A Guide to Quality Control Chemical Testing of Aseptically Prepared Products

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1. Scope

This document covers laboratory chemical analysis of aseptically prepared products for any of the reasons outlined in section 2 below. All aseptically prepared products ranging from simple draw up of solution into a syringe to complex compounded parenteral nutrition are within the scope of this document.

The case studies presented within this document are examples only and should be subjected to local validation in accordance with standard assay validation procedures before being used for product analysis.

2. Background

Products are often manipulated aseptically within aseptic compounding units, either under the terms of a Manufacturers Specials Licence or under Section 10 exemption of the Medicines Act 1968 (by or under the supervision of a pharmacist). This might be a single item for an individual patient, on a batch manufacturing basis (licensed units only), or something in-between, for example the preparation of a bulk fluid for packing of multiple doses for one or more patients.

For this product group there are various points at which quality control analysis as part of product quality assurance, process validation, equipment validation and operator validation, as well as product stability assessment and monitoring, can be considered. Furthermore, analysis may be required as part of investigations into patient incidents or where errors are suspected to have taken place during a preparation process.

2.1 MHRA Q&As[1]

The MHRA Guidance for Specials Licence holders does contain some advice for product analysis for this product group, and whilst much of that is focussed on sterility assurance there are some clauses of relevance to this document.

3.6.15 Do we need a finished product specification?
• A product specification (or equivalent document) should be available. The BMR may fulfil this requirement in some circumstances. Where product release requires the results from prospective testing, this should be clearly defined.
• If there is a BP monograph for the material, this should be used as the basis for the specification and any omissions should be justified.

3.6.16 What is the expectation for finished product testing?
• The requirement for finished product testing should be commensurate with patient risk, taking into account the intended use of the product, and the methodology of manufacture. Typically, where manufacture involves a discrete bulk manufacturing step, there is an expectation that finished product testing will be performed. This is likely to include assay and ID confirmation as a minimum. Where these expectations are not met, there should be a documented justification for the approach taken. (See table 3.6.18).

• *Where appropriate, consideration should be given to the implementation of newer analytical methods E.g. ICAP, biochemical analysis, rapid micro methods which provide results in a timelier manner than current traditional tests*.

Also in table 3.6.18 is the statement regarding finished product testing for aseptically prepared products (Sterile product using PL + "diluent"):

Finished Product Testing
Over 90 days shelf life would expect FP testing on identified attribute(s). Testing rationale should include consideration of risk e.g. electrolyte check on TPN. Consideration should be given to batch homogeneity and validation of manufacturing process.
Finished Product Reference Samples - For products with shelf life of 90 days or greater
Comments
FP testing – may not be to full spec (release spec must be defined) but should have assurance that product would comply with full specification if tested.

The following statement within the document covers ongoing stability assessment for which some product end of shelf life analytical testing may form part of the ongoing review:

3.6.13 What are the requirements for stability testing of Specials?
• *A periodic review of the assigned shelf lives for all products should be in place in the light of any new published information and a consideration of received complaints.*
• *It is expected that a risk assessment is carried out which details the justification for performing or not performing annual stability testing for each product. Factors such as use of the product, therapeutic index, patient population, shelf life, source of the formulation, end of shelf life testing if carried out, storage conditions etc. should be considered in the assessment.*
• *For certain materials e.g. simple salt solutions, stability testing may not be required if a risk assessment was written which scientifically indicates that the solution does not degrade in solution.*

2.2 British Pharmacopoeia[2]

The BP and other Pharmacopoeias provide publicly available standards which apply throughout the shelf life of aseptically prepared products. The BP standards are intended to apply to the sample available. Any product subject to a monograph must comply with that monograph throughout its period of use.

There is no specific requirement to test products, but if they are tested then pharmaceutical products must comply with:

- Any relevant specific monograph
- All relevant general monographs (Specials, dosage forms etc.)
- Product formulations where these are specified

The BP and other pharmacopoeias contain suggested analytical methodology, although alternative methods can be used where justified and validated if they are at least equivalent (in specificity and accuracy) to the pharmacopoeial method.

2.3 Toft report[3]

The Independent review of the circumstances surrounding a serious untoward incident that occurred in the Aseptic Manufacturing Unit, Royal Surrey County Hospital on Monday, 18 June 2012 conducted by Professor Brian Toft, had the recommendation 16 which stated 'A final automated check should be developed and introduced nationally into NHS aseptic manufacturing units for the testing of high risk products to ensure they are safe before their dispatch to patients. The test should be capable of being undertaken without a physical sample of the finished product being required.

At the time of this report there was not really a practical solution to meet this recommendation, however, since then various instruments based on UV or UV and Raman spectroscopy have been developed and are much used in some countries particularly France for pre-release testing of cytotoxic and other drugs[4,5].

3. Considerations for product analysis

There are some special considerations for these product types, for example where the dose is added to an intravenous fluid, the fluid bag may contain a significant overage which will impact on the expected concentration of the solution.

Furthermore starting materials are licensed pharmaceutical products and not raw materials; this can lead to significant variation in the content of such starting materials. For example many drug products have specifications of 95 – 105% stated content of active substance, this can lead to more variation as the product is generally manipulated based on an assumption that it is 100% of stated content.

Overall the level of chemical testing undertaken on aseptically prepared products should be commensurate with the risk and should be based on a local risk assessment which considers the knowledge and assurances already in place, the potential points of failure, the risks associated with the product and the patient group being treated. This document is a guide to the options available and some of the points to consider but is not a standards document. Auditors, however, may ask about product analysis and ask to see your risk assessments and testing strategies, both around accuracy and acceptability of products produced and considerations for shelf-life assignment.

3.1 Final product / intermediate analysis

The MHRA Q&As document (see section 2.1) suggests that product testing should be considered, and in fact is expected, where there is a bulk intermediate stage in the preparation process. This would include preparation of a bulk solution from which the final product is filled. Some examples of this would include:

- Preparation of a reconstituted solution from which multiple doses of intra-ocular injection are drawn
- Preparation of an IV bag containing a full course of antibiotics for a homecare patient which is subsequently packed into infusers or syringes
- Preparation of a bulk insulin dilution for packing into syringes
- Preparation of a bulk neonatal PN formula for packing into aliquots

Overall whether or not there is a bulk manufacturing stage then testing should be commensurate with risk, and may also depend on the availability of process validation information and robust in-process controls.

3.2 End of shelf life testing

End of shelf life testing can be a vital part of ongoing assurance of drug stability. Many units depend on published data, information from starting material suppliers, in-house or commissioned stability data. Much of this is old data and may not be fully compliant with NHS guidance[6,7,8]. In order to meet requirements for on-going review of shelf life or to go some way towards authenticating historic data then end of shelf life testing of products is an important consideration.

End of shelf life testing can also be useful and important in validating extrapolation of stability data, such as where data is extrapolated from one manufacturer (of starting material) to another manufacturer where formulations are similar.

The frequency of end of shelf life testing should be in line with local risk assessment and based on the products and the information (data) on which the shelf life assignment was originally based.

Note that in order to give a true indication of stability all parameters should be considered which could impact the shelf life assigned. For some studies a T=0 time point may also be required to demonstrate the initial concentration of the active ingredient. In other cases analysis of degradation product levels, pH and sub-visible particles as well as appearance will need to form part of the test protocol.

End of shelf-life testing for biopharmaceuticals should follow the full yellow cover guidance for stability testing of these molecules[7] although if this is an ongoing confirmation of robust initial stability studies abridged testing can be considered as long as the assays used will pick up changes within the molecule, for example an activity based assay, sub-visible particle counts and mass spectroscopic assay may be sufficient, depending on suitable validation. There must also be a standard or at least a T=0 sample (freshly prepared from the same batch of drug product starting material) alongside the end of shelf life testing as methods are comparative looking at changes within the assay data set.

The case studies within this document are not applicable to end of shelf-life testing where assays must be stability indicating and should be validated as such. There is an NHS guidance document covering assay validation[11] which can be referred to for further guidance.

3.3 Process / operator validations

Validation of process and /or operator accuracy can make use of simulated product production with suitable analysis. With simulations it is best to use simple methodology with good precision and accuracy so that analytical variation does not impact the validation significantly. Such simulations should make use of worst case scenario products, for example using dilution of potassium chloride or magnesium sulfate concentrates which are difficult to mix.

3.4 Equipment validations

The validation of equipment from simple pumps to complex PN compounders may make use of laboratory analysis of simulated products; ongoing validations may make use of testing of live products or in-process sample bags.

3.5 Investigations

Laboratory chemical analysis can be used for the investigation of patient incidents where the medicine was prepared in pharmacy or on the ward. It can also be useful in investigating the impact of process deviations or potential errors, such as where final reconciliation of starting materials indicates that an error may have been made.

4. Product types

Any aseptically prepared products can be considered for analysis, although some will present considerably more of a challenge than others. The following considerations need to be taken into account.

4.1 Cytotoxic products

Products which are a straight draw up from a vial into a syringe would present a low error potential and that can be controlled by other measures such as in-process checking and final reconciliation of starting materials and syringe fill volumes. More complex products may be considered for analysis, for example those with a reconstitution step, a dilution in a bag, or more complex dilutions for example for filling elastomeric infusers.

The health and safety risks of handling cytotoxic products in the laboratory are a major concern and analysis should be carried out using containment devices and closed vessels such as sealed UV cuvettes. There are techniques available (see below) to use UV spectrometry and/or Raman spectroscopy on small samples removed from cytotoxic infusions, and in countries such as France this analysis is carried out routinely[4,5,9]. Standard UV methods can also be used, ideally utilising capped disposable cuvettes.

Testing may be prospective with results available to inform product release or retrospective as part of ongoing process and operator validations.

Case study 1: Analysis of cytotoxic products using UV / Raman Spectroscopy[4]

Within France the analysis of cytotoxic products compounded for an individual patient is carried out prospectively and products cannot be released for use until a pass result from this analysis has been obtained. The use of coupled UV spectroscopy and Raman Spectroscopy (QC Prep®) has enabled the efficient analysis of a range of cytotoxic drug preparations over a 2 minute analysis time. The combination of UV and Raman spectroscopy provides enough information to identify and discriminate some structurally related molecules from the spectra and also to identify the solvent. A 1.2mL sample is required for analysis this may be significant for small volume infusions (50mL or less) but would not be significant for larger volumes, for volumes below 50mL an additional 1ml is included as part of the product so that on removal of the sample the intended volume was presented.

The main drugs studied in the article on which this case study is based were asparaginase, cyclophosphamide, cytarabine, daunorubicin, doxorubicin, etoposide (base and phosphate),ifosfamide, methotrexate, vinblastine and vincristine

4.2 CIVAs products

This is probably the simplest product group for which various analytical techniques are available; the techniques used range from HPLC and uHPLC methodology to simple UV spectroscopy and ion analysis using various techniques. Although there may be some health and safety concerns, for example where handling antibiotics or potent pharmaceuticals (e.g. for preparation of standard solutions), these are normally relatively easy to control.

Batch prepared CIVAs products, particularly where there is a bulk fluid stage ahead of packing, should be considered for routine chemical analysis, whether these are prepared for stock or for a specific patient. It should be noted that homecare patients may not be monitored as closely as hospitalised patients and may not have an easy method of reporting problems so these patients should be considered at higher risk of being impacted by errors in preparation.

Testing may be prospective with results available to inform product release or retrospective as part of ongoing process and operator validations.

Case study 2: analysis of Ceftazidime from a bulk manufacturing stage

CEFTAZIDIME ASSAYof 3g/100ml

Transfer 5ml of the solution into a beaker. Micropipette 100µl into a 200ml volumetric flask add 5ml dilute hydrochloric acid and make up to volume with water and mix well. Determine the absorbance of the solution scanning from 310 to 210nm using water as a blank. There is a maxima at about 260nm.

$$\% \text{ label strength} = \frac{\text{Absorbance} \times 4 \times 100}{0.953 \times 3}$$

Limits 90.0 - 110.0% (To account for variation in the original vial plus variation in the preparation method and analytical method)

Case study 3: analysis of Meropenem from a bulk manufacturing stage

MEROPENEM ASSAY: 90.0 - 110.0% of 10mg/ml
Transfer 5ml of the solution into a beaker. Micropipette 100µl into a 100ml volumetric flask and make up to volume with water and mix well. Determine the absorbance of the solution scanning from 350 to 250nm using water as a blank. There is a maxima at about 298nm.

$$\% \text{ label strength} = \frac{\text{Absorbance} \times 100}{0.275}$$

Limits 90.0 - 110.0% (To account for variation in the original vial plus variation in the preparation method and analytical method)

4.3 Parenteral Nutrition (PN)

PN is usually the most complex product prepared within aseptic services, although more recently there has been a move to standardisation and using off-the-shelf bags. Testing should be commensurate with risk but should be considered where bags are compounded from scratch using automated compounders or gravity-fill methods. In the case of automated compounders analysis will form a significant part of initial validation of the equipment, and the revalidation following servicing or repair, it should also be part of ongoing validation of the compounder set-up and its performance for example by using a daily test bag to confirm this. Ideally test bags should be carried out at the beginning and end of each session (once the tubing set has been set-up and just before it is removed).

For bags made using other pump systems and gravity fill techniques or where there are substantial additions to a base bag then testing on an individual bag basis should be considered although, in order not to impact on sterility assurance, samples need to be taken before final seals are in place.

Testing may be prospective with results made available to inform product release or retrospective assessment after product release as part of ongoing process and operator validations. There is now a monograph for Parenteral Nutrition Solutions within the British Pharmacopoeia[2], this covers analysis of the main cations, assessment of dextrose and a limit test for aluminium alongside sterility and endotoxin requirements.

Case study 4: Analysis of a compounded lipid containing parenteral nutrition solution

Following compounding, with the parenteral nutrition bag still within the grade A zone and before the final seals are added to the bag, a 5ml sample is taken from the bag and supplied to the QC laboratory.
The laboratory splits the sample into three appropriate aliquots the first aliquot is diluted and used for ICP or AA analysis of sodium, potassium, magnesium and calcium levels which are compared with calculated concentrations of these electrolytes based on the formulation.
The second aliquot is passed through a 0.2 micron glass fibre filter straight onto the refractometer plate. The result (on the glucose scale of the refractometer) is compared to the theoretical calculated result for the formulation. The third aliquot undergoes the BP test for phosphates, with a light yellow colour indicating the presence of only organic phosphate (sodium glycerophosphate), and a dark yellow colour indicating the presence of inorganic phosphate in the sample (there may additionally be organic phosphate present).

4.4 Biopharmaceuticals

In general these are too complex to carry out full final product analysis, although some techniques such as UV absorbance will give a very non-specific assay result or protein content provided the product is a simple solution in water or saline. Bazin et al[10] report using combined UV and IR spectroscopy to analyse a range of monoclonal antibody products for which a library had been built (case study 5).

As stated above end of shelf-life testing for biopharmaceuticals should follow the full yellow cover guidance[7] although if this is an ongoing confirmation of robust initial stability studies abridged testing can be considered as long as the assays used will pick up changes within the molecule, for example an activity-based assay, sub-visible particle counts and mass spectroscopic assay may be sufficient, depending on suitable validation. There must also be a standard or T=0 freshly prepared sample using the same original batch number of the active drug product, sample alongside the end of shelf life testing as methods are comparative looking at changes.

Case study 5: Analysis of Monoclonal antibody products using combined UV/ IR spectroscopy[10]

Implementation of a systematic control for preparations based upon monoclonal antibodies using a Multispec automaton which combines ultraviolet (UV) with infrared spectroscopy. Using a new in-house spectral library with restricted zones in the infrared domain and another correlation calculation mode enabled the generation of fast and reliable results. The unit are currently using the technique for the routine control for every monoclonal antibody that they handle (alemtuzumab, bevacizumab, cetuximab, gemtuzumab ozogamycin, panitumumab, rituximab and trastuzumab).

5. Analytical Methods

The methods discussed here are those which may be used for the first three product groups as appropriate. For further information on analytical techniques used for biopharmaceuticals please refer to A Standard Protocol for Deriving and Assessment of Stability Part 2 – Aseptic Preparations (Biopharmaceuticals)[7]. There is also information on the analysis of parenteral nutrition in A Standard Protocol for Deriving and Assessment of Stability Part 4 – Parenteral Nutrition[8].

5.1 Appearance

The appearance of the solution can be an important marker of problems either with the formulation or stability hence it is important that all analytical specifications include a product descriptor and ensure compliance with it.

5.2 High performance liquid chromatography (HPLC) / ultraHPLC (uHPLC)

HPLC and uHPLC are commonly used laboratory techniques which can be used for analysis of a variety of pharmaceuticals including complex mixtures such as the analysis of specific amino acids and vitamins in parenteral nutrition. Size exclusion chromatography is also a major technique in biopharmaceutical analysis. In general HPLC offers an assay and identification (by comparison with a standard) in the same

technique. It can be quite time consuming and may not be a practical solution if results are required prospectively for a short shelf life or named patient product, however there have been recent innovations to increase the throughput of the technique. (Case study 6)

Case study 6 : Analysis of Morphine 1mg/mL using HPLC Method

Injection Volume	50 µL
Mobile Phase A	Acetonitrile (20%)
Mobile Phase B	0.05M KH_2PO_4 (80%)
Flow Rate	1.0 mL/ min
Column	Phenosphere CN, 150 x 4.6mm, 5µm
Column Temperature	20 ^{o}C
Wavelength	240 nm

Standard uses original licenced morphine product used as a starting material and previously tested against a reference standard. Standard system suitability tests need to be run ahead of the test samples.

Run time: 6 minutes

Morphine peak: 2.8 minutes

5.3 UV / visible spectroscopy

Can also provide an assay and identification test in one analytical technique and is useful for many CIVAs type products including antibiotics, pain control agents also for cytotoxic drugs and as a crude assay of protein content with biopharmaceuticals. In general a calibration curve is required and an extinction coefficient determined for each molecule (A 1%, 1cm). There is then no requirement for a standard for subsequent analysis. There is potential for interferences from other constituents in a formulation including anti-microbial preservatives and at certain wavelengths diluents including dextrose.

5.4 Infra-red / Raman spectroscopy

Standard Infra-red analysis (FTIR) tends to be excellent for identification but is less used as a quantification technique. However, techniques such as Raman spectroscopy are now being used for rapid analysis of pharmaceuticals. Alongside a UV assay the Raman spectrum can provide confirmation of product identity.

5.5 Combined UV / IR spectroscopy

Methods combine the fingerprint identification of the IR spectrum with the UV assay for the active ingredient.

5.6 Atomic Absorption (AA), Atomic Emission (AE) and Inductively Coupled Plasma (ICP) testing for electrolyte levels

Sodium and potassium levels can be measured using AE spectroscopy or Flame Photometry (FP). Levels of these and other key cations including calcium and magnesium can be measured using AA spectroscopy or Inductively Coupled Plasma (ICP) spectrometry, techniques which are also suitable for sodium and potassium. ICP can also be used to measure many of the other elemental constituents of PN including certain non-metals, trace elements and also impurities such as aluminium.

5.7 Refractive Index

Refractive index can be used to assay sugars and to confirm the general composition of a PN formulation when it will be mainly influenced by the glucose and amino acid concentrations in the formulation. High levels of electrolytes and organic salts such as gluconate and glycerophosphate will also have an influence on the final refractive index. A matrix calculation can be used to generate a theoretical refractive index and to compare with the measured level. For lipid-containing admixtures the lipid will need to be filtered out (using a 0.2micron or similar filter) or centrifuged out ahead of testing and a relevant adjustment made to the calculation (see below for an example).

5.8 Optical rotation

This can be a useful technique for the analysis of sugars and parenteral nutrition composition, similar to the situation with refractive index there can be interferences from other constituents of complex formulations and a theoretical value may need to be calculated based on the influencing ingredients.

5.9 Other physical measurements

Osmolality or specific gravity can also offer some indication of the correct compounding of the admixture. Note that all of these methods are non-specific and the measured values are influenced by all components present in the mixture, hence they are only indicative. They can, however, be used on the whole sample including a lipid phase.

5.10 Test tube identification tests

The BP test for phosphates is suitable for determination of the phosphate salt used in PN. Lipid bound phospholipid gives a negative result within the normal test timeframe (no colour change). If required the total amount of phosphate can be assessed by chemical methods or using ICP.

Calculation for theoretical Refractive Index for a lipid containing Parenteral Nutrition

Glucose is a non-linear relationship therefore first calculate the glucose concentration in the bag

300ml glucose 50% in 2000ml = $\frac{300 \times 50}{2000}$ = 7.5%

This gives a factor of 0.96* from the table

Factors for Calculation of Dextrose Refractive Index

Final Glucose Concentration	Refractive Index Factor
0 - 5%	0.98
5.1 - 10%	0.96
10.5 - 15%	0.95
15.1 - 20%	0.93
20.1 - 25%	0.91
25.1 - 30%	0.89
30.1 - 35%	0.88
35.1 - 40%	0.87
40.1 - 45%	0.86
45.1 - 50%	0.84

Ingredient	Volume (V)	RI factor (R)	V x R
Synthamin 17 EF	444ml	12.2	5417
Glucose 50%	300ml	50 x 0.96*	14400
Sodium Chloride 30%	7.7ml	28.4	219
Potassium Chloride 15%	30ml	12.5	375
Sodium Glycerophospate 21.6%	10.3ml	21.0	216
SMOFlipid 20%	300ml	2.4	720
Magnesium sulphate 50%	4.0ml	26.2	105
Calcium chloride 14.7%	10ml	19.8	198
Solivito	10ml	0	0
Additrace	10ml	0	0
Water for injection	874ml	0	0
Total volume	2000ml		21650

Volume adjustment 300ml 20% lipid therefore remove 60ml use volume 2000 – 60 = 1940ml

Theoretical refractive index = $\frac{21650}{1940}$ = **11.2**

Measure the actual refractive index on the refractometer glucose scale after filtration to remove the lipid.

5.11 pH

pH may be an important test for some products including antibiotics compounded with buffers in order to offer enhanced stability and shelf-life. pH changes can also be an early sign of product instability, and pH limits are often specified in BP monographs.

5.12 Biological reaction tests

These may be useful for analysis of dilutions of heparin and work on the same principle as the clinical action of the drug, these can be sourced as CE marked kits such as the chromogenic assay kit. These have been largely superseded by other techniques such as HPLC but can be quick to use and accurate at low concentrations.

6. Method validation

All methodology used should be validated to ensure it will perform consistently and reliably. Method validation should be carried out initially and may need to be repeated on occasion based on a risk based decision. NHS Guidance[11] and ICH guidelines[12] can be referred to for more detail on this matter. Furthermore, for techniques such as HPLC system suitability tests are run on each analysis to demonstrate ongoing validation.

7. Endotoxin testing considerations

Where preparation is largely in compliance with the SmPC, e.g. when preparing a batch of antibiotic infusions or cytotoxic pre-filled syringes then the endotoxin limit on the starting materials and containers should ensure that the final product is compliant and unless the product has been contaminated during processing the aseptically prepared product should always comply. For complex products, however, where multiple starting materials are used in preparation and multiple components are used during the preparation process additionally to the final container then there should be an assessment as to whether endotoxin testing of the final product is required, either as a product validation or as a routine test. Note that the more complex a product the greater the difficulty in validating the endotoxin test due to the potential for interfering factors.

8. Sampling strategies

When sampling involves the removal of product from the batch at the end of processing sampling should be at random. Where sampling is for process validation it is important to ensure traceability of samples, particularly the first and last filled samples. If sampling is by removal of a sample from a bulk then it must be ensured that adequate mixing has taken place prior to the sampling process, for example by ensuring a validated shaking time. It must also be ensured that the last added ingredient has not remained pooled in the additive port as, even if this is to a small degree, it would have a significant impact on the result obtained.

9. Data Integrity Considerations

Data handling for all techniques should take place in accordance with good data integrity practice and audit trails within equipment data handling software and result recording systems should be enabled. Systems should be risk assessed for compliance with the MHRA Data Integrity for GxP guidelines[13].

10. Out of Specification (OOS) results and considerations for investigations

Where products are being analysed prospectively then OOS investigations and decisions on product release can follow standard processes[14,15], although timescales for such investigations may need to be truncated where a patient is awaiting treatment.

For products which are analysed retrospectively then there must still be a full investigation to identify the root cause of the issue causing the OOS result. A

decision will need to be quickly reached as to whether any remaining product needs to be recalled, or whether the treating physician should be informed of the issue.

Following an OOS result then the validation status of the product, and other related products which may also be impacted, should be reviewed. Process revalidation should be considered as appropriate, the fate of other products produced using the same process validation should also be considered.

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