A Standard Protocol for Deriving and Assessment of Stability

Part 5 – Sterile Products (end sterilised products)

Edition 1

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Industrial, academic and regulatory experts have been consulted in the preparation of this protocol.

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Edition 1	Issued April 2017
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1. Scope

Standards produced by the NHS Pharmaceutical Quality Assurance Committee and its sub-committees are produced with a distinctive yellow cover and are therefore known as Yellow Cover Documents (YCD). This document is the first edition of the fifth in a series that considers the stability of pharmaceuticals, and has been produced by the Pharmaceutical Research and Development Group.

This document applies to small molecule products of all presentations prepared by manufacture from non-sterile starting materials and sterilised in their final container using heat or irradiation, or those filter sterilised into their final sterile containers. In this context, a small molecule is defined as a medicinal drug compound having a molecular weight of less than 2000 Daltons.

2. Introduction

This protocol, which has been prepared by the NHS Pharmaceutical Research and Development Working Group, presents a standardised methodology to establish shelf life for manufactured sterile 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 product suppliers when products such as Specials are outsourced, and Appendix 2 may be used to support that task.

The principles that inform this protocol are:

2.1 Many injectable products are not commercially available as licensed products and these often have to be procured or made as Specials or on rare occasions made extemporaneously.

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

2.3 Manufacturers of Specials should have an in-house stability programme to ensure that they have robust data to support the use of their products. For multi-dose products such as eye drops this should also include an assessment of in-use shelf life.

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

2.5 The principles of ICH guidance[1,2,3,4,5] should be followed when assigning a shelf life to sterile manufactured products although it is acknowledged that full compliance is not required in law.

Appendix 2 of this document is supplied to assist procurement staff in assessing the suitability of products to be procured as unlicensed sterilised 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 Small Molecule Products should be completed for all assessments of stability for this product group[15].

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'[6] and ICH Q2(R1) [7] (implemented as CPMP/ICH/281/95) should be followed, as appropriate.

4. Containers

4.1 General considerations

The container which will be used to contain the product should be the one used in the stability study. Extrapolation to other container types can only be made with a strong understanding of the characteristics of both the product and container, and the rationale and justification must be recorded in a change control assessment.

Critical physical properties of a container include oxygen permeability, water permeability (water loss), light permeability, material constitution and possible extractives and adsorbent potential.

4.2 Glass ampoules, vials and bottles

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. Glass is liable to be a source of extractives including metals such as Aluminium[8]. ICH Q3D[9] should be consulted for information on risk assessment for Elemental Impurities in products. Certain products are more likely to extract elemental impurities from glass than others so this does need to be a product specific assessment and will probably need to be backed up with analytical testing throughout and beyond the proposed shelf life of the product.

The characteristics of individual types of rubber stopper should be evaluated to account for adsorption of active substance or excipient.

4.3 Plastic ampoules, vials and bottles

Although plastics are generally not an issue with elemental impurities the constituents of the plastic need to be understood and the potential for extractives and leachables should be considered and possibly tested for during the stability study if the risk assessment indicates this is required.

4.4 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 also important considerations. The characteristics of individual types of rubber component should be evaluated to account for adsorption of active substance or excipient.

4.5 Intravenous infusion bags

Intravenous infusion bags should generally be non-PVC due to concerns regarding extractables with PVC bags. The moisture loss potential from the bags under various storage conditions should be well understood, remembering that water loss can have a concentrating effect on solutions and may mask product degradation particularly in the longer term. Bags used for stability studies should be subjected to the same overwrapping as the product will have in real life.

4.6 Syringes

Syringes are not normally used for sterile Specials but if they are to be used then the impact of the sterilisation procedure must be understood and extractables and leachables must be fully assessed, together with container integrity.

5 Sterilisation methods

Stability samples must be subjected to the worst case scenario as far as the sterilisation process is concerned. For filter sterilised products it will probably be the worst case to take the first accepted sample for stability testing in order to assess any loss in the filters or filling lines. For products sterilised by irradiation the worst case scenario may be simulated for example by subjecting samples to a double radiation dose. Autoclaved products (and dry heat sterilised) need to have been subjected to the worst case scenario cycle which would be within protocol, again the exposure to two cycles could be considered as pre-treatment for stability samples, but this will be too great a challenge for some drugs.

6. Concentrations

The product should be stability tested in each concentration that it is to be supplied, and also in each container size. A bracketing and matrixing approach can be used where this has been assessed as representative for the whole product range; ICH Q1D[4] gives more information on this approach.

7. Storage Conditions

Standard storage conditions can be found in Table 1. Control of relative humidity is not necessarily required for sterile products particularly those in glass ampoules, vials and bottles. However, the properties of the container do need to be assessed and understood and relative humidity may be more significant for plastic containers, and will undoubtedly be an issue for intravenous bags.

Studies should be carried out in temperature controlled storage chambers or devices.

Table 1. A summary of stability testing temperature requirements

Representative situation	Temperature
1. Refrigerated without exposure to UV light	5ºC +/- 3ºC
2. Room temperature without exposure to UV light	25ºC +/- 2ºC or 30ºC +/- 2ºC
3. Elevated temperature (accelerated studies)	40ºC +/- 2ºC for accelerated data
4. Room temperature with exposure to UV light	25ºC +/- 2ºC or 30ºC +/- 2ºC, exposed to continuous fluorescent light
5. Frozen	-20 ºC +/- 5^{o}C

8. Storage and sampling protocols

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

8.1 Room Temperature stored products

For this product group it is desirable to be able to store at controlled room temperature if stability will allow it. This is particularly true for large volume bulk products where refrigerated storage will cause particular issues for end users.

8.2 Refrigerator stored products

Products for which there is insufficient room temperature stability to allow a usable shelf life should be stored in the refrigerator and hence the stability study should be conducted in these conditions.

8.3 Products stored frozen

This is not a common storage option for this product group although it may need to be considered for less stable products including some eye drops. 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.

8.4 Light exposure

The effect of light on the stability of a medicinal product requires assessment unless the exposure to light is eliminated during routine storage and 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[2]. If the photostability has not been assessed then product primary

packaging should provide adequate light protection or labelling must ensure the product remains within light protective secondary packaging before use.

8.5 Contact with closure

For multicomponent containers such as vials and bottles the protocol should include some containers stored on their side so that the effect of contact with the closure can be assessed.

8.6 Study length 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.

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 including the appearance of degradation products or container extractables or the loss of excipients

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.

8.7 In-use stability data

Stability studies for multi-dose sterile products such as eye drops and multi-dose vials should include consideration of in-use shelf life from a microbiological viewpoint but also in terms of chemical stability and considering the risk of spoilage. In use storage should match the label requirements for the product and should simulate normal handling.

Preservative Efficacy Testing (PET)[8] should be part of the protocol for preserved multi-use products. For unpreserved multi-use eye drops in-use periods are normally the responsibility of the end user who may better understand the local conditions of handling. In all cases this should be kept to a minimum (maximum seven days refrigerated). Any in-use period assigned to the product must be supported with data to assess the impact of a microbiological load and chemical stability, consideration should also be given to supplying the product in single unit dosage forms.

9. Sample Numbers

For 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 and a similar approach is desirable for products which are made routinely. There should also be a review and reassessment of stability following changes to starting materials, primary containers or the production process or site of manufacture. There should also be a programme to repeat the stability study at suitable intervals depending on specific product characteristics.

Although the initial stability assessment for a Special may be based on a single batch, two further batches should be studied during the early part of the product lifecycle in order to assure the robustness of the data generated. Ideally these three batches should be made with different batches of API, however, this may not be possible where an API batch will last for many years. If a new batch of API is introduced a considerable time after the initial stability study, then a confirmatory repeat study using the new batch is suggested.

Even where only one batch of product is to be tested it must be assured that there are at least three replicates (separate containers). 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.

9.1 Sampling considerations

For this product group where there is assurance through validation studies that the solution is homogeneous before filling it is normal to use a new container or several containers at each sample point of the stability trial. It must be ensured that suitable samples are laid down to allow for each sample point planned plus some repeat testing that may be necessary plus potentially additional sample points which may be needed during the study.

If a single container is to be used at more than one sample point such as may be possible for large volume infusions, then this container should be sampled aseptically and the impact of the increasing container headspace and decreasing volume will need to be understood.

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 indicate 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 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 be expected to increase during subsequent storage of the product.

10.5 Excipient concentrations

The concentration of excipients may be critical to the ongoing physical or chemical stability of the product or its in-use shelf life for example with preservative concentrations. Each excipient should be assessed and its need to be included in the stability studies should be considered.

10.6 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[11], if carried out to the Pharmacopoeial standard tests this technique does need relatively large sample volumes. There is evidence that a smaller sample volume will provide equivalent accuracy in terms of particle level analysis[12] and therefore smaller sample sizes for particle analysis may be acceptable. The Microscopic Particle Count test may also be used if appropriate[11].

10.7 Particle size distribution analysis

For suspensions it is expected that assessment of the particle size of the suspension be included in the stability protocol, for emulsions then droplet size is an important measure. Further assessment of homogeneity may also form part of the stability protocol for suspensions and emulsions.

Additional tests are to be included where applicable

10.8 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 plus the addition of Relative Humidity control).

10.9 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. However, some APIs and excipients in the formulation may cause extraction of elemental impurities and other chemicals from the container. One such example is the extraction of aluminium from glass by compounds such as calcium gluconate[8].

10.10 Sterility and endotoxin levels

Provided there is robust container integrity then it would not be expected that the product sterility or endotoxin levels would have been impacted by storage. For multi-use containers this may be part of the in-use shelf life assessment.

11. Shelf Life allocation

11.1 Data Analysis

A simple plot of analytical results against time is usually insufficient 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)[5], 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 for less stable 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 and eye drops 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. A margin of safety should be applied during assignment of shelf life in line with the requirements of the MHRA Guidance for Specials Licence Holders[13].

It is acknowledged that many historical stability studies may not comply with the requirements of this document. 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[14].

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.

11.3 In-use period

For multi-dose products such as eye drops and preserved injections the in-use period should be assessed at or towards the end of the product shelf life to ensure it is a worst case scenario. The parameters mentioned above should not be exceeded during this in-use period and the microbiological integrity will also need to be assessed using PET or an equivalent method (section 8.7).

For injectable products requiring dilution or drawing up into a syringe etc. ahead of use then the stability of the product should be investigated and assured as part of the stability studies.

12. Stability Study Reports

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

Introduction

• Giving the reasons 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 and any bracketing and matrix approach used.

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 including any in-se shelf life period

• 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 studied concentrations. Extrapolation of data beyond that studied is a risk based process and a strong understanding of the drug concerned, its reaction kinetics, its solubility and its ability to adsorb to surfaces are all important considerations that require 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.

In the event of an extrapolation a new stability study should be planned and undertaken as soon as possible in order to fully assess the impact of the change.

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

MA - Marketing Authorisation

MS – Mass Spectrometry

UHPLC – Ultra High Performance Liquid Chromatography

UV Ultra-violet

References

1. Stability testing of new drug substances and products Q1A(R2) www.ich.org/products/guidelines.html

2. Stability testing: photostability testing of new drug substances and products Q1B

3. Stability testing for new dosage forms Q1C

4. Bracketing and matrixing designs for stability testing of new drug substances and products Q1D

5. Evaluation for stability data Q1E

6. 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

7. ICH Q2(R1) Validation of Analytical Procedures: Methodology

8. Calcium gluconate injection in small-volume glass containers: new contraindications due to aluminium exposure risk, MHRA Drug Safety Update, Volume 4, Issue 1, August 2010 .

9. ICH, Q3D Guideline for Elemental Impurities (2014)

10. British Pharmacopoeia 2017 Appendix XVIC – Efficacy of antimicrobial preservation

11. British Pharmacopoeia 2017, Appendix XIII A. Particulate Contamination: Sub-visible Particles (Ph. Eur. method 2.9.19).

12. Pharmaceutical feasibility of sub-visible particle analysis in parenterals with reduced volume light obscuration methods, European Journal of Pharmaceutics and Biopharmaceutics 85 (2013) 1084–1087, Andrea Hawe , Frank Schaubhut , Raimund Geidobler, Michael Wiggenhorn, Wolfgang Friess, Markus Rast, Christian de Muynck , Gerhard Winter

13. Guidance for Specials Manufacturers, MHRA edition 2, January 2015 https://www.gov.uk/government/publications/guidance-for-specials-manufacturers

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

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

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 Specials sterile products

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	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 (Record and proceed) / No (source a suitable formulation)	
2) Shelf life assigned	2.1) What shelf life is assigned by the manufacturer		
	2.2) Is this based on a specific stability study (in-house or specifically commissioned)	Yes (go to 3.1) / No (go to 2.3)	
	2.3) 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, diluent, excipients, final container, storage conditions)	Yes (go to 3.2) / No (get an expert opinion (e.g. from the NHS R&D Group) 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)
	4.2b) Study storage period; does the study include in-use stability assessment.	Yes / No / Not applicable	
	4.3) Does the study include the 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 multi-dose products does the data support the in-use period for the product.	Yes (Go to 5.1) / No (in-use shelf life will be the responsibility of the user to assign)
5) Analytical techniques / results	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) Assay of excipients	Satisfactory / Not satisfactory / Not applicable / Not tested
	5.4) Appearance / visible particles	Satisfactory / Not satisfactory / Not applicable / Not tested
	5.5) Sub-visible particles / particle size / droplet size	Satisfactory / Not satisfactory / Not tested
	5.6) Container extractables and leachables	Satisfactory / Not satisfactory / Not applicable / Not tested
	5.7) pH	Satisfactory / Not satisfactory / 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[15]**