STANDARD PROTOCOL for DERIVING and ASSESSMENT of STABILITY

Part 1
Aseptic Preparations (Small Molecules)

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Part 1 - Aseptic Preparations (Small Molecules)

1. Scope

This document is intended to cover aseptically manipulated products of all presentations for small molecules.

A small molecule is defined as a medicinal drug compound having a molecular weight of less than 2000 Daltons and excluding those made up of peptide sequences.

Biopharmaceuticals and small molecule products manufactured using a filter sterilisation step followed by aseptic filling are not within the scope of this document but will be covered by future documents.

2. Introduction

The NPSA Patient safety Alert N° 20 [1] recommended the provision of ready-to-administer products, at least for high risk injectables, rather than preparation in clinical areas. The practicality of this is partly predicated on the availability of valid and reliable stability information.

This protocol, 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 for establishing shelf lives for aseptically prepared products. It is expected that the principles of the protocol are used when conducting in-house stability trials and when assessing the validity of published stability data or commercially supplied stability data. Evidence of its use should also be requested when products are outsourced.

The principles informing the protocol are:

2.1 Information obtainable from manufacturer's SPCs is often not helpful, and they do not always supply further stability data that is not part of the MA for their drug.

2.2 Published stability data may be of limited value because of inappropriate analytical methodology, failure to commit the study for long enough to establish the full life of the product, and improper processing of analytical data.

2.3 Shelf lives are derived from various sources of data including physico-chemical, microbiological, and facility and licensed status considerations. Once allocated the shelf life should be subject to ongoing validation.

2.4 As well as chemical stability data, evaluation of aseptic product shelf lives must involve evaluation of physical characteristics, and microbiological stability validation (container integrity). The latter is unit and process specific and is outside the scope of this protocol.

2.5 This protocol applies to all drug substances except biopharmaceuticals (i.e. all small molecules).

3. Analytical Methods

The development, validation, and adoption of analytical methods are beyond the scope of the protocol except to say that methods used must be stability indicating, robust and fully validated.. The principles of 'Guidance on the Validation of Pharmaceutical Quality Control Analytical Methods' [4] should be followed, also, where appropriate, ICH Q2(R1) [5] (implemented as CPMP/ICH/281/95).

4. Diluents

The default diluent should be 0.9% sodium chloride, with 5% glucose where applicable and other diluents maybe added or supplemented, if recommended in the SPC.

5. Containers

5.1 General considerations

In general the container used for the stability study should be the one proposed to store the product.

It may be possible to extrapolate data between different containers and infuser devices as long as the physical properties of the container are well understood. Critical physical properties 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 media must be fully validated including microbiological ingress and physical robustness. Please refer to the 'Microbiological protocol for the integrity testing of syringes'3.

The syringes used in the trial, together with the closure system, should be given in the protocol. Consideration should be given to including the Sterifill SCF syringes or equivalent CE marked drug storage syringe in any new study.

Two piece polypropylene syringes may be required for some products.

It is preferable that syringes, with the plunger attached, should not be filled to higher than 90% of their marked capacity, to prevent undue plunger movement and thereby compromise microbial integrity during shipping/distribution.

5.3 Infusion Containers

It is recommended that non-PVC containers (polyolefin) are used as first choice container. PVC containers can also be included where appropriate.

5.3 Infuser Device Chambers (as appropriate)

There are a range of elastomeric devices and also bags of PVC or other materials. These should be included in any study where these will be used for administration. It is the drug contact part that needs to be understood if extrapolating data.

5.4 Glass vials

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

5.5 Eye dropper bottles

These may be capped glass bottles, or with the dropper attached, or plastic three piece eye dropper bottles. The stability study must be carried out in the container as it will be supplied, again physical robustness and potential for microbiological ingress are important considerations.

6. Storage Conditions

Standard storage conditions are given in Table 1 below. Relative humidity control is not required for CIVAs type products which are essentially aqueous solutions and the storage times are comparatively short , however, the properties of the container do need to be assessed and understood (e.g. water loss by weight loss on storage).

1. Refrigerated in the absence of light	5ºC +/- 3ºC
2. Room temperature	25ºC +/- 2ºC
3. Body temperature / elevated temperature	Representing the worst case for device reservoirs worn under clothes and also accelerated stability data for products to be stored at room temperature. Normally 37ºC or 40ºC +/- 2ºC
4. Room temperature in the light	At ambient temperature, exposed to continuous fluorescent light
5. Frozen	Frozen at -20 ºC

Table 1 – A summary of stability testing temperature requirements

7. Concentrations

Ideally each drug should be studied at a low and high clinically significant concentration. In this way, if the drug shows consistent degradation reaction kinetics then it should be possible to interpolate to concentrations in between the two.

8. Storage Protocols

Conditions referred to in this section are referenced in Table 1 above.

8.1 Refrigerator stored products

Products will generally be stored refrigerated as required by the Farwell Report [2] unless precluded by physical considerations, particularly in unlicensed units. The assessment of the maximum refrigerated shelf life and room temperature 'in-use' shelf life should be assessed as part of the study (see "Allocation of Shelf Lives"). This may be followed by a second study including storage refrigerated (Table 1 condition 1) followed by in-use conditions (Table 1 condition 2 or 3) for an appropriate period prior to testing.

8.2 Room Temperature stored products

Products for which there are solubility issues can be stored at room temperature, this may also be appropriate for Controlled Drugs due to restricted storage options. For these products the stability trial will be conducted at 25 ºC (see Table 1 storage condition 2).

8.3 Devices worn at body temperature

For device reservoirs and where products will be worn close to the skin or in implantable pumps located under the skin, the second study should adopt the protocol; Condition 1 or 2 from Table 1 as appropriate (maximum shelf life) followed by Table 1 Condition 3 for an appropriate period.

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

8.4 Products stored frozen

For products to be stored frozen then the process of defrosting must be documented and fully validated for its impact on stability, together with the stability of the product once defrosted which can be either Table 1 Condition 1 (Refrigerated), Condition 2 (Room Temperature) or even Condition 3 (Body Temperature) as appropriate

8.5 Consideration of light exposure

The effect of light on the stability of a product needs to be assessed unless light exposure is eliminated in normal usage. Table 1 Condition 4 is appropriate if the product shelf life is dependant on light induced degradation. Further details as to the techniques to be used can be found in ICH Q1(B)[7].

8.6 Study period and sampling periods

Sampling times are study specific and the intrinsic stability of the system will decide the overall study period.

The study should be carried on for sufficient time to allow the critical parameter (i.e. that which will control the shelf life of the product) to reach beyond the appropriate confidence interval of its specification limits.

A minimum of 4 time points plus the initial data is needed. Note that increasing the number of time points can help minimise the 95% confidence interval which otherwise may restrict allocated shelf lives. This is particularly applicable to studies of drugs in syringes where between day repeatability may be higher than for other container types.

In the case of the critical parameter being API concentration, it is desirable for the study period to allow the concentration to fall to a value which allows proper understanding of the reaction kinetics. This will not be possible for stable materials (however, see point 2.3).

Consideration should be given to carrying out accelerated stability studies particularly for products expected to be or known to be relatively stable. Condition 3 (40°C) 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.

In general, for studies for aseptically prepared products, it is usual to carry out the initial stability assessment on a single batch, however, this must include at least three replicates (independent containers) from each starting concentration.

For containers larger 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 smaller containers 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 tested at each time point in duplicate or preferably triplicate. Note that increasing the number of replicates can help minimise the 95% confidence interval which otherwise may restrict allocated shelf lives. This is particularly applicable to studies of drugs in syringes where between day repeatability may be higher than for other container types.

Each sample should be reported independently or by including a standard deviation with the mean result. For example for samples tested in triplicate this should be reported as an average and standard deviation for each sample together with the overall population mean and variance for the three samples. 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 samples should be reported as a percentage of the starting concentration, in this way variations in initial concentration have no significance. For an example of how to express results please see **appendix 1**.

10. Testing Protocols

The minimum testing protocol should include;

- Colour, clarity and precipitations
- pH
- API concentration
- Sub-visible particle counts
- Degradation product concentration and an understanding of the degradation mechanism and / or a risk assessment of the properties of the degradation products.

Additional parameters are to be included where applicable, for example;

- Moisture loss – by weight (particularly applicable to infusion bags – see storage condition 2 in Table 1 above).
- Container extractables and leachables.
- Excipient concentrations

11. Allocation of Shelf Lives

11.1 Analysis of data

A simple plot of analytical results against time is not acceptable for assigning shelf life. There are various options available for data handling and generally the one selected will depend on the data set. A simplified statistical approach is suggested, where the one-sided lower 95% confidence limit of the slope is used to calculate the time to 5% degradation (see 11.2 below). This may be calculated using a spreadsheet.

The principles of ICH Q1E (Evaluation of Stability Data) [6], implemented as CPMP/ICH/420/02, should be followed where appropriate, however, this document does offer flexibility of approach and the above approach would be acceptable for many studies.

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, 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 5% degradation is the physico-chemical shelf life.

This technique, however, requires specialised statistical software and unless the distribution of data around the regression line is carefully analysed using a statistical approach and is expertly interpreted, then significant errors could occur. The method can 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 CIVAs type products.

It is often not desirable to use a statistical approach where little or no degradation occurs over the course of the study. As mentioned in section 8, a well designed study should allow for a significant level of degradation to allow good understanding of the reaction kinetics, however, this is not always possible for stable materials.
It is likely for these products that shelf life will be assigned for other reasons.
(e.g. length of study, maximum storage time in syringes etc.)

11.2 Acceptance criteria

The Pharmacopoeial 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 Pharmacopoeial specification is generally 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.

It is acknowledged by the authors that many historical stability studies may not comply with the requirements and that studies need to be optimally designed for certain container types, particularly syringes, in order to maximise the confidence in the data generated.

It is suggested that some pragmatism is needed in interpretation of such historical studies, but the rationale for accepting more than 5% loss of an active ingredient within a shelf life needs to be carefully considered. If working to a larger percentage loss then the clinical significance, including assessment of degradation products must be carefully considered.

It is important that, when using semi-permeable containers, the impact of water loss is accounted for when calculating API concentrations. Water loss will have a concentrating effect of 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.

Other approaches may be used, particularly the Confidence Bound or Maximum Rate method[8], which can be calculated with a spreadsheet.

Knowledge of degradation products will be critical, the structure and identity and toxicology, metabolism and clinical effects need to be understood. It may be that the level of a degradation product is the critical parameter, hence, where it can be justified; the level of a degradant may be the key parameter in assigning shelf life.

12. Stability Study Reports

Stability study reports should be submitted following the agreed format outlined below:

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.

Storage Conditions
- Describing the storage conditions used, and the rationale for their choice.

Concentrations
- Describing the concentrations studied, along with 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, along with 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.

Allocation of Shelf Lives
- Description of 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.

Glossary

SPC = Summary of Product Characteristics

MA = Marketing Authorisation

API = Active Pharmaceutical Ingredient

CIVAs = Central Intravenous Additives

References

1. NPSA Patient Safety alert 20 (28 March 2007) – Promoting Safer Use of Injectable Medicines.

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

3. Microbiological protocol for the integrity testing of syringes - NHS PQA Committee February 2006.

4. Guidance on the Validation of Pharmaceutical Quality Control Analytical Methods - NHS PQA Committee March 2005.

5. ICH Q2(R1) Validation of Analytical Procedures: Methodology - International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use.

6. ICH Q1E Evaluation of Stability Data - International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use.

7. ICH Q1B Photostability Testing of New Active Substances and Medicinal Products.

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

Document History	Issue date and reason for change
Guidance Doc	2008 – NHS PQAC response to queries on this topi
Version 1	January 2009 –and issued as NHS PQAC yellow cover document
Version 2	November 2010 issued Feb 2011 updated to incorporate ICH Guidance

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%