANA® concentrated injection

1. It is unclear from the information provided in the submission whether the excipient, polysorbate 80, is purchased with the pH already adjusted to pH 3.5 **or** whether the drug product manufacturer makes the pH adjustment using citric acid monohydrate prior to use in the manufacturing process. **Please clarify.** If the later option is applicable, the applicant will need to provide an assurance that the following items have been addressed;

    - Citric acid monohydrate will need to be included in the drug product formulation
    - Citric acid monohydrate will need to be added as an excipient to the JEVTANA® Product Information.
    - An assurance is to be provided to state that citric acid monohydrate is tested for compliance with relevant pharmacopoeial monographs

2. With regard to the proposed drug product specification, please confirm that each test will be performed on every batch, or justify otherwise.

3. With regard to the batch analysis results quoted for *total degradation products*, please provide an explanation for the observed difference in results for batches D8A653, D8C599, D8C600 and D8C601.

4. With regard to the proposed specifications applied to the drug product;

    (a) Please tighten the proposed expiry assay limit to 95.0 – 105.0% to be consistent with the release limits, or justify otherwise.

    (b) Based on batch release and stability data generated to date, please propose a tighter expiry limit for *total degradation products*, or justify otherwise.

    (c) Please include an appropriate test and limit for *extractable* volume in the specification and test methods, or justify otherwise.

    (d) Based on batch release and stability data generated to date, please tighten the water content limits, or justify otherwise.

5. With regard to the drug product container/closure system, please specify supplier names, manufacturing address and any associated product codes for the elastomeric components of the container closure system.

6. The stability data in the submission does not support the proposed shelf life of 24 months when stored below 30ºC. Please provide updated stability data for batches DI-01567, DI-01568 and DI-01569 to support the proposed shelf life.

Drug Product – JEVTANA® DILUENT

7. With regard to the proposed drug product specification;

   (a) Please confirm that each test will be performed on every batch, or justify otherwise.

   (b) Please include an appropriate test and limit for *extractable* volume in the specification and test methods, or justify otherwise.

Module 1 Matters

8. Please provide an update of the regulatory status of any overseas submissions, which have changed since the date of submission for the Australian dossier.

9. At the time of submission, the GMP clearance for the drug substance manufacturer, s47G [redacted] was still pending. Please advise as to the current status of this matter and provide a copy of any GMP clearance letter since issued by the Office of Manufacturing Quality.

10. The GMP clearance letter for s47G [redacted] was acceptable at the time of submission, but has since expired (16-Jan-2011). Please advise as to the current status of this matter and provide a copy of any GMP clearance letter since issued by the Office of Manufacturing Quality.

11. In relation to the proposed JEVTANA® concentrate injection **carton** and **vial** labels, please address the following and provide revised colour mock-up labels for evaluation.

    (a) Please replace 'ethanol 96%' with 'ethanol' to reflect the Australian Approved Name (AAN) for the excipient.

    (b) The Product Information (PI) refers to the co-packaged diluent vial containing 13 %w/w ethanol in water for injection as 'DILUENT', but the carton label refers to it as 'solvent'. For consistency, please replace 'solvent' with 'diluent'.

    (c) Although the applicant has identified on the front label that the dosage form of the drug product is a concentrated injection, the evaluator has concerns with the statement "Cabazitaxel 60 mg in 1.5 mL for intravenous injection" which is located prominently beneath the drug substance name. It would be preferable to revise the statement to *"Contains 60 mg of cabazitaxel in a 1.5 mL concentrated injection"*, or something to that effect. The applicant should be asked to comment and revise the carton label if necessary.

    (d) For consistency, please use either 'mL' or 'ml' on the carton label, but not both.

    (e) Please adjust the placement of 'anti' so that the word 'antimicrobial' is visualised as one word.

    (f) The statement "CYTOTOXIC AGENT. To prepare and administered by trained personnel" does not read correctly. Please revise the statement to read as "To **be** prepare**d** and administered by trained personnel".

    (g) As per TGO 69, Clause 3(11)(c), the name or registered trademark of the sponsor or supplier of the proprietary name should be included on the JEVTANA® **vial** label.

12. In relation to the JEVTANA® DILUENT **vial** label, please address the following and provide revised colour mock-up labels for evaluation.

    (a) The PI refers to the co-packaged diluent vial containing 13 %w/w ethanol in water for injection as 'DILUENT', but the vial label refers to it as 'SOLVENT'. For consistency, please replace 'SOLVENT with 'DILUENT'.

    (b) The statement "60 mg/1.5 mL concentrated injection" is considered misleading on the diluent vial as this information is relevant only to the JEVTANA® concentrated injection vial. Please remove the statement and increase the prominence of the vial contents i.e "Each vial contains 13 %w/w ethanol in water for injections to 4.5 mL".

    (c) As per TGO 69, Clause 3(11)(c), the name or registered trademark of the sponsor or supplier of the proprietary name should be included on the label.

13. In relation to the draft **Package Insert** provided inside the carton, please address the following and provide a revised package insert for evaluation.

    (a) The PI refers to the co-packaged diluent vial containing 13 %w/w ethanol in water for injection as 'DILUENT', but the package insert refers to it as 'solvent'. For consistency, please replace 'solvent' with 'diluent'.

    (b) For consistency, please use either 'mL' or 'ml' in the package insert, but not both.

    (c) Beneath the Shelf Life and Special Precautions for Storage heading, 5th paragraph, please correct the sentence to read as "….has been demonstrated for 48 hours under ~~refrigerate~~ refrigerate**d** conditions".

14. In relation to the draft **Product Information** document (PI), please address the following and provide a revised document for evaluation.

    <u>Description section (Page 1)</u>

    (a) Please correct the chemical name of the drug substance, cabazitaxel to "(2α,5β,7β,10β, 13α)-4-(acet**yl**oxy)-13-({(……".

    (b) Please replace "835.93 (for the diluent free)" with "835.93 (for the **solvent** free)".

    (c) Please remove "(anhydrous and diluent free)" from the 4th paragraph after cabazitaxel.

VI. Annexes to this Report

Copies of the following documents are appended to this report.

Appendix	Document
1	Cabazitaxel (acetone solvate) drug substance specification
2	Manufacturing process flow chart for the JEVTANA® concentrate injection drug product
3	Copy of JEVTANA® concentrate injection release and expiry specification
4	Manufacturing process flow chart for the JEVTANA® diluent
5	Copy of JEVTANA® diluent release and expiry specification

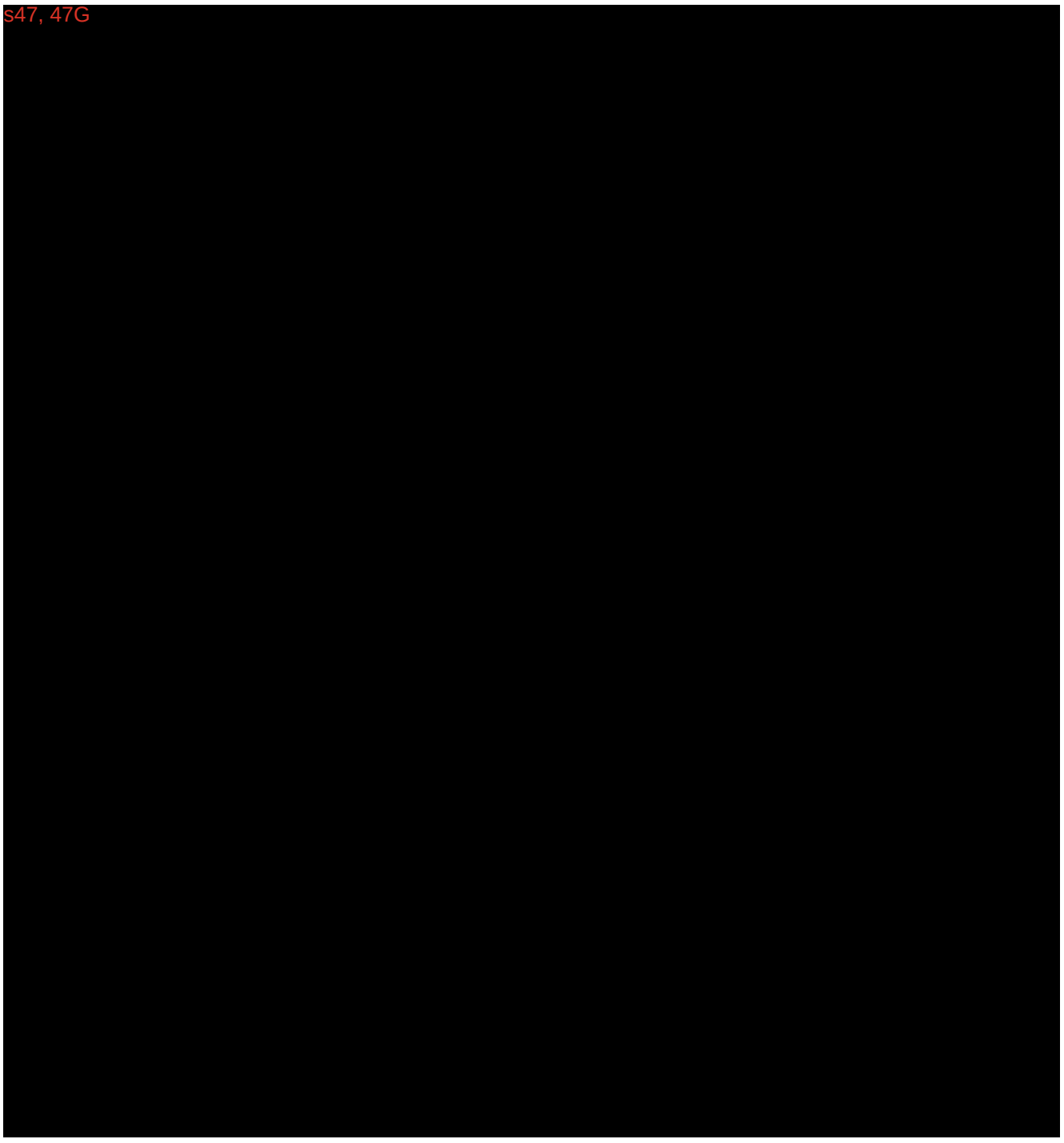
s22 [redacted]

s22 [redacted]
PharmaReg Consulting Pty Ltd

18 March 2011

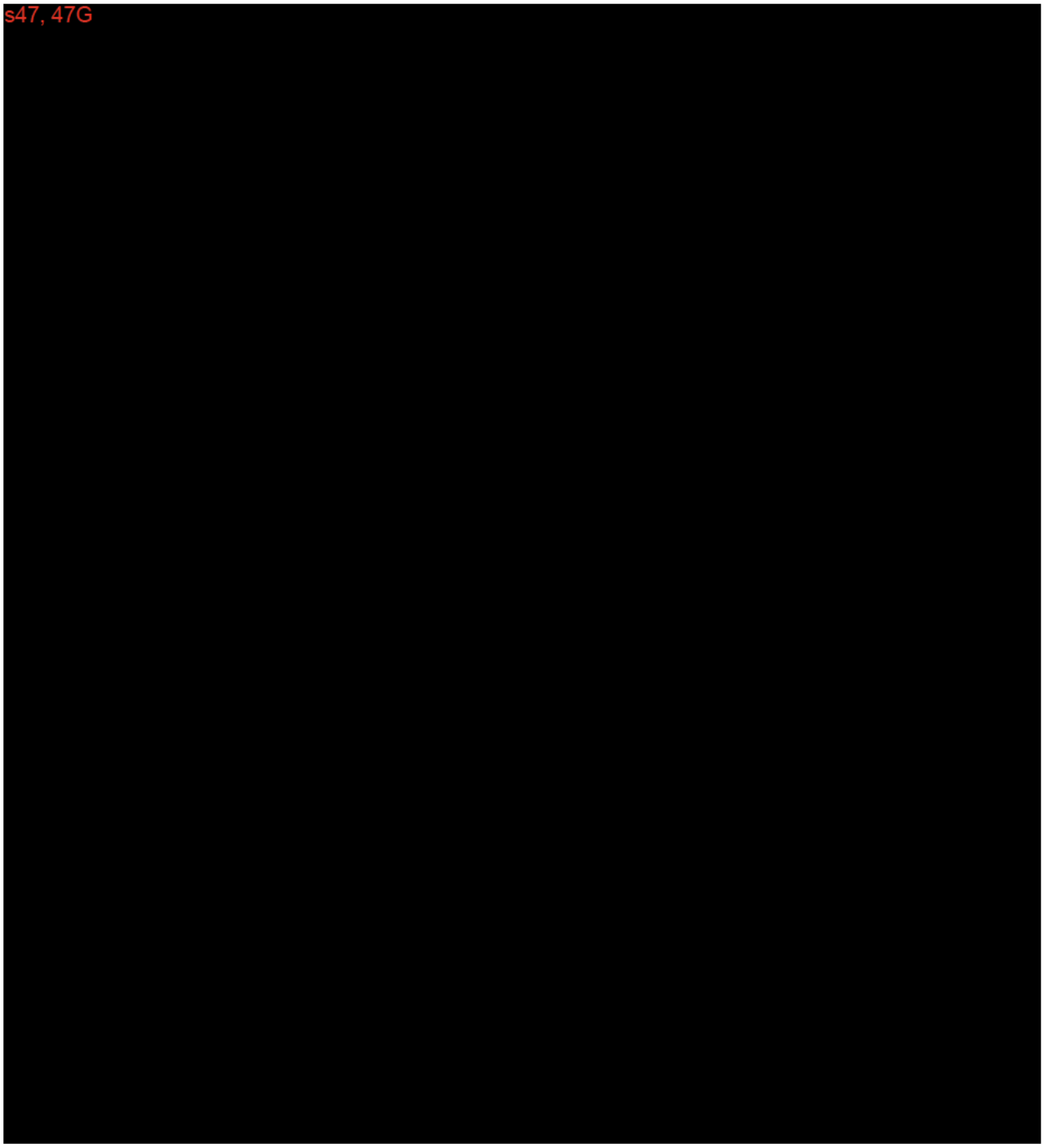
Appendix 1

s47, 47G



Appendix 2

s47, 47G



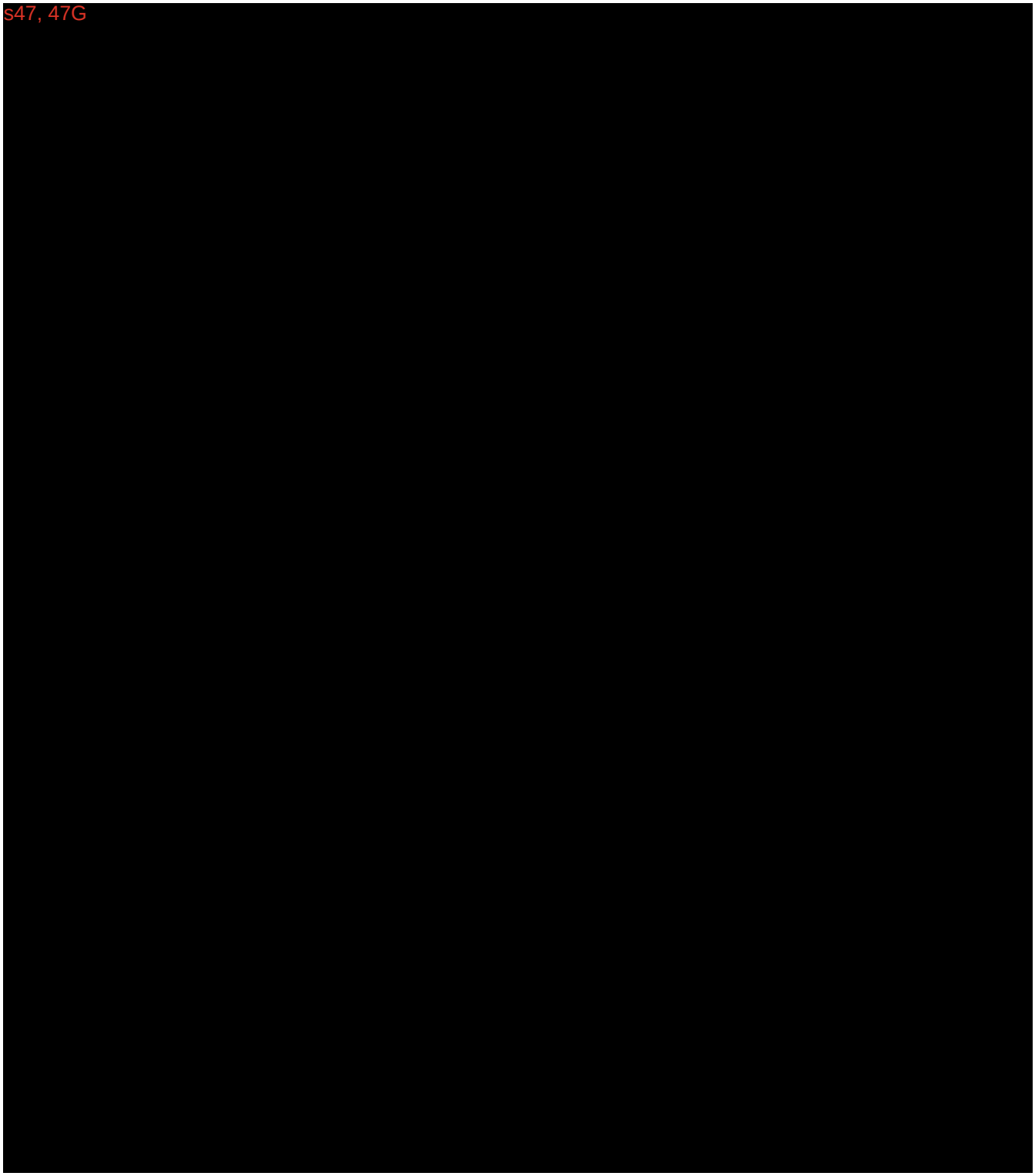
s47, 47G

[redacted]

Appendix 4

s47, 47G

s47, 47G



3.2.P.2.6 COMPATIBILITY

Cabazitaxel, concentrate for solution for infusion, 60 mg/1.5 mL

Date: Jan-2010 Total number of pages: 43

3.2.P.2.6 COMPATIBILITY
Cabazitaxel, concentrate for solution for infusion

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1 INTRODUCTION

This report presents the results of the compatibility study performed to support the conditions of use of cabazitaxel infusion solution (storage time, storage conditions, compatibility with various infusion bags).

The infusion solution is prepared from an intermediate premix solution at 60 mg/ 6 mL (nominal concentration).
This premix solution is prepared under aseptic conditions by adding the contents of the solvent vial (4.5 mL nominal volume of 13 % w/w ethanol solution in water for injection) to the cabazitaxel concentrate for solution for infusion vial (cabazitaxel 60 mg/1.5 mL concentrate).
Based on the targeted dose to be administered, the required quantity of premix is then diluted under aseptic conditions with 0.9 % sodium chloride solution or 5 % dextrose by a healthcare professional.
The final concentration of the diluted solution can range between 0.10 and 0.25 mg/mL.

In order to support the targeted instructions for use of the infusion solutions, three studies were conducted :

- a chemical compatibility study with infusion containers (bags/bottles),
- a physical compatibility study with infusion containers (bags/bottles),
- an in-use stability study mimicking infusion conditions,

The different infusion containers selected were :

- glass bottle,
- multilayer polyolefin bag made of polypropylene as external layer and polyethylene as internal layer,
- low density polyethylene bag and
- DEHP containing polyvinyl chloride (PVC) bag.

The different infusion tubings (or infusion sets) selected were made of PVC /DEHP, PVC DEHP-free, polyolefin (PVC lined with polyethylene) and polyurethane, with 0.22 µm on-line filter (supplied with the sets or added). Since use of *peristaltic pumps* is considered as a more stressful way of infusion compared to gravity, all the tests have been performed using the pump adapted to the different sets.
The different sets have been tested with cabazitaxel infusion solutions prepared at 0.10 or 0.26 mg/mL in 250 mL glass bottle of 5 % dextrose or 0.9 % sodium chloride according to an experimental matrix and infused through the sets for 2 hours (worst case as compared to recommended one-hour infusion time).

For the chemical compatibility study, the infusion bags, prepared from an extemporaneously reconstituted premix (used within 1 hour), were stored up to 48 hours *in static position* at 5°C and 30 °C and evaluated at different time points in terms of visual appearance, pH, assay and

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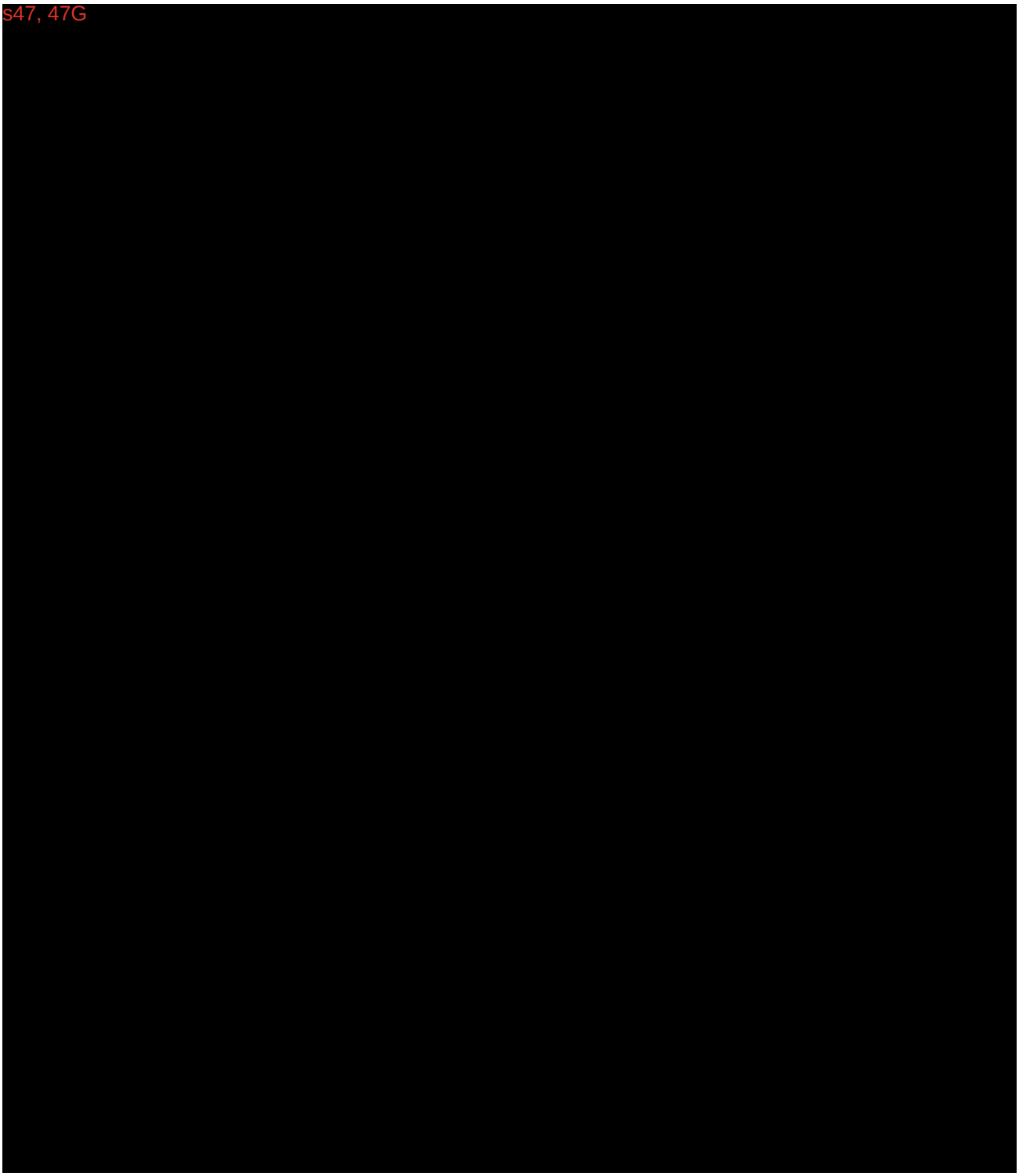

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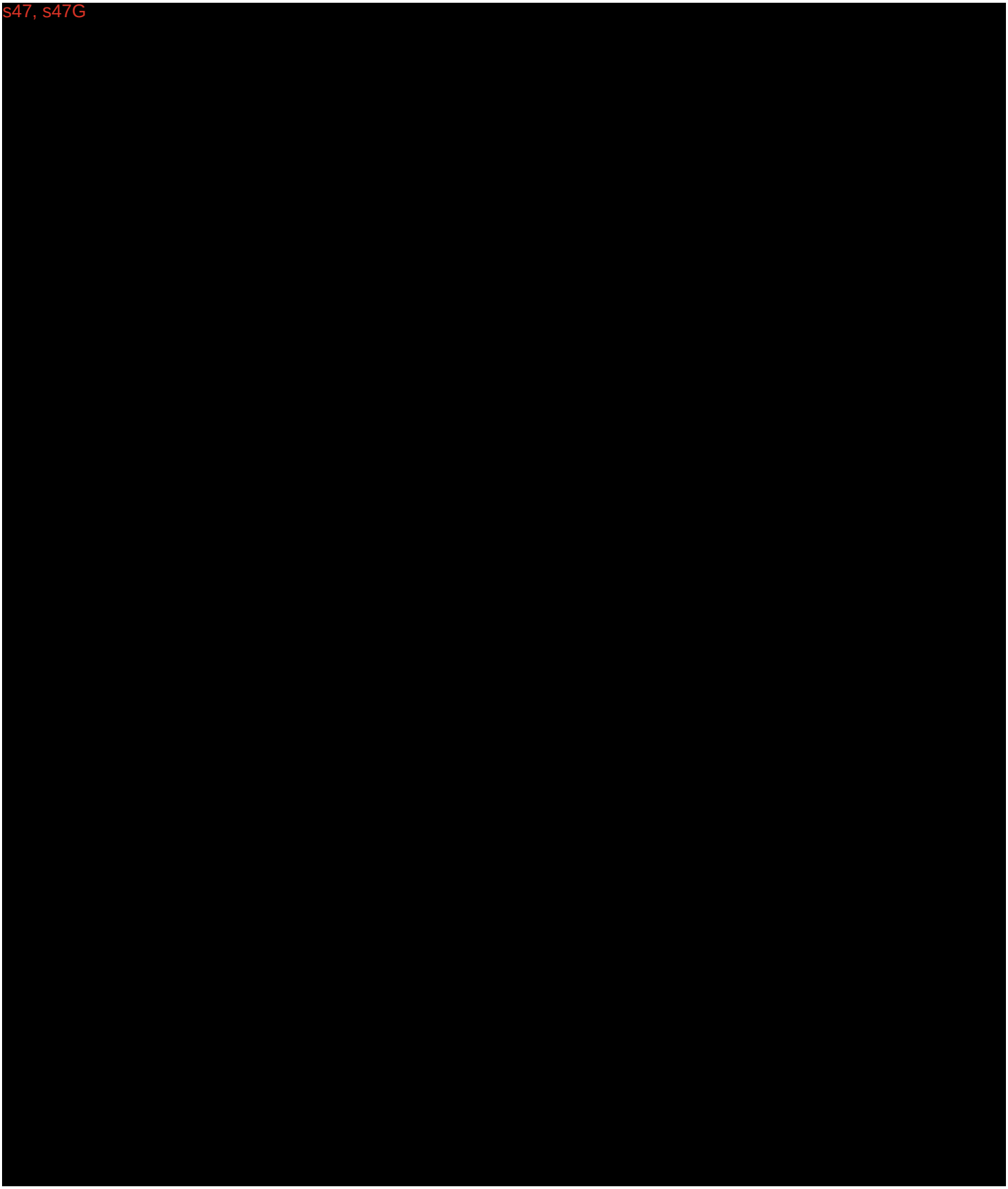

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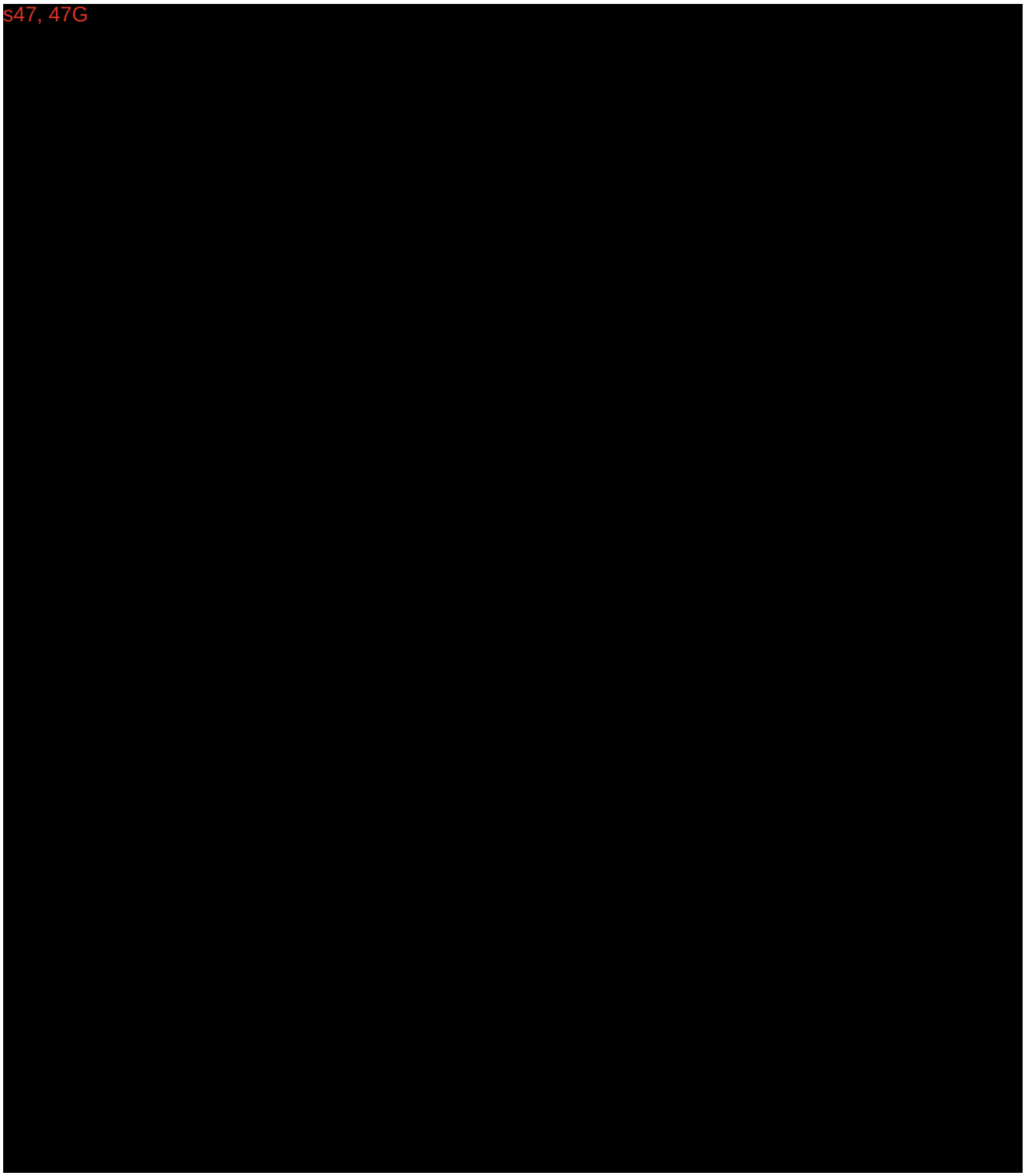

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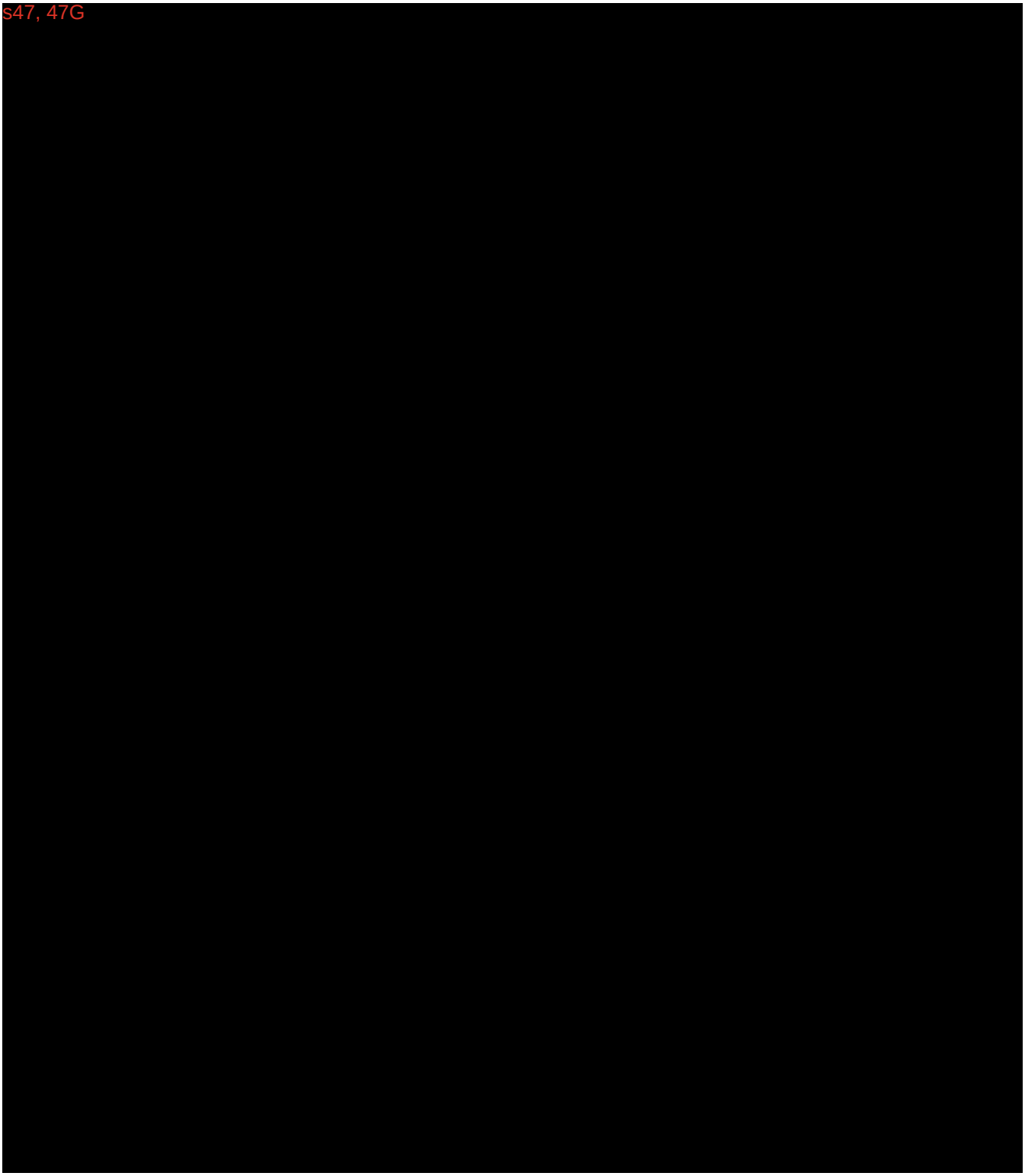

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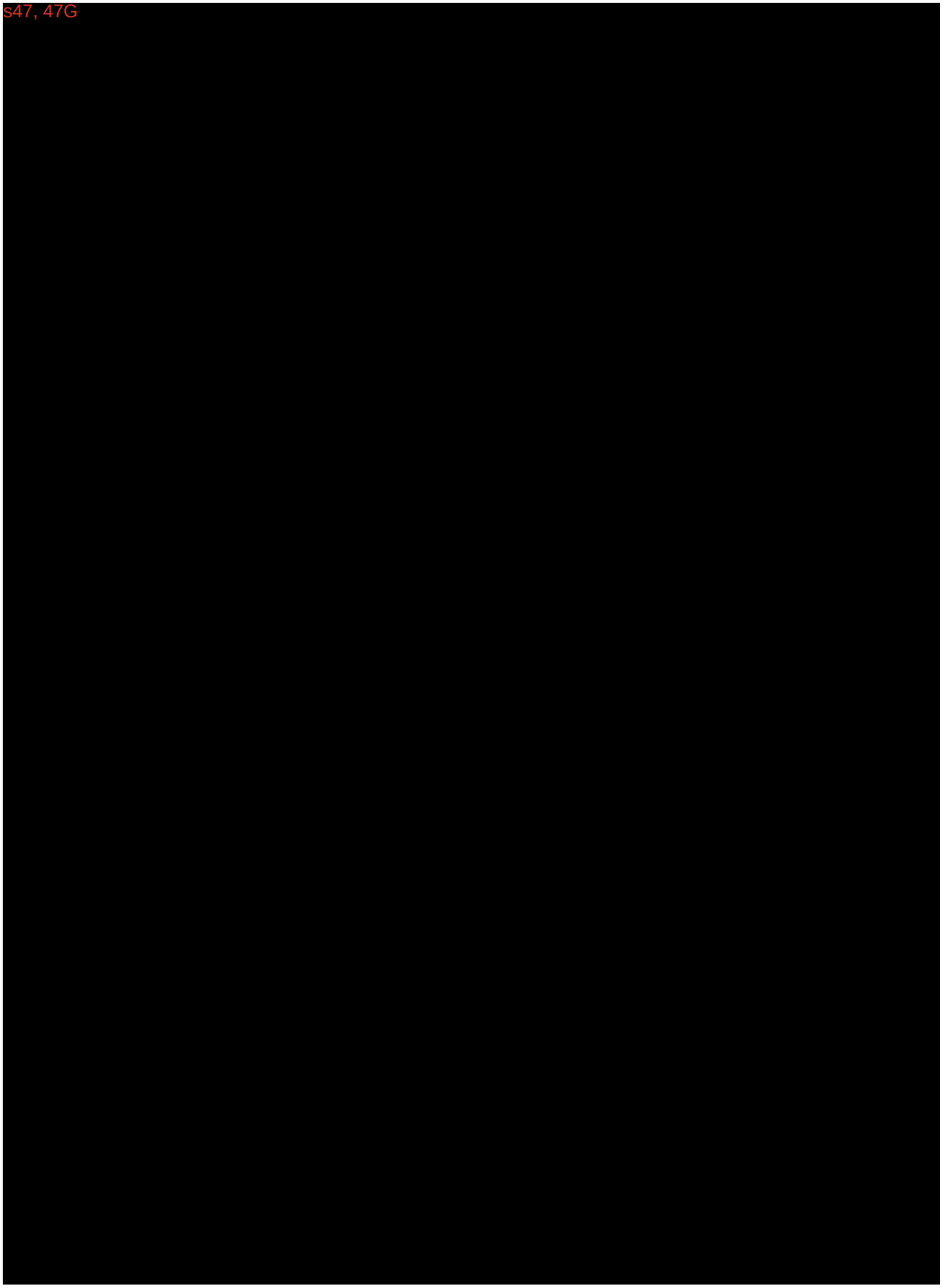

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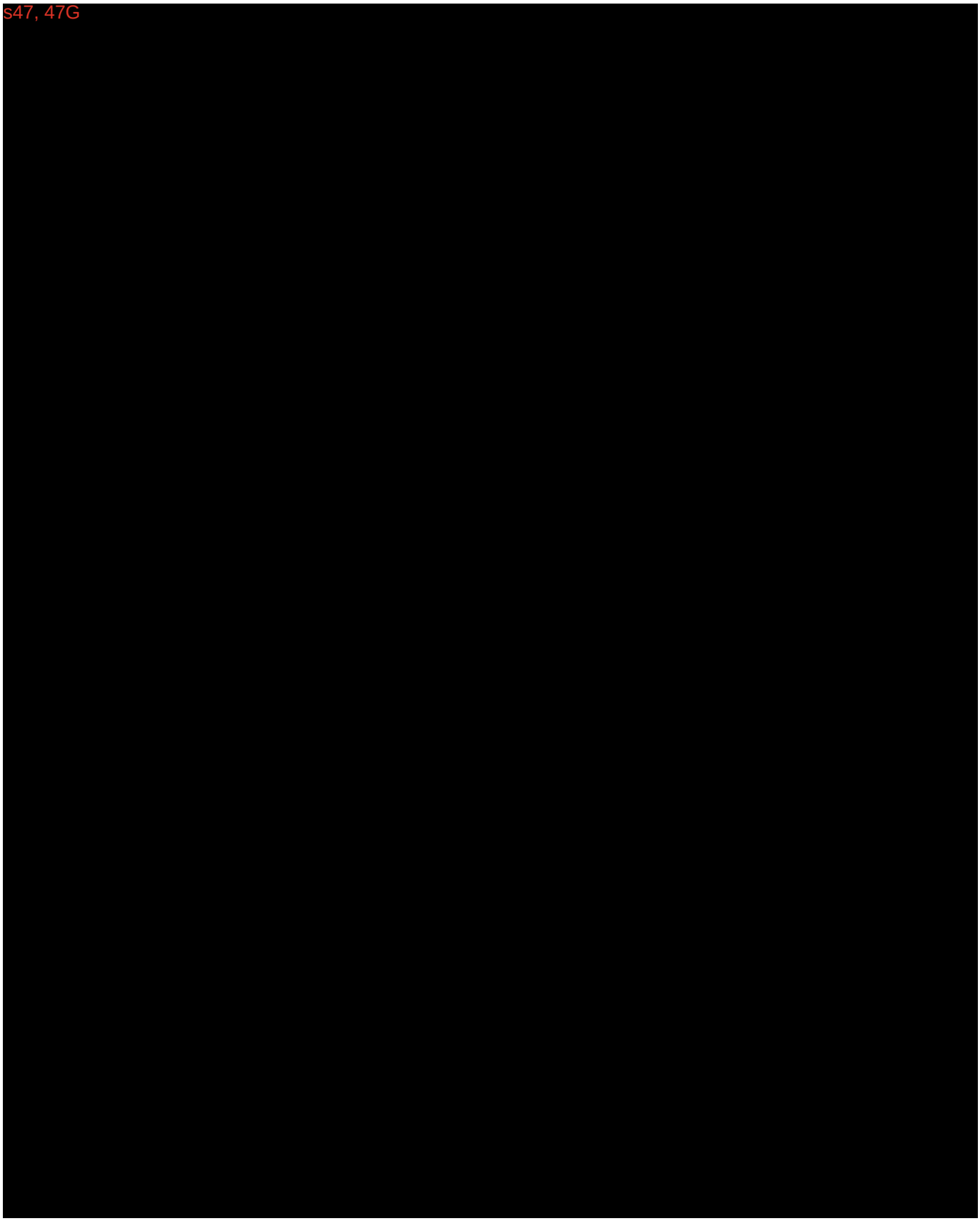

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3.2.P.2.6 COMPATIBILITY
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Table 11 – Chemical compatibility with infusion containers - pH results (1/2)

Container #	Supplier	Material	Diluent	Concentration	Temperature	pH				
						Diluent	T0	T 8H	T 24H	T 48H
1	CDM Lavoisier	Glass	NaCl 0.9 %	0.26 mg/mL	5°C	6.1	4.5	4.4	4.4	4.4
2	Ecoflac Braun	Polyethylene low density	Dextrose 5 %	0.26 mg/mL	30°C	4.1	4.1	4.0	4.0	4.0
3	CDM Lavoisier	Glass	NaCl 0.9 %	0.26 mg/mL	5°C	6.1	4.4	4.4	4.4	4.4
4	CDM Lavoisier	Glass	NaCl 0.9 %	0.26 mg/mL	5°C	6.1	4.4	4.4	4.4	4.4
5	Ecoflac Braun	Polyethylene low density	NaCl 0.9 %	0.10 mg/mL	30°C	6.0	4.8	4.8	4.7	4.7
6	Ecoflac Braun	Polyethylene low density	Dextrose 5 %	0.10 mg/mL	5°C	4.1	4.1	4.0	4.0	4.0
7	CDM Lavoisier	Glass	Dextrose 5 %	0.26 mg/mL	30°C	4.3	4.1	4.1	4.1	4.1
8	Ecoflac Braun	Polyethylene low density	Dextrose 5 %	0.10 mg/mL	30°C	4.1	4.0	4.0	4.0	4.0
9	CDM Lavoisier	Glass	Dextrose 5 %	0.10 mg/mL	5°C	4.3	4.2	4.2	4.1	4.2
10	CDM Lavoisier	Glass	Dextrose 5 %	0.26 mg/mL	5°C	4.3	4.1	4.1	4.0	4.1
11	Viaflo Baxter	Polyolefin	NaCl 0.9 %	0.26 mg/mL	30°C	6.0	4.4	4.4	4.4	4.4
12	Viaflo Baxter	Polyolefin	Dextrose 5 %	0.10 mg/mL	5°C	4.3	4.2	4.1	4.2	4.2
13	Viaflo Baxter	Polyolefin	NaCl 0.9 %	0.10 mg/mL	30°C	6.0	4.8	4.8	4.8	4.8
14	Ecoflac Braun	Polyethylene low density	NaCl 0.9 %	0.26 mg/mL	30°C	6.0	4.4	4.4	4.4	4.4
15	Ecoflac Braun	Polyethylene low density	NaCl 0.9 %	0.26 mg/mL	5°C	6.0	4.4	4.4	4.4	4.4
16	Ecoflac Braun	Polyethylene low density	Dextrose 5 %	0.26 mg/mL	5°C	4.1	4.0	4.0	4.0	4.0
17	Viaflo Baxter	Polyolefin	Dextrose 5 %	0.26 mg/mL	5°C	4.3	4.1	4.0	4.1	4.1
18	Ecoflac Braun	Polyethylene low density	NaCl 0.9 %	0.10 mg/mL	5°C	6.0	4.7	4.7	4.7	4.7

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Cabazitaxel, concentrate for solution for infusion

Table 12 – Chemical compatibility with infusion containers - pH results (2/2)

Container #	Supplier	Material	Diluent	Concentration	Temperature	pH				
						Diluent	T0	T 8H	T 24H	T 48H
19	Viaflo Baxter	Polyolefin	Dextrose 5 %	0.10 mg/mL	30°C	4.3	4.3	4.2	4.2	4.2
20	Viaflo Baxter	Polyolefin	NaCl 0.9 %	0.26 mg/mL	5°C	6.0	4.4	4.4	4.4	4.4
21	Viaflo Baxter	Polyolefin	NaCl 0.9 %	0.10 mg/mL	5°C	6.0	4.9	4.8	4.8	4.8
22	Viaflo Baxter	Polyolefin	Dextrose 5 %	0.26 mg/mL	30°C	4.3	4.1	4.1	4.1	4.1
23	CDM Lavoisier	Glass	Dextrose 5 %	0.10 mg/mL	30°C	4.3	4.1	4.2	4.2	4.2
24	CDM Lavoisier	Glass	NaCl 0.9 %	0.26 mg/mL	30°C	6.1	4.4	4.4	4.4	4.4
25	CDM Lavoisier	Glass	NaCl 0.9 %	0.10 mg/mL	30°C	6.1	4.9	4.9	4.9	4.8
26	CDM Lavoisier	Glass	NaCl 0.9 %	0.10 mg/mL	5°C	6.1	4.9	4.8	5.0	5.0
27	Bioluz	PVC/DEHP	NaCl 0.9 %	0.26 mg/mL	5°C	4.6	4.2	4.1	4.2	4.3
28	Bioluz	PVC/DEHP	Dextrose 5 %	0.10 mg/mL	30°C	4.2	4.2	4.2	4.3	4.1
29	Bioluz	PVC/DEHP	NaCl 0.9 %	0.26 mg/mL	30°C	4.6	4.2	4.1	4.3	4.3
30	Bioluz	PVC/DEHP	Dextrose 5 %	0.26 mg/mL	30°C	4.2	3.7	4.2	4.2	4.1
31	Bioluz	PVC/DEHP	Dextrose 5 %	0.26 mg/mL	5°C	4.2	3.8	3.9	4.1	4.1
32	Bioluz	PVC/DEHP	NaCl 0.9 %	0.10 mg/mL	30°C	4.6	4.4	4.3	4.4	4.4
33	Bioluz	PVC/DEHP	Dextrose 5 %	0.10 mg/mL	5°C	4.2	4.2	4.0	4.2	4.2
34	Bioluz	PVC/DEHP	NaCl 0.9 %	0.10 mg/mL	5°C	4.6	4.4	4.3	4.5	4.5

3.2.P.2.6 COMPATIBILITY
Cabazitaxel, concentrate for solution for infusion

Table 13 – Chemical compatibility with infusion containers - Cabazitaxel assay results (1/2)

Container #	Supplier	Material	Diluent	Concentration	Temperature	Assay						
						T0	T 8H		T 24H		T 48H	
						mg/mL	mg/mL	%/T0	mg/mL	%/T0	mg/mL	%/T0
1	CDM Lavoisier	Glass	NaCl 0.9 %	0.26 mg/mL	5°C	0.253	0.253	100	0.253	100	0.252	100
2	Ecoflac Braun	Polyethylene low density	Dextrose 5 %	0.26 mg/mL	30°C	0.240	0.240	100	0.242	101	0.241	100
3	CDM Lavoisier	Glass	NaCl 0.9 %	0.26 mg/mL	5°C	0.256	0.257	100	0.256	100	0.256	100
4	CDM Lavoisier	Glass	NaCl 0.9 %	0.26 mg/mL	5°C	0.249	0.250	100	0.249	100	0.249	100
5	Ecoflac Braun	Polyethylene low density	NaCl 0.9 %	0.10 mg/mL	30°C	0.102	0.103	101	0.103	101	0.103	101
6	Ecoflac Braun	Polyethylene low density	Dextrose 5 %	0.10 mg/mL	5°C	0.095	0.094	99	0.094	99	0.095	100
7	CDM Lavoisier	Glass	Dextrose 5 %	0.26 mg/mL	30°C	0.258	0.259	100	0.260	101	0.260	101
8	Ecoflac Braun	Polyethylene low density	Dextrose 5 %	0.10 mg/mL	30°C	0.090	0.090	100	0.090	100	0.090	100
9	CDM Lavoisier	Glass	Dextrose 5 %	0.10 mg/mL	5°C	0.103	0.103	100	0.103	100	0.103	100
10	CDM Lavoisier	Glass	Dextrose 5 %	0.26 mg/mL	5°C	0.257	0.259	101	0.258	100	0.258	100
11	Viaflo Baxter	Polyolefin	NaCl 0.9 %	0.26 mg/mL	30°C	0.239	0.242	101	0.241	101	0.241	101
12	Viaflo Baxter	Polyolefin	Dextrose 5%	0.10 mg/mL	5°C	0.093	0.092	99	0.093	100	0.093	100
13	Viaflo Baxter	Polyolefin	NaCl 0.9 %	0.10 mg/mL	30°C	0.097	ND	ND	0.098	101	0.099	102
14	Ecoflac Braun	Polyethylene low density	NaCl 0.9 %	0.26 mg/mL	30°C	0.241	0.242	100	0.241	100	0.241	100
15	Ecoflac Braun	Polyethylene low density	NaCl 0.9 %	0.26 mg/mL	5°C	0.247	0.247	100	0.247	100	0.247	100
16	Ecoflac Braun	Polyethylene low density	Dextrose 5 %	0.26 mg/mL	5°C	0.240	0.240	100	0.240	100	0.239	100
17	Viaflo Baxter	Polyolefin	Dextrose 5 %	0.26 mg/mL	5°C	0.240	0.240	100	0.240	100	0.240	100

ND : not determined

3.2.P.2.6 COMPATIBILITY
Cabazitaxel, concentrate for solution for infusion

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Cabazitaxel, concentrate for solution for infusion

Table 15 – Chemical compatibility with infusion containers - Degradation products results (1/2)

Container #	Supplier	Material	Diluent	Concentration	Temperature	Degradation products (DP)			
						T0		T8H ; T24H ; T48H	
						DP > 0.20%	Sum of DP (%)	DP > 0.20%	Sum of DP (%)
1	CDM Lavoisier	Glass	NaCl 0.9 %	0.26 mg/mL	5°C	0	< 0.10	0	< 0.10
2	Ecoflac Braun	Polyethylene low density	Dextrose 5 %	0.26 mg/mL	30°C	0	< 0.10	0	< 0.10
3	CDM Lavoisier	Glass	NaCl 0.9 %	0.26 mg/mL	5°C	0	< 0.10	0	< 0.10
4	CDM Lavoisier	Glass	NaCl 0.9 %	0.26 mg/mL	5°C	0	< 0.10	0	< 0.10
5	Ecoflac Braun	Polyethylene low density	NaCl 0.9 %	0.10 mg/mL	30°C	0	< 0.10	0	< 0.10
6	Ecoflac Braun	Polyethylene low density	Dextrose 5 %	0.10 mg/mL	5°C	0	< 0.10	0	< 0.10
7	CDM Lavoisier	Glass	Dextrose 5 %	0.26 mg/mL	30°C	0	< 0.10	0	< 0.10
8	Ecoflac Braun	Polyethylene low density	Dextrose 5 %	0.10 mg/mL	30°C	0	< 0.10	0	0.12
9	CDM Lavoisier	Glass	Dextrose 5 %	0.10 mg/mL	5°C	0	< 0.10	0	< 0.10
10	CDM Lavoisier	Glass	Dextrose 5 %	0.26 mg/mL	5°C	0	< 0.10	0	< 0.10
11	Viaflo Baxter	Polyolefin	NaCl 0.9 %	0.26 mg/mL	30°C	0	< 0.10	0	< 0.10
12	Viaflo Baxter	Polyolefin	Dextrose 5 %	0.10 mg/mL	5°C	0	< 0.10	0	< 0.10
13	Viaflo Baxter	Polyolefin	NaCl 0.9 %	0.10 mg/mL	30°C	0	< 0.10	0	< 0.10
14	Ecoflac Braun	Polyethylene low density	NaCl 0.9 %	0.26 mg/mL	30°C	0	< 0.10	0	< 0.10
15	Ecoflac Braun	Polyethylene low density	NaCl 0.9 %	0.26 mg/mL	5°C	0	< 0.10	0	< 0.10
16	Ecoflac Braun	Polyethylene low density	Dextrose 5 %	0.26 mg/mL	5°C	0	< 0.10	0	< 0.10
17	Viaflo Baxter	Polyolefin	Dextrose 5 %	0.26 mg/mL	5°C	0	< 0.10	0	< 0.10

3.2.P.2.6 COMPATIBILITY
Cabazitaxel, concentrate for solution for infusion

Table 16 – Chemical compatibility with infusion containers - Degradation products results (2/2)

Container #	Supplier	Material	Diluent	Concentration	Temperature	Degradation products			
						T0		T8H ; T24H ; T48H	
						DP > 0.20%	Sum of DP (%)	DP > 0.20%	Sum of DP (%)
18	Ecoflac Braun	Polyethylene low density	NaCl 0.9 %	0.10 mg/mL	5°C	0	< 0.10	0	< 0.10
19	Viaflo Baxter	Polyolefin	Dextrose 5 %	0.10 mg/mL	30°C	0	< 0.10	0	< 0.10
20	Viaflo Baxter	Polyolefin	NaCl 0.9 %	0.26 mg/mL	5°C	0	< 0.10	0	< 0.10
21	Viaflo Baxter	Polyolefin	NaCl 0.9 %	0.10 mg/mL	5°C	0	< 0.10	0	< 0.10
22	Viaflo Baxter	Polyolefin	Dextrose 5 %	0.26 mg/mL	30°C	0	< 0.10	0	< 0.10
23	CDM Lavoisier	Glass	Dextrose 5 %	0.10 mg/mL	30°C	0	< 0.10	0	< 0.10
24	CDM Lavoisier	Glass	NaCl 0.9 %	0.26 mg/mL	30°C	0	< 0.10	0	< 0.10
25	CDM Lavoisier	Glass	NaCl 0.9 %	0.10 mg/mL	30°C	0	< 0.10	0	< 0.10
26	CDM Lavoisier	Glass	NaCl 0.9 %	0.10 mg/mL	5°C	0	< 0.10	0	< 0.10
27	Bioluz	PVC/DEHP	NaCl 0.9 %	0.26 mg/mL	5°C	NP	NP	NP	NP
28	Bioluz	PVC/DEHP	Dextrose 5 %	0.10 mg/mL	30°C	NP	NP	NP	NP
29	Bioluz	PVC/DEHP	NaCl 0.9 %	0.26 mg/mL	30°C	NP	NP	NP	NP
30	Bioluz	PVC/DEHP	Dextrose 5 %	0.26 mg/mL	30°C	NP	NP	NP	NP
31	Bioluz	PVC/DEHP	Dextrose 5 %	0.26 mg/mL	5°C	NP	NP	NP	NP
32	Bioluz	PVC/DEHP	NaCl 0.9 %	0.10 mg/mL	30°C	NP	NP	NP	NP
33	Bioluz	PVC/DEHP	Dextrose 5 %	0.10 mg/mL	5°C	NP	NP	NP	NP
34	Bioluz	PVC/DEHP	NaCl 0.9 %	0.10 mg/mL	5°C	NP	NP	NP	NP

NP : not performed

3.2.P.2.6 COMPATIBILITY
Cabazitaxel, concentrate for solution for infusion

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5.1.3 Statistical analysis

A statistical analysis was performed on results after 48 hours of storage using SAS JMP v6.0.2 software. A two-factor interaction model with 4 factors was applied for both responses of interest (pH and assay).

Considering the low level of impurities, individual and sum, and the very rare variations in the experimental domain of interest (no individual impurities over 0.20 % until 48 hours and the sum of impurities always lower than 0.1 % until 48 hours), no formal statistical analysis of these responses was conducted.

5.1.3.1 Statistical results for pH response

Statistical results for pH response are presented in Table 18 and Table 19.

Table 18 – Summary fit for pH

Statistic	Value
RSquare	0.983074
RSquare Adj	0.962763
Root Mean Square Error	0.051501
Mean of Response	4.329412
Observations (or Sum Wgts)	34

The quality of fitted model is very good (R^2=0.98). Residuals are well distributed around 0.

Table 19 – Effect tests for pH

Source	Nparm [(a)]	Degree of Freedom	Sum of Squares	F Ratio	Prob > F
CONTAINER	3	3	0.1186332	14.9090	<.0001
DILUENT	1	1	1.5015135	566.1003	<.0001
CONC	1	1	0.3443879	129.8410	<.0001
TEMPERATURE	1	1	0.0034623	1.3054	0.2711
CONTAINER*DILUENT	3	3	0.1018158	12.7955	0.0002
CONTAINER*CONC	3	3	0.0577143	7.2531	0.0031
CONTAINER*TEMPERATURE	3	3	0.0041205	0.5178	0.6763
DILUENT*CONC	1	1	0.1622363	61.1663	<.0001
DILUENT*TEMPERATURE	1	1	0.0007658	0.2887	0.5989
CONC*TEMPERATURE	1	1	0.0063908	2.4094	0.1414

(a) : number of parameters

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Cabazitaxel, concentrate for solution for infusion

At the 1 % significance level, the factors and interactions showing a significant effect on the pH at 48 hours are, by decreasing order:

- the Diluent, with greater pH with the Saline medium NaCl 0.9 % than with the Dextrose 5 % one (Least-Squares (LS) Mean of 4.5 vs 4.1 for Dextrose),
- the Concentration,
- the Diluent * Concentration interaction, with a clear decrease of pH with Concentration for the Saline medium,
- the Container, with noteworthy specific behavior of the PVC bag containing DEHP (lowest LSMean of 4.2),
- the Container * Diluent and Container * Concentration interactions, with again specific behavior of the PVC bag containing DEHP.

The predictions from model for pH fitted on the 34 runs are provided in Table 20 with their 90 % confidence interval:

Table 20 – Predicted mean pH with 90 % CI

Run n°	Predicted Mean	90 %LCL	90 %UCL	Conclusion
1	4.4	4.4	4.5	Predicted Mean & CI ⊂ [3.0; 7.0]
2	4.0	3.9	4.1	Predicted Mean & CI ⊂ [3.0; 7.0]
3	4.4	4.4	4.5	Predicted Mean & CI ⊂ [3.0; 7.0]
4	4.4	4.4	4.5	Predicted Mean & CI ⊂ [3.0; 7.0]
5	4.7	4.6	4.7	Predicted Mean & CI ⊂ [3.0; 7.0]
6	4.0	3.9	4.1	Predicted Mean & CI ⊂ [3.0; 7.0]
7	4.1	4.0	4.1	Predicted Mean & CI ⊂ [3.0; 7.0]
8	4.0	3.9	4.1	Predicted Mean & CI ⊂ [3.0; 7.0]
9	4.3	4.2	4.3	Predicted Mean & CI ⊂ [3.0; 7.0]
10	4.1	4.0	4.1	Predicted Mean & CI ⊂ [3.0; 7.0]
11	4.4	4.3	4.5	Predicted Mean & CI ⊂ [3.0; 7.0]
12	4.2	4.1	4.3	Predicted Mean & CI ⊂ [3.0; 7.0]
13	4.8	4.7	4.8	Predicted Mean & CI ⊂ [3.0; 7.0]
14	4.4	4.3	4.5	Predicted Mean & CI ⊂ [3.0; 7.0]
15	4.4	4.3	4.5	Predicted Mean & CI ⊂ [3.0; 7.0]
16	4.0	3.9	4.0	Predicted Mean & CI ⊂ [3.0; 7.0]
17	4.1	4.0	4.1	Predicted Mean & CI ⊂ [3.0; 7.0]
18	4.7	4.6	4.8	Predicted Mean & CI ⊂ [3.0; 7.0]
19	4.2	4.1	4.3	Predicted Mean & CI ⊂ [3.0; 7.0]
20	4.4	4.3	4.5	Predicted Mean & CI ⊂ [3.0; 7.0]

3.2.P.2.6 COMPATIBILITY
Cabazitaxel, concentrate for solution for infusion

Run n°	Predicted Mean	90 %LCL	90 %UCL	Conclusion
21	4.8	4.7	4.9	Predicted Mean & CI ⊂ [3.0; 7.0]
22	4.1	4.0	4.2	Predicted Mean & CI ⊂ [3.0; 7.0]
23	4.2	4.1	4.3	Predicted Mean & CI ⊂ [3.0; 7.0]
24	4.4	4.3	4.5	Predicted Mean & CI ⊂ [3.0; 7.0]
25	4.8	4.8	4.9	Predicted Mean & CI ⊂ [3.0; 7.0]
26	4.9	4.8	5.0	Predicted Mean & CI ⊂ [3.0; 7.0]
27	4.3	4.2	4.3	Predicted Mean & CI ⊂ [3.0; 7.0]
28	4.1	4.0	4.1	Predicted Mean & CI ⊂ [3.0; 7.0]
29	4.2	4.2	4.3	Predicted Mean & CI ⊂ [3.0; 7.0]
30	4.1	4.1	4.2	Predicted Mean & CI ⊂ [3.0; 7.0]
31	4.2	4.1	4.2	Predicted Mean & CI ⊂ [3.0; 7.0]
32	4.5	4.4	4.5	Predicted Mean & CI ⊂ [3.0; 7.0]
33	4.1	4.1	4.2	Predicted Mean & CI ⊂ [3.0; 7.0]
34	4.5	4.5	4.6	Predicted Mean & CI ⊂ [3.0; 7.0]

It can be noted that, for all runs, the predicted mean pH and 90 % CI fall systematically within the specifications after 48 hrs storage.

5.1.3.2 Statistical results for assay

Statistical results for assay are presented in Table 21 and Table 22.

Table 21 – Summary fit for recovery of initial titer

Statistic	Value
RSquare	0.895593
RSquare Adj	0.770304
Root Mean Square Error	2.765542
Mean of Response	97.84944
Observations (or Sum Wgts)	34

The quality of fitted model is quite good (R^2=0.90), even if the fit is, in particular, poorer for PVC bags containing DEHP (for which the recovery of initial titer at 48 hours is in general lower than for the 3 other recipients). Residuals are nevertheless well distributed around 0.

3.2.P.2.6 COMPATIBILITY
Cabazitaxel, concentrate for solution for infusion

Table 22 – Effect tests for recovery of initial titer

Source	Nparm [(a)]	Degree of Freedom	Sum of Squares	F Ratio	Prob > F
CONTAINER	3	3	450.78110	19.6464	<.0001
DILUENT	1	1	8.09715	1.0587	0.3198
CONC	1	1	16.19377	2.1173	0.1662
TEMPERATURE	1	1	88.54613	11.5773	0.0039
CONTAINER*DILUENT	3	3	8.81188	0.3840	0.7660
CONTAINER*CONC	3	3	87.41355	3.8098	0.0327
CONTAINER*TEMPERATURE	3	3	241.53425	10.5268	0.0006
DILUENT*CONC	1	1	8.20890	1.0733	0.3166
DILUENT*TEMPERATURE	1	1	1.67430	0.2189	0.6466
CONC*TEMPERATURE	1	1	9.24482	1.2088	0.2889

(a) : number of parameters

At the 1 % significance level, the factors and interactions showing a significant effect on the recovery of initial titer at 48 hours are, by decreasing order:

- the Container, with noteworthy specific behavior of the PVC bag containing DEHP (LSMean of 91.4 % vs LSmeans > 99.5 % for the 3 other recipients),
- the Container * Temperature interaction (with, especially, an important decrease of the recovery with Temperature in case of the PVC bag containing DEHP),
- the Temperature (of which the main effect remains quite small, compared to the previous factors).

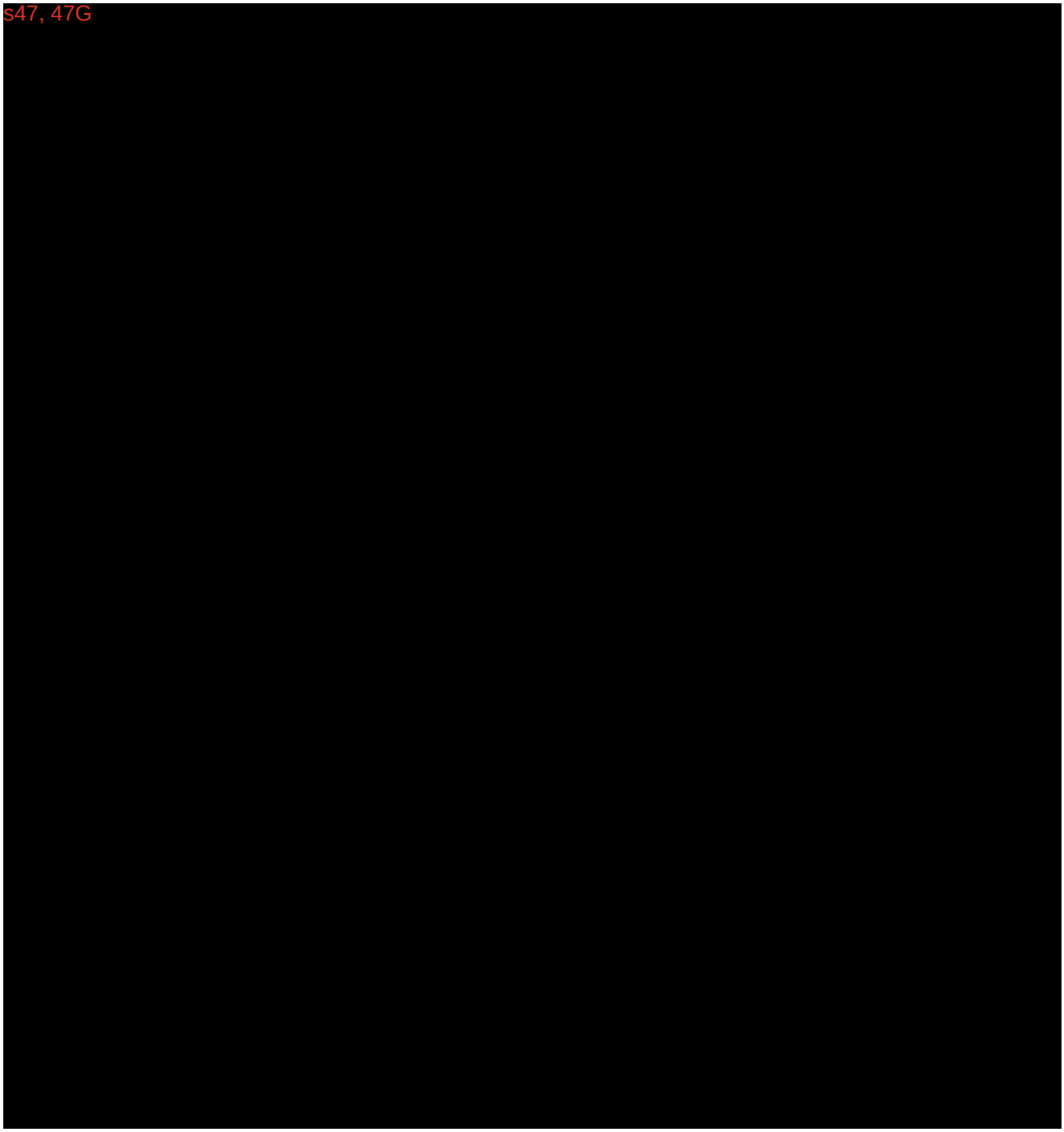
The predictions from model for assay fitted on the 34 runs are provided in Table 23 with their 90 % confidence interval:

Table 23 – Predicted mean recovery with 90 % CI

Run n°	Predicted Mean (%)	90 %LCL	90 %UCL	Conclusion
1	99	97	102	Predicted Mean & CI ⊂ [94 %; 105 %]
2	101	97	104	Predicted Mean & CI ⊂ [94 %; 105 %]
3	99	97	102	Predicted Mean & CI ⊂ [94 %; 105 %]
4	99	97	102	Predicted Mean & CI ⊂ [94 %; 105 %]
5	101	97	105	Predicted Mean & CI ⊂ [94 %; 105 %]
6	100	97	104	Predicted Mean & CI ⊂ [94 %; 105 %]
7	101	98	105	Predicted Mean & CI ⊂ [94 %; 105 %]
8	99	95	103	Predicted Mean & CI ⊂ [94 %; 105 %]

3.2.P.2.6 COMPATIBILITY
Cabazitaxel, concentrate for solution for infusion

s47, 47G

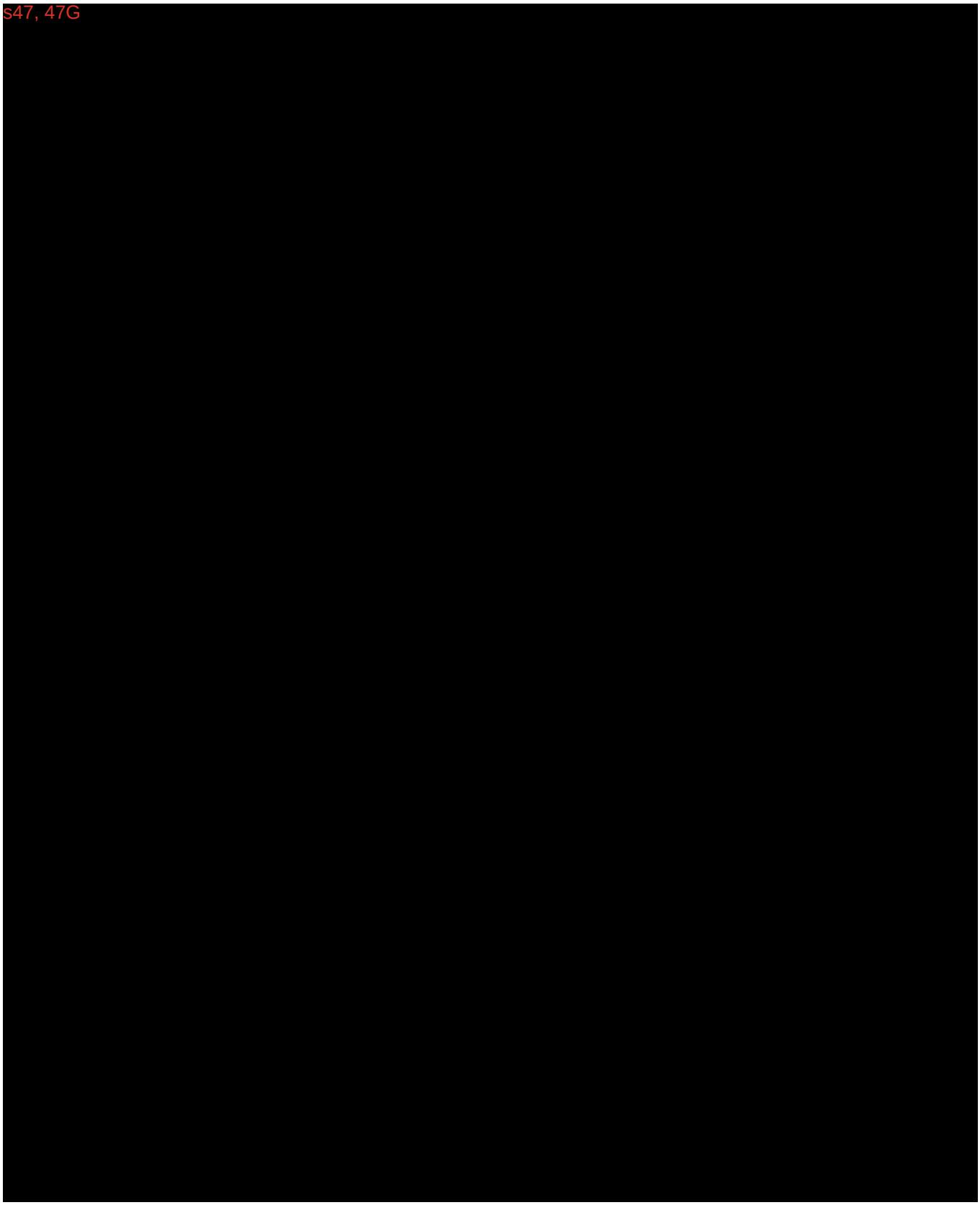


For all runs performed with glass bottles and polyethylene low density bags, the predicted mean and 90 % CI fall systematically within the specifications after 48 hours of storage. For the polyolefin bags, the predicted mean and 90 % CI are also falling within specification limits, excepting for one run where the CI slightly overlaps the specification limits.

At the opposite, the predicted mean and CI fall outside the specification limits with the PVC bag containing DEHP at the 30°C storage temperature.

3.2.P.2.6 COMPATIBILITY
Cabazitaxel, concentrate for solution for infusion

s47, 47G



3.2.P.2.6 COMPATIBILITY
Cabazitaxel, concentrate for solution for infusion

s47, 47G

5.2.2 Results

The different bags were visually examined for crystallization after 24 and 48 hours.

No crystallization was observed at 5°C after 48 hours of storage whatever the type of bags or bottles and whatever the infusion diluents.

When bags were stored at 30°C, crystallization occurs at 48 hours in sodium chloride for the polyethylene low density bag and in dextrose 5 % for the PVC/DEHP bag.

5.2.3 Data tables

Each container was visually inspected at each time point for the presence of crystals according to the classification presented below:

A No crystals visible
B 1 – 2 crystals either in suspension or on the inner surface of the bags
C 3 – 12 crystals as above
D > 12 < 100 crystals as above
E > 100 crystals as above.

Data are presented in Table 26 to Table 29.

3.2.P.2.6 COMPATIBILITY
Cabazitaxel, concentrate for solution for infusion

Table 26 – Physical stability study – crystallization results for glass bottle - batch DI-01569

Dextrose 5 %								Sodium chloride 0.9 %							
Storage	5°C			Storage	30°C			Storage	5°C			Storage	30°C		
Bag #	T0	24hr	48hr	Bag #	T0	24hr	48hr	Bag #	T0	24hr	48hr	Bag #	T0	24hr	48hr
1	A	A	A	11	A	A	A	21	A	A	A	31	A	A	A
2	A	A	A	12	A	A	A	22	A	A	A	32	A	A	A
3	A	A	A	13	A	A	A	23	A	A	A	33	A	A	A
4	A	A	A	14	A	A	A	24	A	A	A	34	A	A	A
5	A	A	A	15	A	A	A	25	A	A	A	35	A	A	A
6	A	A	A	16	A	A	A	26	A	A	A	36	A	A	A
7	A	A	A	17	A	A	A	27	A	A	A	37	A	A	A
8	A	A	A	18	A	A	A	28	A	A	A	38	A	A	A
9	A	A	A	19	A	A	A	29	A	A	A	39	A	A	A
10	A	A	A	20	A	A	A	30	A	A	A	40	A	A	A

A : No crystals visible.

3.2.P.2.6 COMPATIBILITY
Cabazitaxel, concentrate for solution for infusion

s47, 47G

3.2.P.2.6 COMPATIBILITY
Cabazitaxel, concentrate for solution for infusion

Table 28 – Physical stability study - crystallization results for polyolefin bag - batch DI-01569

Dextrose 5 %								Sodium chloride 0.9 %							
Storage	5°C			Storage	30°C			Storage	5°C			Storage	30°C		
Bag #	T0	24hr	48hr	Bag #	T0	24hr	48hr	Bag #	T0	24hr	48hr	Bag #	T0	24hr	48hr
81	A	A	A	91	A	A	A	101	A	A	A	111	A	A	A
82	A	A	A	92	A	A	A	102	A	A	A	112	A	A	A
83	A	A	A	93	A	A	A	103	A	A	A	113	A	A	A
84	A	A	A	94	A	A	A	104	A	A	A	114	A	A	A
85	A	A	A	95	A	A	A	105	A	A	A	115	A	A	A
86	A	A	A	96	A	A	A	106	A	A	A	116	A	A	A
87	A	A	A	97	A	A	A	107	A	A	A	117	A	A	A
88	A	A	A	98	A	A	A	108	A	A	A	118	A	A	A
89	A	A	A	99	A	A	A	109	A	A	A	119	A	A	A
90	A	A	A	100	A	A	A	110	A	A	A	120	A	A	A

A : No crystals visible.

3.2.P.2.6 COMPATIBILITY
Cabazitaxel, concentrate for solution for infusion

s47, 47G

5.2.4 Conclusion

As crystallization occurred at 30°C after 48 hours with the polyethylene low density bag in sodium chloride 0.9 % and with the PVC/DEHP bag in dextrose 5 %, storage in infusion bag or bottle until 48 hours should thus be restricted to storage at 5°C and storage under ambient temperature should be limited to a maximum of 24 hours.

5.3 OVERALL CONCLUSION

Based on the chemical compatibility study in infusion containers, the use of PVC/DEHP bags should be excluded due to loss of content at 30°C from 8 hours onwards.

Based on the physical compatibility study in infusion containers, stability has been demonstrated for 48 hours under refrigerated conditions and up to 24 hours at ambient temperatures. As an added precaution to ensure there is no risk of crystallization, the recommendations for storage of the infusion solutions at ambient temperatures will be limited to 8 hours.

6 IN-USE STUDY MIMICKING INFUSION CONDITIONS

6.1 STUDY DESIGN

The in-use study mimicking infusion conditions was performed with infusion solutions at 0.10 and 0.26 mg/mL prepared in glass bottles filled with both diluents and immediately infused during 2 hours through the different infusion sets selected (2.3).
The flow rate of the pump was fixed at 2 mL/min to simulate infusion in 2 hours, meaning lasting two times longer compared to usual infusion time.

The experiments were conducted in the run order presented in Table 30.

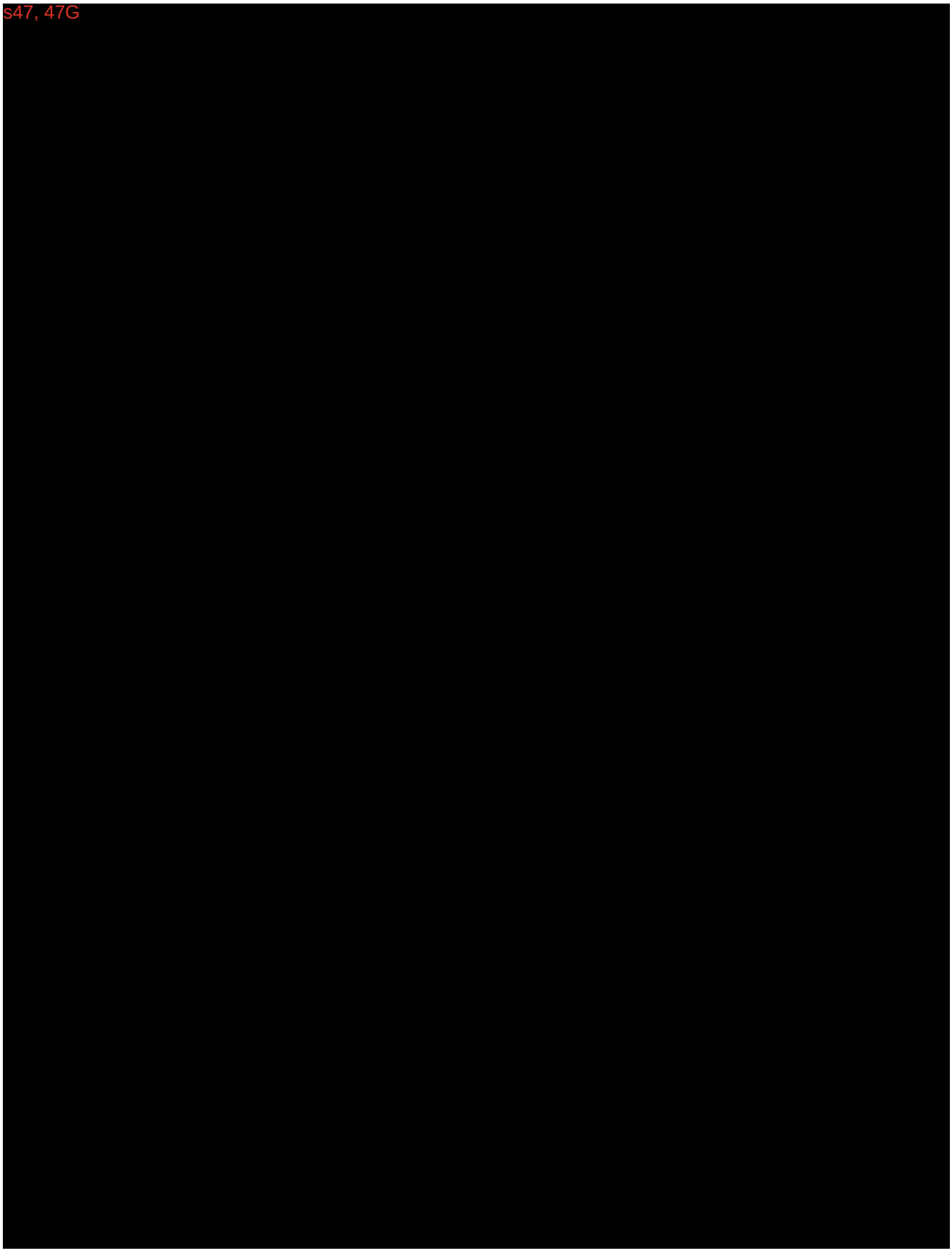
Table 30 – Compatibility with infusion sets – Testing design

Run	Factor 1 Material of infusion set	Factor 2 Infusion diluent of the glass bottle	Factor 3 Infusion solution concentration (mg/mL)
1	PVC DEHP	DEXTROSE	0.26
2	PVC DEHP Free	DEXTROSE	0.26
3	PVC DEHP	DEXTROSE	0.26
4	PVC DEHP	DEXTROSE	0.26
5	PVC DEHP Free	DEXTROSE	0.10
6	POLYURETHANE	DEXTROSE	0.10
7	POLYURETHANE	DEXTROSE	0.26
8	PVC DEHP Free	SALINE	0.10
9	PVC DEHP Free	SALINE	0.26
10	PVC/DEHP	SALINE	0.10
11	PVC/DEHP	SALINE	0.26

3.2.P.2.6 COMPATIBILITY

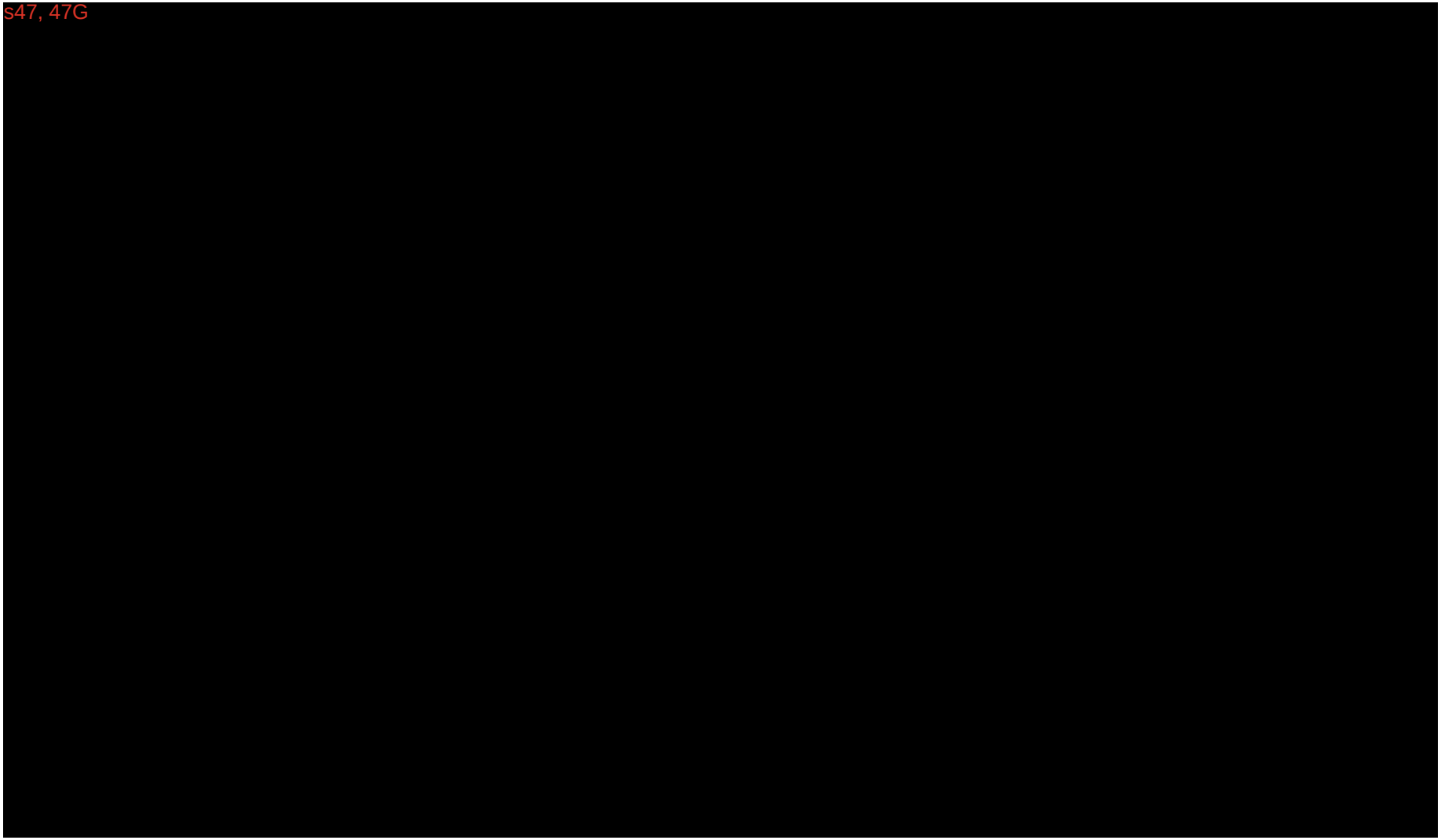
Cabazitaxel, concentrate for solution for infusion

s47, 47G



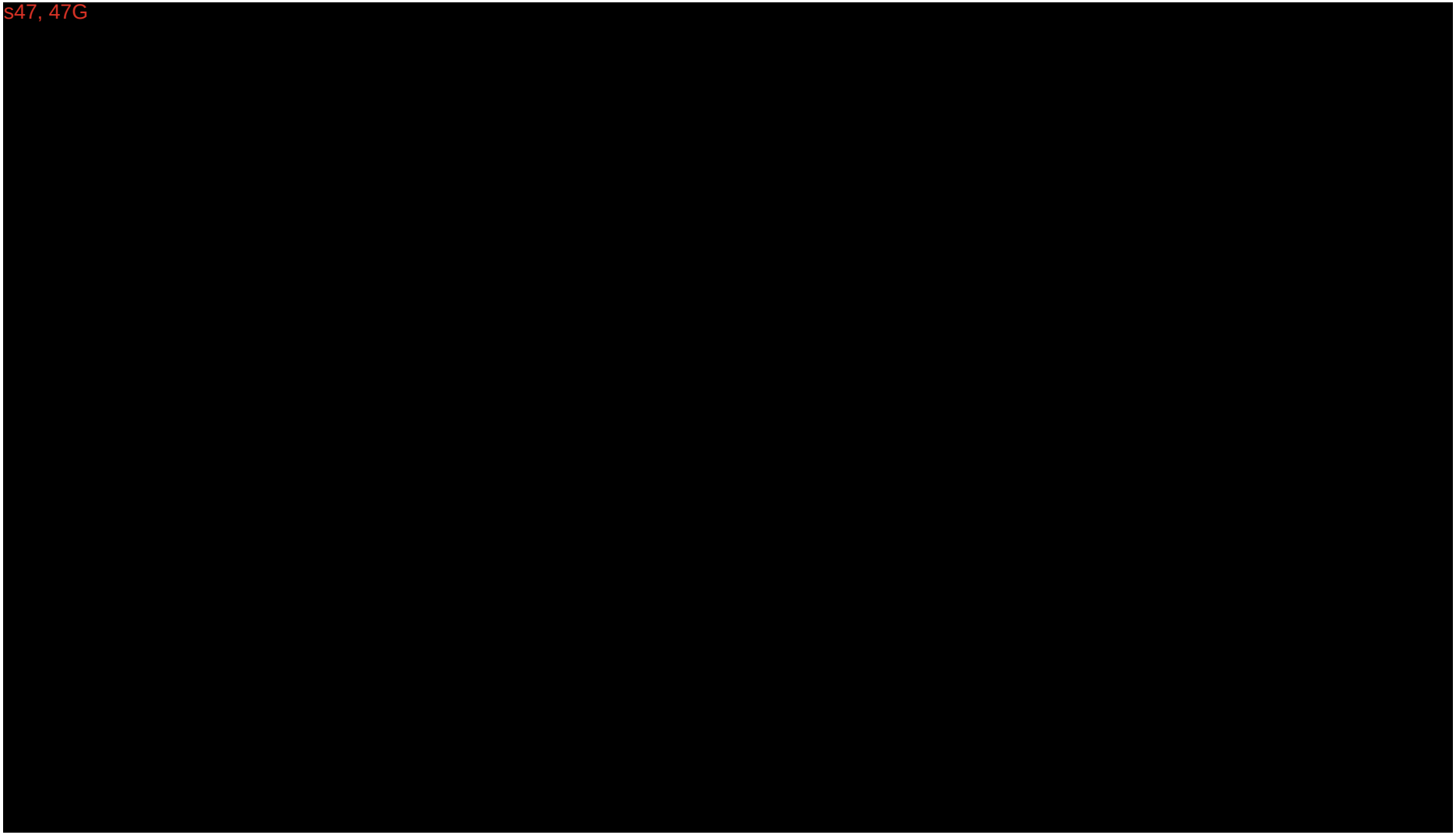
3.2.P.2.6 COMPATIBILITY
Cabazitaxel, concentrate for solution for infusion

s47, 47G



3.2.P.2.6 COMPATIBILITY
Cabazitaxel, concentrate for solution for infusion

s47, 47G



3.2.P.2.6 COMPATIBILITY
Cabazitaxel, concentrate for solution for infusion

Table 34 – In-use study mimicking infusion conditions - Degradation products results

Container #	Supplier	Material	Diluent	Concentration	Pump	Degradation products (DP)			
						DP > 0.20%	Sum of DP (%)	DP> 0.20%	Sum of DP (%)
1	Braun	PVC/DEHP	Dextrose 5 %	0.26 mg/mL	Space line	0	<0.10	0	<0.10
2	Alaris	PVC DEHP Free	Dextrose 5 %	0.26 mg/mL	Alaris GP	0	<0.10	0	<0.10
3	Braun	PVC/DEHP	Dextrose 5 %	0.26 mg/mL	Space line	0	<0.10	0	<0.10
4	Braun	PVC/DEHP	Dextrose 5 %	0.26 mg/mL	Space line	0	<0.10	0	<0.10
5	Alaris	PVC DEHP Free	Dextrose 5 %	0.10 mg/mL	Alaris GP	0	<0.10	0	<0.10
6	Braun	POLYURETHANE	Dextrose 5 %	0.10 mg/mL	Space line	0	<0.10	0	<0.10
7	Braun	POLYURETHANE	Dextrose 5 %	0.26 mg/mL	Space line	0	<0.10	0	<0.10
8	Alaris	PVC DEHP Free	NaCl 0.9 %	0.10 mg/mL	Alaris GP	0	<0.10	0	0.12
9	Alaris	PVC DEHP Free	NaCl 0.9 %	0.26 mg/mL	Alaris GP	0	<0.10	0	<0.10
10	Braun	PVC/DEHP	NaCl 0.9 %	0.10 mg/mL	Space line	0	<0.10	0	<0.10
11	Braun	PVC/DEHP	NaCl 0.9 %	0.26 mg/mL	Space line	0	<0.10	0	<0.10
12	Braun	PVC/DEHP	Dextrose 5 %	0.10 mg/mL	Space line	0	<0.10	0	<0.10
13	Braun	POLYURETHANE	NaCl 0.9 %	0.26 mg/mL	Space line	0	<0.10	0	<0.10
14	Braun	POLYURETHANE	NaCl 0.9 %	0.10 mg/mL	Space line	0	<0.10	0	<0.10
15	Alaris	POLYETHYLENE	Dextrose 5 %	0.26 mg/mL	Ivac 598	0	<0.10	0	<0.10
16	Alaris	POLYETHYLENE	NaCl 0.9 %	0.10 mg/mL	Ivac 598	0	<0.10	0	<0.10
17	Alaris	POLYETHYLENE	Dextrose 5 %	0.10 mg/mL	Ivac 598	0	<0.10	0	<0.10
18	Alaris	POLYETHYLENE	NaCl 0.9 %	0.26 mg/mL	Ivac 598	0	<0.10	0	<0.10

3.2.P.2.6 COMPATIBILITY
Cabazitaxel, concentrate for solution for infusion

Table 35 – In-use study mimicking infusion conditions - DEHP assay results

Container #	Supplier	Material	Diluent	Concentration	Pump	DEHP assay (ppm) T 2hours
1	Braun	PVC/DEHP	Dextrose 5 %	0.26 mg/mL	Space line	6
3	Braun	PVC/DEHP	Dextrose 5 %	0.26 mg/mL	Space line	7
4	Braun	PVC/DEHP	Dextrose 5 %	0.26 mg/mL	Space line	7
10	Braun	PVC/DEHP	NaCl 0.9 %	0.10 mg/mL	Space line	5
11	Braun	PVC/DEHP	NaCl 0.9 %	0.26 mg/mL	Space line	9
12	Braun	PVC/DEHP	Dextrose 5 %	0.10 mg/mL	Space line	5

6.3 STATISTICAL ANALYSIS

A statistical analysis was performed on results after the 2 hours infusion using SAS JMP v6.0.2 software. A two-factor interaction model with 3 factors is applied for both responses of interest (pH and assay).

6.3.1 Statistical results for pH response

Statistical results for pH response are presented in Table 37 and Table 39.

Table 36 – Summary fit for pH

Statistic	Value
RSquare	0.995096
RSquare Adj	0.83325
Root Mean Square Error	0.045774
Mean of Response	4.472222
Observations (or Sum Wgts)	18

The quality of fitted model is very good (R^2=0.995). Residuals are well distributed around 0.

Table 37 – Effect tests for pH

Source	Nparm [(a)]	Degree of Freedom	Sum of Squares	F Ratio	Prob > F
SET	3	3	0.0634509	10.0945	0.0146
DILUENT	1	1	1.1855118	565.8124	<.0001
CONCENTRATION	1	1	0.3931488	187.6392	<.0001
SET*DILUENT	3	3	0.0132738	2.1117	0.2174
SET*CONCENTRATION	3	3	0.0354960	5.6471	0.0462
DILUENT*CONCENTRATION	1	1	0.2015238	96.1818	0.0002

(a): Nparm : number of parameters

At the 1 % significance level, the factors and interactions showing a significant effect on the pH at 2 hours are, by decreasing order (see Scaled estimates table in appendix):

- the Diluent, with greater pH with the Saline medium than with the Dextrose one (LSMean of 4.8 vs 4.2 for Dextrose),
- the Concentration, with decreasing effect on pH,
- the Diluent * Concentration interaction, with a more important decrease of pH with Concentration for the Saline medium.

3.2.P.2.6 COMPATIBILITY
Cabazitaxel, concentrate for solution for infusion

The predictions from model for pH fitted on the 18 runs are provided in Table 38 with their 90 % confidence interval.

Table 38 – Predicted mean pH with 90 % CI

Run n°	Predicted Mean (%)	90 %LCL	90 %UCL	Conclusion
1	4.2	4.1	4.2	Predicted Mean & CI ⊂ [3.0; 7.0]
2	4.2	4.1	4.3	Predicted Mean & CI ⊂ [3.0; 7.0]
3	4.2	4.1	4.2	Predicted Mean & CI ⊂ [3.0; 7.0]
4	4.2	4.1	4.2	Predicted Mean & CI ⊂ [3.0; 7.0]
5	4.4	4.3	4.5	Predicted Mean & CI ⊂ [3.0; 7.0]
6	4.2	4.1	4.3	Predicted Mean & CI ⊂ [3.0; 7.0]
7	4.2	4.1	4.3	Predicted Mean & CI ⊂ [3.0; 7.0]
8	5.3	5.2	5.4	Predicted Mean & CI ⊂ [3.0; 7.0]
9	4.6	4.5	4.7	Predicted Mean & CI ⊂ [3.0; 7.0]
10	5.0	4.9	5.1	Predicted Mean & CI ⊂ [3.0; 7.0]
11	4.5	4.4	4.6	Predicted Mean & CI ⊂ [3.0; 7.0]
12	4.3	4.2	4.4	Predicted Mean & CI ⊂ [3.0; 7.0]
13	4.5	4.4	4.6	Predicted Mean & CI ⊂ [3.0; 7.0]
14	5.0	4.9	5.1	Predicted Mean & CI ⊂ [3.0; 7.0]
15	4.2	4.1	4.3	Predicted Mean & CI ⊂ [3.0; 7.0]
16	4.9	4.8	5.0	Predicted Mean & CI ⊂ [3.0; 7.0]
17	4.2	4.1	4.3	Predicted Mean & CI ⊂ [3.0; 7.0]
18	4.5	4.4	4.6	Predicted Mean & CI ⊂ [3.0; 7.0]

For all the runs, the predicted mean pH and 90 % CI fall systematically within the specifications after 2 hours infusion.

6.3.2 Statistical results for assay

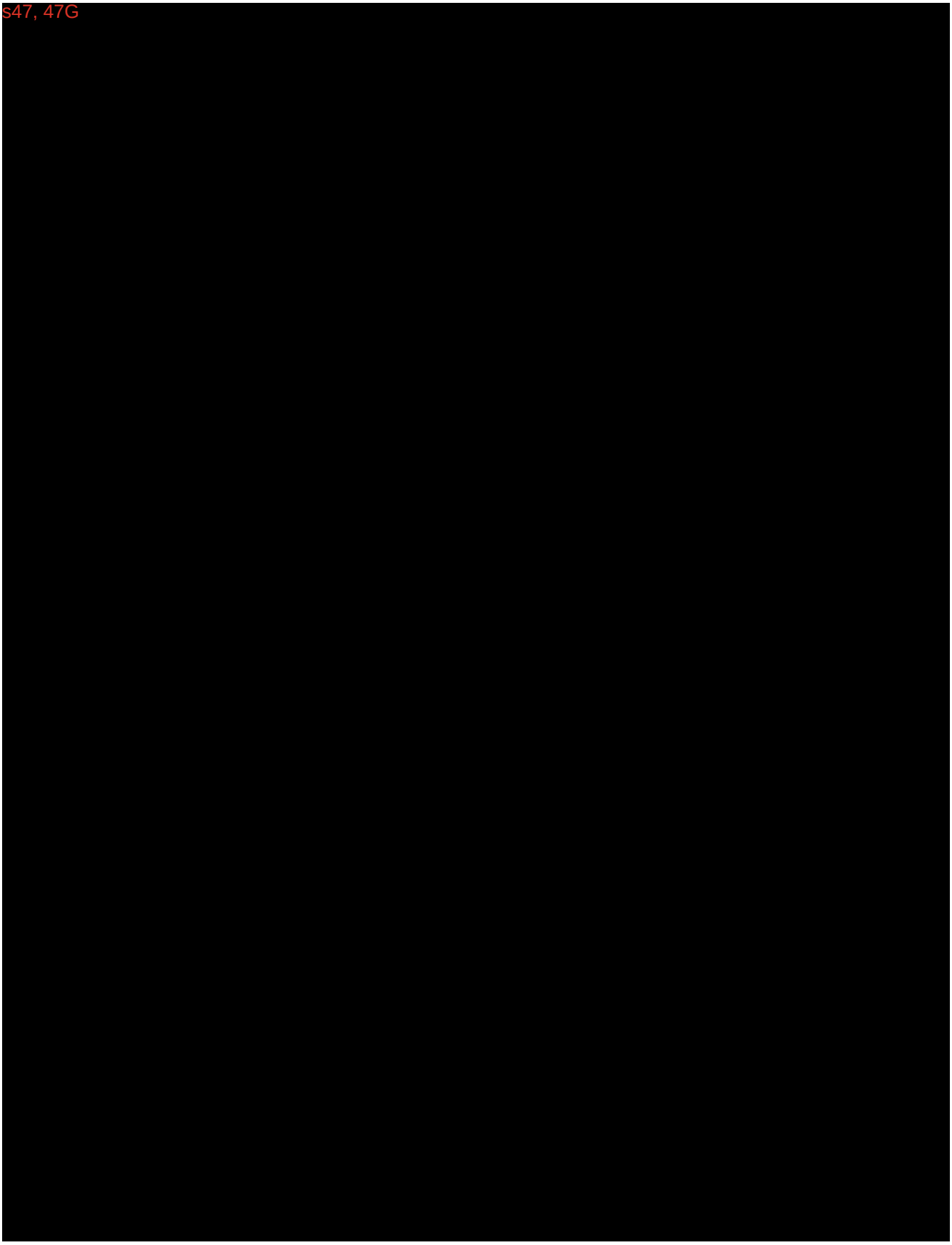
Statistical results for assay response are presented in Table 39 and Table 40.

Table 39 – Summary fit for recovery of initial titer

Statistic	Value
RSquare	0.996039
RSquare Adj	0.986534
Root Mean Square Error	0.505422
Mean of Response	96.1755
Observations (or Sum Wgts)	18

3.2.P.2.6 COMPATIBILITY
Cabazitaxel, concentrate for solution for infusion

s47, 47G



3.2.P.2.6 COMPATIBILITY
Cabazitaxel, concentrate for solution for infusion

Run n°	Predicted Mean (%)	90 %LCL	90 %UCL	Conclusion
13	92	91	93	Predicted Mean & CI outside specs
14	86	85	87	Predicted Mean & CI outside specs
15	99	98	100	Predicted Mean & CI ⊂ [94 %; 105 %]
16	99	98	100	Predicted Mean & CI ⊂ [94 %; 105 %]
17	98	97	99	Predicted Mean & CI ⊂ [94 %; 105 %]
18	99	98	100	Predicted Mean & CI ⊂ [94 %; 105 %]

s47, 47G

7 OVERALL CONCLUSION (STORAGE CONDITIONS OF INFUSION SOLUTIONS)

Based on the overall physico-chemical data generated during the compatibility/in-use studies and taking into account the fact that the infusion solution is supersaturated, it is recommended to limit the storage to 8 hours at ambient temperature, including 1-hour intravenous infusion.

In addition, chemical and physical stability of the infusion solutions has been demonstrated for 48 hours under refrigerated conditions.

It is recommended not to use PVC bags and polyurethane infusion sets for cabazitaxel infusion solutions.

Cabazitaxel solution for infusion can be infused over 1 hour at ambient temperature (approximately 25°C) and under normal lighting conditions.