A STANDARD PROTOCOL for DERIVING and ASSESSMENT of STABILITY

Part 1 – Aseptic Preparations (Small Molecules)

3rd Edition

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This document has been produced on behalf of the NHS Pharmaceutical Quality Assurance Committee, the NHS Pharmaceutical Production Committee and the NHS Pharmaceutical Aseptic Services Group by the NHS Pharmaceutical Research and Development Working Group. Membership of the NHS Pharmaceutical Research and Development Working Group is shown below.

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Industrial, academic and regulatory experts have been consulted in the preparation of these standards.

A Standard Protocol for Deriving and Assessment of Stability

Part 1 - Aseptic Preparations (Small Molecules)

1. Scope

This document applies to small molecule products of all presentations prepared by aseptically manipulation of sterile pharmaceutical products. In this context, a small molecule is defined as a medicinal drug compound having a molecular weight of less than 2000 Daltons, with two main exceptions. The first exception is any medicinal drug compound comprised of peptide sequences and the second exception are small molecule products produced using sterilisation by filtration that is followed by aseptic filling. For Biopharmaceuticals please refer to "A Standard Protocol for Deriving and Assessment of Stability: Part 2 - Aseptic Preparations (Biopharmaceuticals)[1]".

2. Introduction

The 2007 NPSA (National Patient Safety Agency) alert 20[2] recommended the supply of ready-to-administer products, at least for high risk injectables, rather than aseptic preparation in clinical areas. The practicality of this is in part reliant on the availability of valid and robust stability data.

This protocol, which has been prepared jointly by the R & D sub-group of the NHS Pharmaceutical Aseptic Services Group, the NHS Pharmaceutical Quality Assurance Committee and the NHS Pharmaceutical Production Committee, and updated by the NHS Pharmaceutical Research and Development Working Group, presents a standardised methodology to establish shelf life for aseptically prepared products. It is expected that the principles of this protocol are used for local stability trials, stability trials outsourced to third parties and when the validity of published stability data or commercially supplied stability data need to be assessed. Compliance with this protocol should also be sought from compounded product suppliers when products are outsourced, and Appendix 2 may be used to support that aim.

The principles that inform this protocol are:

2.1 Information available from a manufacturer may not offer the required stability data, for example from the relevant SmPC or additional information from the medical information department.

2.2 Published stability data may be of limited value because of inappropriate or inadequate analytical methodology, limited study duration or improper processing of analytical data.

2.3 Shelf lives are derived from diverse sources of data including physico-chemical stability, microbiological integrity, consideration of licensed status of the preparation facilities and their compliance with standards.

2.4 Once allocated, the shelf life should be subject to on-going validation including robust control of any changes to materials or components.

Appendix 2 of this document is supplied to assist procurement staff in assessing the suitability of products to be procured as unlicensed small molecule aseptically prepared products, including assessment of the shelf life assigned and stability information supplied or otherwise available for the specific product.

The R&D Group Assessment Template for Aseptic Small Molecule Products should be completed for all assessments of stability for this product group.

3. Analytical Methods

The development, validation, and adoption of analytical methods are beyond the scope of this protocol except to note that any method used must be able to indicate stability, be robust and be fully validated. The principles of 'Guidance on the Validation of Pharmaceutical Quality Control Analytical Methods'[3] and ICH Q2(R1)[4] (implemented as CPMP/ICH/281/95) should be followed, as appropriate.

4. Diluents

The default diluent will normally be 0.9% w/v sodium chloride as a typical diluent used in practice, but 5% w/v glucose should be used where applicable and other diluents may be added or supplemented, if recommended in the SmPC or otherwise required.

5. Containers

5.1 General considerations

Care should be taken to check the container proposed to store the product is the same used for each supporting stability study.

Extrapolation of data between different containers and infuser devices may be permissible provided the drug degradation pathway and physical properties of the container are well understood. Critical physical properties of a container include oxygen permeability, water permeability (water loss), light permeability, material constitution and possible extractives and adsorbent potential. Any extrapolation must be evaluated and justified.

5.2 Syringes

Syringes used as storage containers must be fully validated, including adequate consideration of microbiological ingress and physical robustness. Please refer to the 'Microbiological protocol for the integrity testing of syringes'[5]. Any syringe used to store medicines must be assessed as compliant with the BP Monograph for plastic syringes 'Appendix XIX G'[6].

In each case, syringes used in a stability trial, together with the specific closure system, should be specified in the protocol. Consideration should be also given to the inclusion of suitable CE marked drug storage syringes in any new study. Two piece polypropylene syringes may be required for some products although past history indicates that there may be more failures during the integrity testing with these syringes[7].

It is preferable that syringes with the plunger attached should not be filled beyond 85% of their marked capacity in order to prevent undue plunger movement, which may compromise microbial integrity during shipping/distribution.

It is noteworthy that syringes currently used for storage of aseptically prepared medicines are not CE registered as drug storage devices, which has meant manufacturers have often made important changes to the syringes they manufacture without informing the end users. In some cases, changes to syringes have had apparent effects on drug stability and/or adsorption[8] when the syringe is used to store aseptically prepared medicines. Therefore, for these products an on-going programme of stability reassessment is strongly recommended. This could take the form of repeated stability testing at defined regular intervals or a programme of end of shelf life testing for the products that feeds into an annual Product Quality Review (PQR).

5.3 Infusion Containers

Non-PVC containers (polyolefin) should routinely be the first choice container. The choice of flexible versus semi-rigid containers is product and/or study specific but it may not always be possible to extrapolate between the two due to fundamental differences in certain properties, which include the material and quantity of residual air.

5.4 Ambulatory Infuser Devices

There are a range of elastomeric devices as well as other ambulatory infuser devices. These should be included in studies when such devices will be used for administration. In addition, the drug contact surfaces need to be understood if data is extrapolated between types of elastomeric and other infusion devices.

5.5 Glass vials

The type of glass and the nature of the vial stopper are important considerations when using glass vials as final containers. The physical robustness and potential for microbiological ingress should also be considered.

5.6 Eye dropper bottles

Eye dropper bottles may include capped glass bottles (with a screw top or dropper) or plastic three piece eye dropper bottles. A stability study must be carried out in the container in which the product will be supplied; physical robustness and container integrity are important considerations.

6. Concentrations

Ideally each drug should be studied at each of a low and high clinically significant concentration. In this way, if there is consistent degradation reaction kinetics of the drug then it should be possible to interpolate to concentrations in between the two. If there is likely to be a significant difference in stability across a range of concentrations or another physical stability issue then additional concentrations may also be required.

7. Storage Conditions

Standard storage conditions can be found in Table 1. Control of relative humidity is not required for aseptically prepared products because they are essentially aqueous solutions and the storage times comparatively short. However, the properties of the container need to be assessed and understood (e.g. water loss by weight loss on storage, see above).

Table 1. A summary of stability testing temperature requirements

1. Refrigerated without exposure to UV light	5ºC +/- 3ºC
2. Room temperature without exposure to UV light	25ºC +/- 2ºC
3. Body temperature / elevated temperature	Normally 37ºC +/- 2ºC for in-use 'near to body studies'[a] (above 32ºC may be acceptable if validated), 37ºC +/- 2ºC for preparations in implantable reservoirs or 40ºC +/- 2ºC for accelerated data
4. Room temperature with exposure to UV light	25ºC +/- 2ºC, exposed to continuous fluorescent light
5. Frozen	-20 ºC +/- 5^{o}C

[a] Represents a "worst case scenario" for device reservoirs worn under clothes

8. Storage Protocols

The conditions referred to within this section can be found in Table 1.

8.1 Refrigerator stored products

Products should routinely be stored refrigerated as required by the Farwell Report[9] unless that is precluded by physical considerations. The assessment of the maximum refrigerated shelf life and 'in-use' shelf life at room temperature should be assessed as part of a study. This may be followed by a second 'sequential' study including refrigerated storage followed by in-use conditions for an appropriate period prior to testing (Table 1).

8.2 Room Temperature stored products

Products for which there are solubility issues under refrigeration can be stored at room temperature, which may also be appropriate for Controlled Drugs due to their storage requirements. For Controlled Drugs stability trials may need to be conducted at room temperature without exposure to UV light (Table 1).

8.3 Devices worn at body temperature

For device reservoirs, products that will be worn close to the skin or implantable pumps located under the skin, the second study should address condition 1 or 2 from Table 1 as appropriate (maximum shelf life) followed by condition 3 from Table 1 for an appropriate period. As indicated in Table 1, for drug solutions stored in implanted reservoirs the in-use period should be considered to be 37^{o}C +/- 2^{o}C and for those worn close to the skin stability studies should also be conducted at 37^{o}C +/- 2^{o}C. However, there is evidence that, particularly with elastomeric reservoirs[10], this may be unrepresentative and where it can be assured that solutions do not exceed 32^{o}C in the in-use condition the recommendation is that the study is conducted at above 32^{o}C.

The rationale behind this temperature is that 32^{o}C is the temperature for the EP dissolution test for transdermal devices[11] (which is based on a harmonised worldwide standard). Note that the set point for the stability chamber should ensure that the temperature remains above 32^{o}C

throughout the study. Care needs to be taken with implantable reservoirs where the device is refilled *in situ* and therefore drug solutions may be stored within them for longer than expected.

8.4 Products stored frozen

For products to be stored frozen the process of defrosting must be documented and fully validated for its impact on stability. In addition, the stability of the product once defrosted must be validated, which may involve refrigeration, or storage at room temperature or body temperature (Table 1). It is not normally recommended that plastic syringes are frozen but if this is necessary robust integrity testing must be undertaken at all stages of storage, thawing and any post thaw storage. There may also be risks associated with freezing products in elastomeric reservoirs that need to be assessed.

8.5 Light exposure

The effect of light on the stability of a medicinal product requires assessment unless the exposure to light is eliminated during routine clinical use. Condition 4 in Table 1 may apply if the product shelf life is dependent on light induced degradation. Under these circumstances further details as to the techniques to be used can be found in ICH Q1(B) Photostability Testing of New Active Substances and Medicinal Products[12].

8.6 Study and sampling periods

Sampling periods are study specific and the intrinsic stability of the system will determine the overall study duration as well as each sampling time point.

Sufficient time to allow critical parameters (i.e. those that which will control the shelf life of the product) to be assessed beyond the appropriate confidence interval of its specification limits needs to be built into the stability study. A minimum of 4 justified time points plus the initial data is the minimum required. Note that increasing the number of time points can help minimise the 95% confidence interval, which may otherwise restrict the allocated shelf life. This is particularly applicable to studies of drugs in syringes in which between-day repeatability may be higher than for other container types.

In the case of the critical parameter being the Active Pharmaceutical Ingredient (API) concentration, the study period should allow the concentration to fall to a value that allows a complete understanding of the reaction kinetics. This will not, however, be possible for very stable drugs. Other factors may also be relevant in determining shelf life (see 2.3).

Consideration should be given to carrying out accelerated stability studies for products expected to be or known to be relatively stable. Condition 3 in Table 1 is the temperature normally selected for this purpose.

9. Sample Numbers

For licensed products and regularly manufactured specials there should be a programme of ongoing stability work. It is required that three independent batches have been studied for licence submissions[13].

For studies of aseptically prepared products, the initial stability assessment is often carried out on a single batch, but this must include at least three replicates (independent containers) from each of the starting concentrations selected. The use of two or three fully independent batches (i.e. unique batches of stating materials) affords a much higher level of assurance to studies.

For containers with a capacity greater than 60mL, individual units may be regarded as a batch and multiple samples taken from them, pulled dosage units being replaced in storage condition. Note that samples must be removed aseptically to prevent the risk of spoilage. For containers with a capacity of less than 60mL it will be necessary to prepare a fully mixed bulk before filling into its storage container to ensure all such containers contain an identical homogenous solution.

The three samples must be analysed at each time point in duplicate or preferably triplicate. Note that increasing the number of replicates for analysis can help minimise the 95% confidence interval which otherwise may restrict allocated shelf lives.

The result of each sample test should be reported independently or if summarised a measure of spread provided, such as the standard deviation. For example, for samples tested in triplicate an average and spread for each set of triplicate samples as well as an average and spread for all the samples combined for each time point should be reported (example in Appendix 1). For samples tested in duplicate this should be reported as a range for each sample together with the population mean and variance of the three samples.

Ideally test results should be reported as a percentage of the baseline concentration, so as to fully understand the degradation levels.

10. Testing Protocols

The minimum testing protocol should include a consideration of the following points.

10.1 Colour, clarity and precipitation

The appearance of the product may be the stability limiting factor, particularly with the formation of visible particles / precipitates. Significant colour changes, even when associated with relatively low levels of degradation, may make the product unacceptable or non-compliant with standards (see relevant BP Monograph).

10.2 pH

The pH is likely to be critical to the stability of most drugs and changes in pH are likely to be indicative of other changes in the stored container that need investigation.

10.3 API concentration

Often API concentration is the critical shelf life limiting factor, usually assayed by HPLC either linked to Diode Array Detector (DAD) or with a standard UV detector, other stability indicating methods may be suitable including UHPLC-MS-MS (see further section 10.5). Analytical method validation needs to be in line with the documents referenced in point 3 above whichever method is used.

10.4 Sub-visible particle counts

The BP test for sub-visible particulates is an important part of any stability protocol and will normal follow the BP Light Obscuration technique but the Microscopic Particle Count test may also be used if appropriate[14]. For suspensions for injection it is expected that assessment of the particle size of the suspension be included in the stability protocol.

10.5 Degradation product concentration

Degradation product concentration may be a critical parameter in shelf life assignment, together with an understanding of the degradation mechanism and/or a risk assessment of the properties of the degradation products. With a validated HPLC assay, the resolution factor between the active ingredient and degradation products is a critical stage of the assay validation procedure.

UHPLC with dual Mass Spectrophotometer detection (UHPLC-MS-MS) allows chemical species to be separated both temporally and spatially and it does not rely upon achieving a physical separation in the same way as standard HPLC methodology. Provided the system suitability is demonstrated in terms of the instrument response factor for each compound being determined (if analysing a mixture without a physical separation being achieved) it allows the simultaneous quantitative determination of different chemical species in a very short analysis time without prior physical separation. This technique may alleviate the need for forced degradation studies as species detected will enable full identification of the degradants.

There is generally no need to include other related substance tests where these are process impurities that would not result from aseptic manipulation and subsequent storage of the product.

Additional tests are to be included where applicable

10.6 Moisture loss

Moisture loss is usually measured by weight change over time, which may be particularly applicable to infusion bags (storage condition 2 in Table 1).

10.7 Container extractables and leachables.

For many studies with water soluble drugs, understanding of the container leachables is more of a generic issue connected to container type. If, however, the drug formulation contains solubilising agents or other excipients the level of extractables may need to form part of the stability study.

10.8 Excipient concentrations

Excipients can be critical to both physical and chemical drug stability and may also be important for the clinical usage of the product (for example the inclusion of tissue permeability enhancers in subcutaneous injections). In these cases the concentration of excipient should be an important consideration of the study.

11. Shelf Life allocation

11.1 Data Analysis

A simple plot of analytical results against time is unacceptable for assignment of a shelf life. Various options are available for data handling and the most appropriate choice is dependent on the specific data set.

The principles of ICH Q1E (Evaluation of Stability Data)[15], implemented as CPMP/ICH/420/02, should be followed where possible. The method favoured by ICH Q1E is where analytical data is subjected to linear regression analysis after determination of the appropriate relationship between critical parameter and time. An appropriate method of shelf life calculation for an attribute which is known to decrease with time utilises the lower one-sided 95% confidence limit of the regression analysis, and calculation of the time required for the critical parameter to reach

the specification limit. For example, if Active Pharmaceutical Ingredient (API) loss is the critical parameter the lower 95% confidence limit of the time to reach 95% of the stated amount is the physico-chemical shelf life.

This technique, however, requires specialised knowledge and statistical software and unless the data are carefully analysed, misinterpretation could occur. This method can therefore only be used if clear statistical conditions and expert knowledge of the analytical system are applied. The potential errors are particularly exacerbated in short-term studies as generally used with aseptic compounded products.

This document offers flexibility of approach and therefore a simplified statistical approach may be acceptable where the one-sided lower 95% confidence limit of the slope is used to calculate the time to 5% degradation (see 11.2 below).

It is often not desirable to use a statistical approach where little or no degradation occurs over the course of the study. Section 8 indicates that a well-designed study should allow for a significant level of degradation to support a good understanding of the reaction kinetics but this is not always possible for stable materials. It is likely for very stable products that shelf life will be assigned for other reasons such as length of study, maximum storage time in syringes, and so on.

11.2 Acceptance criteria

The British Pharmacopoeia (BP) specification for a product is a shelf life specification to which the product must comply at the end of its shelf life. In general, for injections the BP specification is 95 – 105% of stated amount. For this reason it is suggested that, where loss of the active ingredient is the critical parameter, a loss of 5% should constitute the maximum shelf life. The starting concentration for the study must also be within the BP specification for the product.

It is acknowledged that many historical stability studies may not comply with the requirements of this document and that studies need to be optimally designed for certain container types, and particularly syringes, in order to maximise the confidence in the data generated. It is suggested that some pragmatism may be required in the interpretation of such historical studies, but the rationale for accepting more than 5% loss of an active ingredient within a shelf life needs expert consideration.

This may also hold with new studies as there may be certain molecules and presentations where a 10% loss of active can be acceptable, particularly if the BP monograph accepts this range. If working to a larger percentage loss then the clinical significance, including assessment of degradation products, must be fully assessed and understood.

Other statistical approaches to data analysis may be used, particularly the Confidence Bound or Maximum Rate method[16].

It is important that, when using semi-permeable containers, the impact of water loss is accounted for when calculating API concentrations. Water loss will concentrate solutions and therefore could mask degradation if not accounted for. In these cases the two-sided confidence limits of the slope may be appropriate and should be calculated and compared to both the upper and lower specification limits.

Knowledge of degradation products will be critical, the structure and identity and toxicology, metabolism and clinical effects need to be understood. The level of a degradation product may be a critical parameter in assigning shelf life. It is important to understand the difference between related substances that arise as process impurities and genuine degradation products. Where a BP limit exists for a degradation product it will need to be the limit applied to the study, and any other approach will require robust justification.

12. Stability Study Reports

Stability study reports should be submitted following a format consistent with the below recommendations.

Introduction
• Giving the reasons why the study was undertaken.

Literature Search
• Describing how this was undertaken and summarising relevant published prior work.

Analytical Methods
• Describing the development, validation, and/or adoption of analytical methods used. The specificity of the method together with its ability to detect degradants must be described.

Diluents
• Describing the diluents used, and the rationale for their choice.

Container
• Describing the containers used, and the rationale for their choice.

Concentrations
• Describing the concentrations studied, and the rationale for their choice.
Storage Conditions
• Describing the storage conditions used, and the rationale for their choice.

Storage Protocols
• Describing the storage protocols used, and the rational for their choice.

Sample Numbers
• Describing the number of samples and batches tested, and the rationale for their choice.

Testing Protocols
• Describing the test protocols used, and the rationale for their choice.

Results
• Detailed description of all analytical results. It is suggested that results are presented as a percentage of initial concentration; initial concentrations should be given in the report.

Discussion
• Scientific critique and evaluation of the results including any statistical approach taken to analysis of the data.

Allocation of Shelf Lives
• Description of the methods used to calculate shelf lives and the rationale for their use.
• Description of proposed shelf lives determined from the study.

Conclusions
• Overall conclusions from the study.

13. Extrapolation of data

It can be reasonable to interpolate data within the range of the study (concentrations, storage temperatures etc.) as long as consistent results are obtained from the concentrations studied. Extrapolation of data beyond that studied is a risk based process and a good understanding of the drug concerned, its reaction kinetics, its solubility and its ability to adsorb to surfaces are all important considerations that require an expert opinion before a decision is made. Extrapolation to different types of container will require an understanding of the differences in properties between the two containers. Robust change control is required for all changes and extrapolations.

Glossary

API - Active Pharmaceutical Ingredient

BP – British Pharmacopoeia

DAD – Diode Array Detector

EP – European Pharmacopoeia

HPLC – High Performance Liquid Chromatography

ICH - International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use

MA - Marketing Authorisation

MS – Mass Spectrometry

SmPC - Summary of Product Characteristics

UHPLC – Ultra High Performance Liquid Chromatography

UV Ultra-violet

References

1. A Standard Protocol for Deriving and Assessment of Stability: Part 2 - Aseptic Preparations (Biopharmaceuticals) – NHS Pharmaceutical Quality Assurance Committee. www.medicinesresources.nhs.uk/en/Communities/NHS/UKQAInfoZone

2 .NPSA Patient Safety alert 20 (28 March 2007) – Promoting Safer Use of Injectable Medicines. www.nrls.npsa.nhs.uk/resources/?entryid45=59812

3. Guidance on the Validation of Pharmaceutical Quality Control Analytical Methods - NHS Pharmaceutical Quality Assurance Committee March 2005. www.medicinesresources.nhs.uk/en/Communities/NHS/UKQAInfoZone

4.ICH Q2(R1) Validation of Analytical Procedures: Methodology www.ich.org/products/guidelines.html

5. Microbiological protocol for the integrity testing of syringes - NHS Pharmaceutical Quality Assurance Committee, 2nd edition April 2013.
/www.medicinesresources.nhs.uk/en/Communities/NHS/UKQAInfoZone

6. British Pharmacopoeia 2015 Appendix XIX G Sterile Single-use Plastic Syringes (Ph. Eur. method 3.2.8).

7. National collated data from syringe integrity testing – NHS Pharmaceutical R&D Group. www.qcnw.nhs.uk

8. BD Plastipak Field Safety Notice MS-15-637-FA (issued 28th September 2015)

9.Farwell J. Aseptic Dispensing for NHS Patients (The Farwell Report) Department of Health 1995.

10. What is the maximum temperature reached in elastomeric devices under simulated OPAT conditions. Van der Merwe SM, Green H. Poster presented at NPPG November 2015

11. European Pharmacopoeia 8.0, 2.9.4. Dissolution test for Transdermal patches

12. ICH Q1B Photostability Testing of New Active Substances and Medicinal Products. www.ich.org/products/guidelines.html

13. ICH Q1A(R2) Stability Testing of New Drug Substances and Products. www.ich.org/products/guidelines.html

14. British Pharmacopoeia 2015, Appendix XIII A. Particulate Contamination: Sub-visible Particles (Ph. Eur. method 2.9.19).

15. ICH Q1E Evaluation of Stability Data. www.ich.org/products/guidelines.html

16. Norwood, Drug Development & Industrial Pharmacy 12, 553-60, [1986]

17. Assessment Template (Small Molecules) – NHS Pharmaceutical R&D Group. www.qcnw.nhs.uk

Document History	Issue date and reason for change
Version 1	Issued December 2009
Version 2	Issued August 2011 - updated to current practice
Version 3	Issued December 2015 - addition of procurement assessment template, addition of information on analytical techniques, updated statements on syringe storage, updated temperature statement for in-use testing for ambulatory infusion systems, updated references.
Version 4	

Appendix 1 Example of reporting of results from stability trials

For three replicates each tested in triplicate the report at each time point should be presented as:-

Replicate 1 100.3% +/- 1.3%
Replicate 2 99.6% +/- 0.7%
Replicate 3 100.7% +/- 0.5%
Population mean 100.2% variance 0.21%

For three replicates each tested in duplicate the report at each time point should be presented as:-

Replicate 1 99.7% – 100.3%
Replicate 2 100.1% - 101.1%
Replicate 3 99.4% - 100.6%
Population mean 100.2% variance 0.31%

Appendix 2. Checklist for assessment of stability data for procured small molecule aseptically prepared products (Specials)

The following checklist is provided as a quick guide to assessing the suitability of procured aseptically prepared Specials from the stability assessment viewpoint. This should be used alongside other assessment tools for unlicensed products.
Preparation:……
Supplier / Manufacturer:……

1) Formulation	1.1) Is the formulation specified in the product specification including any concentration restrictions	Yes (go to 1.2) / No (return to supplier for specification)
	1.2) Is the formulation fit for purpose and for the patient / patient group	Yes (go to 1.3) / No (source a suitable formulation)
	1.3) Is the preparation made in accordance with the SmPC	Yes / No (Record and proceed)
2) Shelf life assigned	2.1) What shelf life is assigned by the manufacturer	
	2.2) Is the shelf life based on the recommendations in the SmPC	Yes (go to 3.1) / No (go to 2.3)
	2.3) Is this based on a specific stability study (in-house or supplied by starting material manufacturer)	Yes (go to 3.1) / No (go to 2.4)
	2.4) Is it based on an expert assessment of stability based on related product information (extrapolation)	Yes (assess whether this is suitable and whether risks can be mitigated)/ No (Ask supplier for more information or source another supply)
3) Stability study report	3.1) Is the stability study based on the formulation to be procured (Concentration range, diluent, final container, storage conditions)	Yes (go to 3.2) / No (get an expert opinion on the suitability of extrapolation)
	3.2) Does the report follow the format outlined in this document	Yes (go to 4.1) / No (assess the impact of the lack of information)
4) Stability study	4.1) Storage temperatures / Does this support the product storage directions assigned to the product procured	Storage Temperature |
		Accelerated storage temperature |
		Acceptable (go to 4.2) / Not acceptable (get an expert opinion on suitability of extrapolation)
	4.2) Study storage period / does this exceed the applied shelf life	| Yes (go to 4.3)/ No (assess suitability)
	4.3) Does the study include a range of concentrations (or is only one specific concentration required)	Yes (Go to 4.4) / No (consider the robustness of the data to support the range of products procured)
	4.4) Replicates – does the study include at least three replicates (separate samples) tested in triplicate	Yes (Go to 4.5) / No (consider the robustness of the data presented)

	4.5) For products given by infusion does the data support the in-use period at room temperature or body temperature as appropriate.	Yes (Go to 5.1) / No (in-use shelf life will be the responsibility of the user to assign)
5) Analytical techniques / results*[13]	5.1) Stability indicating assay of the active ingredient	Satisfactory / Not satisfactory / Not tested
	5.2) Assay and identification of degradation products	Satisfactory / Not satisfactory / Not tested
	5.3) Appearance / visible particles	Satisfactory / Not satisfactory / Not applicable / Not tested
	5.4) Sub-visible particles	Satisfactory / Not satisfactory / Not tested
	5.5) Container extractables and leachables	Satisfactory / Not satisfactory / Not applicable / Not tested
	5.6) pH	Satisfactory / Not satisfactory / Not tested
	5.7) Assay of preservatives / critical excipients	Satisfactory / Not satisfactory / Not applicable / Not tested
	Overall assessment of data presented	Satisfactory (Go to 6.1) / Not satisfactory (Go back to supplier with concerns)
6) Data analysis	6.1) Does the data presented support the shelf life assigned (with a suitable safety margin) with an appropriate statistical approach	Yes / No (Go back to the supplier with concerns / consider assigning an in-house shortened shelf life)

Summary of risks

Assessment of stability study for
……..

The data supplied: Provides assurance that the product will be suitable, safe and efficacious / does not provide suitable assurance

Approved:……Date:……

Additional risk reduction measures

*** Refer to the R&D Group assessment template for small molecules[17]**