Risks Associated with the Outsourcing of the Aseptic Compounding of Parenteral Nutrition

Edition 1

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ACKNOWLEDGEMENT

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Introduction

In recent years NHS Trusts have tended to increasingly look at the option of outsourcing some or all of their aseptic compounding activities. This has been particularly true for the compounding of parenteral nutrition (PN) solutions.

It is acknowledged that aseptic compounding is one of, if not the, highest risk activities undertaken in pharmacy.

Within the field of aseptic compounding, PN solutions are amongst the most complex and high risk products that are handled, due to their complexity, the number of ingredients, complex stability issues and the potential for the support of microbiological growth.

The high risk nature of PN solutions has unfortunately been highlighted by a number of tragic incidents associated with compounding errors and microbiological contamination in recent years that have at times resulted in patient harm and even death.

These incidents have occurred in the UK and abroad, and within the UK have been seen in both NHS facilities and commercial specials manufacturers.

It is clear that wherever the compounding takes place, there is a risk of these errors and contamination incidents occurring and so robust systems need to be in place to ensure the risks are adequately controlled.

This is equally relevant whether the PN is made in house or when the decision is made by a Trust to outsource PN to an external third party provider whether NHS or commercial.

The purpose of this document is to give guidance to those outsourcing PN compounding on the risks in the outsourcing and supply process and to enable them identify where local risk control strategies will need to be developed and implemented to manage these risks.

However, many of the risks highlighted will also apply to in house compounding and so those NHS units making PN for their own patients may also find this document a useful source of reference.

Exploring the drivers for outsourcing and whether this is in fact the best option for supply of PN solutions is outside of the scope of this document; however these should be considered before an outsourcing decision is made.

Responsibilities

The risks to patients remain when a decision is made to outsource and Chief Pharmacists have a responsibility to ensure appropriate approvals and Quality Assurance checks are in place.

It is essential that the responsibilities of both the contract giver (purchaser) and contract acceptor (manufacturer) are clearly defined and formally agreed by each party in line with EU GMP (1). A full Technical Agreement detailing the key aspects of the service, responsibilities and KPIs needs to be in place. This needs to be more than a standard template document and must consider specific local circumstances and needs. Realistic expectations of service provision must be agreed between both parties and responsibilities for quality must be defined in a technical (quality) agreement

It must be highlighted to all of the purchaser's staff involved in the prescribing, receipt and dispensing of compounded PN solutions that these are unlicensed products and as such this places particular responsibilities on the staff involved.

The NHS Pharmaceutical Quality Assurance Committee guidance document entitled 'Guidance for the Purchase and Supply of Unlicensed Medicinal Products – Notes for Prescribers and Pharmacists' states:

A practitioner prescribing an unlicensed product or for an unlicensed indication, does so on his/her own responsibility. Consequently he/she carries the burden of the patient's welfare and in the event of adverse reactions he/she may be called upon to justify his/her actions.
A pharmacist will share responsibility:

- **As the purchaser of the product, particularly where this involves specifying the product to be purchased;**
- **If his/her actions or omissions have contributed to the harm.**

In addition the manufacturer will be responsible for any breaches of Good Manufacturing Practice.

In light of point 1 above, pharmacists must be particularly aware of their responsibility for specifying a suitable product and not be reliant on the manufacturer ensuring this is the case. As such, pharmacists undertaking this role must have a suitable level of training in and knowledge of the formulation and stability of PN solutions. Quality Assurance measures should be in line with the receiving organisation's (contract giver's) unlicensed medicines policy

It must be noted that external suppliers cannot take responsibility for the clinical suitability of a PN formulation.

Technical Agreements

To capture all the detail above, a formal Technical Agreement must be in place between the purchaser and manufacturer. This needs to be a meaningful, live document that describes how the outsourcing arrangements and associated responsibilities of each party will be managed. It must not simply be seen as a regulatory requirement.

The technical agreement (TA) should be drawn up, agreed and signed by the purchaser and the provider of the service. It should define in practical terms the responsibilities of both parties with regards to the safety and quality aspects of the products provided.
A Service Level Agreement (SLA) will also be needed, defining the arrangements for the provision of a timely, cost effective and efficient service.

A standard template for a TA is to be included in the 5th Edition of the Quality Assurance of Aseptic Preparation Services book, and this is included as Appendix 2 to this document

Capacity and Contingency Plans

Purchasers must assure themselves that suppliers realistically have the capacity to provide the volume of products that they will be using. However purchasers must also enter into agreements with suppliers providing accurate and realistic data about the volume and length of supply likely to be needed.

Suppliers also need to have in place contingency plans to ensure continuation of agreed supplies.
Purchasers must assure themselves that their chosen supplier's plan is realistic and actionable. It may be appropriate to ask the supplier for evidence of the effectiveness of the plan.

Purchasers must be assured that their chosen supplier will not further subcontract work without an agreed written authorisation being received. This should be formalised in the TA.

Supplier Audit

A supplier audit will give a valuable independent insight into actual activities at a supplier's site, however it is only a "snapshot" on the day of the audit. Reliance will often be placed on an audit conducted by a third party.
Obtaining a copy of an audit report is only the start of the process. There needs to be a formal consideration of the audit report with regards to specific local circumstances of the purchaser. This should consider:

- **Knowledge and experience of the auditor**
- **When was the audit performed and is it still relevant?**
- **What was the scope of the audit and if this is relevant to the service required**
- **What was the outcome of the audit and what recommendations were made?**
- **What was the supplier's response to the recommendations and was this appropriate and timely?**

Stability and Shelf Life

Purchasers should not simply accept shelf lives as offered by the supplier but need to have an understanding of the basis for shelf life assignment.

PN stability is a complex issue that inevitably requires a degree of interpretation of available data based on matrices and assessed for each specific formulation, purchasers should have an insight into the source and quality of the data being used as a basis for the decision.

As such, purchasers need to have a sufficient level of knowledge of PN formulation and stability to allow them to make an informed decision as to the robustness of the shelf life being offered by their supplier. If this is not the case, they will need to have access to refer to other NHS colleagues with the appropriate level of knowledge.

Assessment must look at the quality of the data underpinning the allocated shelf life, not just the relative length of the shelf life as compared to other suppliers.

Ordering of PN bags

Ordering of PN bags inevitably results in the meeting of the purchaser's and manufacturer's systems and it must be remembered that where two systems meet there is always the potential for confusion and errors at the interface.

Consideration must be given to standardisation of the format of orders. Whilst inherently, purchasers are likely to prefer to remain with their established system, the overall picture must be considered.

Large suppliers are likely to be dealing with considerable numbers of different purchasers and if all of them continue to use different documentation formats for ordering the overall potential for errors will be considerably increased.
Use of the specific manufacturer's standard format form is therefore encouraged.

Order times should be considered to ensure that the manufacturer has adequate time to process, compound and release the products in a timely and safe manner.

Microbiological Risks

Numerous incidents (2,3) worldwide over many years have highlighted the risks and possible tragic outcomes when PN solutions are contaminated with microorganisms during the compounding process.

Staff involved in the outsourcing process need to have an understanding of these risks, together with knowledge of their chosen supplier's systems and what monitoring and control measures are in place to manage these risks

The TA should require the manufacturer to inform the purchaser of microbiological out of specification results that could potentially impact on the quality of the purchaser's product.

Suitable arrangements should be in place within the purchasing organisation to knowledgeably assess the significance of this information.

Risk of Compounding Errors

Similarly, there have been numerous reported incidents (4) associated with the incorrect compounding (composition) of PN solutions, that have again been associated with patient harm and death.

Most frequently, these have been errors in glucose content of compounded bags, but other ingredients have also been implicated.

Staff responsible for the outsourcing process need to have an understanding of these risks together with knowledge of the compounding process used by their chosen manufacturer including the validation of automated compounders and the controls and tests incorporated into their processes to manage these risks.

Procurement staff should involve their Quality Assurance colleagues to support them in the outsourcing process.

Chemical and Microbiological Testing of PN Bags

Purchasers must be aware of the type and frequency of process validations undertaken and be assured that these, combined with other control measures and testing, offer a satisfactory level of assurance of the compounding process.

Purchasers must be aware of each manufacturer's capability with regards to the chemical and microbiological testing of compounded bags and the type of compounding process used and in conjunction with the manufacturer agree and specify a level of testing that they as the purchaser of the bag are satisfied gives them an adequate level of assurance in the quality of the products supplied.

Purchasers need to be aware of the range of chemical and microbiological testing techniques that may be applied to compounded bags and how this may be affected by the method of compounding.

Acceptance limits must also be agreed with the supplier.

Procurement staff should involve their Quality Assurance colleagues to support them in the outsourcing process.

Chemical testing may be by taking a sample from the compounded bag, or if an automated compounder is used another option is for the manufacturer to run a test bag after set up and every time a critical ingredient is changed and to test this to confirm correct placing of ingredients on the compounder.

The additional risks associated with the extra aseptic manipulation involved in taking a sample must also be considered.

Most chemical testing will be performed on lipid free sample bags or on samples taken before lipid is added as the lipid will add to the complexity of the testing.

However, generally the testing of lipid containing bags is possible and purchasers must be aware of the advantages and disadvantages of testing samples with lipid and without.

The sections below highlight specific testing methods that may be used and that purchasers need to consider and understand how they may be used before selecting a supplier of PN.

Glucose Testing

This can be carried out by refractometry.

Many compounding incidents associated with PN have involved incorrect glucose concentrations, so testing of this component should be considered. This should be specified by the purchaser if required..

Whilst testing gives a level of assurance it is also important to consider process design, for example minimising the number of concentrations of glucose in use and employing robust checking systems.

Other guidance has also highlighted some of the risks associated with the use of multiple strengths of ingredients such as glucose and electrolytes and the need for rationalisation (5).

Refractive index is not a specific test for glucose and other ingredients such as amino acid solutions and indeed high levels of some electrolytes will cause a degree of interference, nevertheless if this is understood it can give a relatively accurate indication of glucose concentration.

Electrolyte Testing

The range of electrolytes to be tested must be agreed between the purchaser and manufacturer and appropriate acceptance criteria set and defined in the TA and on the Certificates of Analysis. Testing is likely to consist of sodium and potassium ion concentrations as a minimum and calcium and magnesium ion concentrations may also be specified. It is feasible to test for other electrolytes and this may be desirable in certain specialised cases.
A range of testing methodologies can be used including atomic emission, atomic absorption (AA), ion chromatography (IC) and inductively coupled plasma techniques (ICP).
ICP offers the advantage of more rapid testing results and greater ability to detect trace elements but does involve greater equipment and validation costs.

Sterility Testing

In general, the approach to sterility testing of PN products has been to either produce additional bags in each batch or to use unused bags. This approach of course assumes the tested bag represents the whole batch.

Arrangements for sterility testing should be agreed between the manufacturer and the purchaser and defined in the TA. As a minimum these should in line with MHRA expectations (6).

As well as sterility testing processes used, purchasers should be aware of what end of session and operator validation schedules the manufacturer is using and be satisfied that the total testing programme provides a sufficient level of sterility assurance for their compounded products.

Traditional sterility testing requires incubation for 14 days and so results are for the most part retrospective and simply give historical assurance data for the process.

New rapid microbiological techniques are being developed and some manufacturers are considering the potential for these to give sterility results before product release.

Purchasers must be aware of (or seek appropriate expert advice on) how these technologies are used and that this gives an appropriate level of sterility assurance for compounded products being purchased.

Particles

It is accepted that the BP and EP specification states practically free from visible particles and a practical approach should be taken.

Particle identification is subjective based on time spent looking, quality of light and individual looking.

Manufacturers should be asked what methods they employ to minimise bags being released with potential particles but it is difficult to guarantee they will be particle free 100% of the time.

Purchasers should also have an understanding of giving sets in use in their Trust to ensure all fluids administered are filtered appropriately during use.

Logistics

Purchasers need to be aware of the logistical arrangements for the delivery of bags to their site(s) and agree with the manufacturers that these are appropriate and will give a high degree of assurance that the bags have not been adversely affected during transport. Evidence to demonstrate compliance with this requirement should be able to be provided by the manufacturer.

Issues to be considered include whether refrigerated transport is used or a time limited cold chain transfer box. What contractors will be used and what are likely transit times?

For refrigerated transport, are delivery specific data available and will notification of excursions be given?

For cold chain transfer boxes, how and for what period have they been validated, did this reflect realistic worst case scenarios and is there ongoing monitoring or revalidation of specific deliveries?

Consideration should be given to any arrangements in place for the receipt of deliveries out of hours.

Complaints and KPIs

Formal systems with agreed, named contacts are needed for communication between the purchaser and manufacturer regarding complaints associated with products and services.

Purchasers need to have knowledge of the supplier systems for dealing with complaints and to be assured that robust systems are in place to provide timely feedback on subsequent investigations and corrective and preventative actions.

Responsibilities in relation to complaints and recalls should be clearly defined in the TA.

A meaningful set of Key Performance Indicators must be agreed by both the purchaser and supplier and these should be subject to discussion at a formal review meeting at least annually.

In addition to service related items, eg turnaround times, KPIs should include some quality indicators such as out of specification results and complaints etc.

Purchasers should however have ongoing programmes of monitoring trends in KPIs and a formal mechanism should be agreed for raising any significant problems identified with the supplier between review meetings if necessary.

Risk Assessment and Supplier Approval

As a result of the complexity of the factors that need to be considered before selecting a manufacturer for the outsourcing of PN compounding, it is recommended a formal documented risk assessment is undertaken and the conclusions endorsed within the organisation at board level. It may be appropriate to place any agreed, accepted risks identified on the organisation's risk register.

A Risk Assessment template is included as Appendix 1.

References:

1. EU Guidelines for Good Manufacturing Practice for Medicinal Products for Human and Veterinary Use, Chapter 7 Outsourced Activities, January 2013.
2. Public Health England, 1st July 2014, Bacillus cereus infections, retrieved from https://www.gov.uk/government/news/bacillus-cereus-infections-1-july-2014 on 8th April 2015
3. Irene Kramer, 2013, Management of a Microbial Contamination incident, retrieved from http://www.gerpac.eu/spip.php?article957 on 8th April 2015
4. BBC News, October 2008, Hospital fine cut over baby death, retrieved from http://news.bbc.co.uk/1/hi/england/london/7649398.stm on 8th April 2015.
5. Improving Practice and reducing risk in the provision of parenteral nutrition for neonates and children, A report from the Paediatric Chief Pharmacists Group, November 2011
6. MHRA Questions and Answers for Specials Manufacturers, January 2015, https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/400232/Guidance_for__specials__manufacturers.pdf

Document History	Issue date and reason for change
Version 1	Issued June 2015
Version 2	
Version 3	
Version 4	

Appendix 1: Risk assessment of Outsourcing Parenteral Nutrition Supply

	Factors for Consideration when determining risks **Tick when high-risk practice is found**	✓	**Suggested risk reduction method**	**Comments/revised score** **Tick if high-risk practice remains unchanged**	✓
1	Clinical prescription requirements		Agree to type of bags required (standard bags with additions or compounded all in one or two bag systems). Consider manufacturing risks of compounded bags and additions to standard bags.		
2	Transcription to order form		Agree to an order form (listing components and quantities in units) and create an SOP and an accreditation to transcribe prescriptions to order forms.		
3	Order deadlines		Establish time for the ward round and transcription activities to be completed if for same day delivery. If prescribing in advance for next day delivery then agree on a secondary deadline to distribute the workload. Consideration for services around weekends and bank holiday services and maintenance days.		
4	Choice of ingredients		Agree on range of ingredients required. If a particular ingredient is required e.g. lipid source, strength of glucose, select trace elements, etc., have these listed as options on the order form and include this in the SLA. Any changes to be mutually agreed to assigning appropriate timelines.		

5	Stability assessment		Audit stability assessment process. Establish criteria for stability assessments and agree to responsibilities for stability assessments and process. Of particular note should be when used mixed manufacturers for bulk ingredients.		
6	End product testing		Establish what end product testing is carried out and agree a specification and limits.		
7	Sterility assurance		Establish alerts and action limits and when to notify users as part of the TA.		
8	Cold chain supply		Validation of the cold chain supply. Special considerations for seasonal variation and distance to travel, especially if an overnight delivery.		
9	Turnaround times and late delivery		Establish out of hours contact time and set deadline for receipt of PN, incorporating dispensing time and distribution from Pharmacy to the ward. Assess risk to patients if there is a break in therapy if the delivery is delayed.		
10	Dispensing of bags		Create an SOP with a training module with an accreditation to be able to dispense outsourced bags. Assess critical criteria to check. Consideration for same day delivery will have implications on late delivery times and possible breaks in therapy on the wards.		
11	Variations on labelling and associated paperwork		Agreement on what will be on the documentation and labels received with the product. In accordance with local requirements, any additional documentation or additional information should be added according to the dispensing SOP. Product specifications should be requested.		

12	Capacity limits of manufacturer		Establish capacity limits of order as part of SLA. Include in the SLA the proviso of notification when capacity exceeded by supplier. Contingency supply plan needs activating at this point. Planned disruptions to service require an agreed notification period to allow for clinical management of supply.		
13	Limited supply		Review contingency plan and local management of supply of standard bags.		
14	No supply		Review contingency plan and potentially SLAs with two other suppliers.		

Point	Hazards			Initial risk			Controls	Reviewed risks		
	Description	Effect on service	Patient	Severity	Likeli-hood	score		Severity	Likeli-hood	Score

Appendix 2

Technical (Quality) Agreements

Introduction

The aim of this Appendix is to provide guidance to aseptic units on technical agreements that are required to define the responsibilities of the unit (the contract giver – CG) and the provider of the service or product that is outsourced (the contract acceptor – CA).

Technical agreements define the responsibilities of both CG and CA with respect to any issue that can impact on product quality, and should be signed off by a person in a "Quality" role. They are different from Service Level Agreements (SLAs) which generally have a financial and legal focus and cover, for example, timeliness of service, period of notice etc. SLAs are appropriately signed off by procurement personnel.

Technical Agreements (TAs) should be in place, and regularly monitored according to EU GMP, for any outsourced activity or product that can have potential quality implications. TAs should be in place with external providers of the following:

- Cleanroom Launderers
- Cleaning services
- Estates (particularly for Private Finance Initiatives)
- Laboratory services
- Outsourced Compounding
- Maintenance services for critical equipment, eg compounders, isolators, laminar flow cabinets, computer software, dose calibrators, air handling units
- Temperature monitoring equipment
- Transport

This list is not exhaustive and serves only to illustrate key services for individual consideration by each aseptic unit. TAs are also referred to in several chapters of the main text.

The following TA is an example of the style of agreement that is generally considered acceptable. The body of the TA defines clearly its scope, relevant standards, and responsibilities in general terms. The Appendix to the TA defines responsibilities in the form of a table, with clarity as to whether the CG or CA is responsible for each aspect. The table should mirror the responsibilities described in general terms in the body of the TA. Other styles of TA may, however, be equally acceptable if they fulfil the same criteria.

QUALITY TECHNICAL AGREEMENT

FOR THE MANUFACTURE AND DELIVERY OF SUPPLEMENTED PARENTERAL NUTRITION

Between

Name of NHS Organisation (Contract Giver – CG)

And

Name of Supplier (Contract Acceptor – CA)

Validity: This agreement is valid for 24 months after the date of the final signature or earlier if requested by either party

Version:
Reference:

QUALITY TECHNICAL AGREEMENT
For the Manufacture and Delivery of Supplemented Parenteral Nutrition

This Technical Agreement is made between:

Name and Address if NHS Organisation (CG)

and

Name and Address of Supplier (CA)

Production Unit Site Address:
MS number:

This contract is supplemental to any financial agreements and any subsequent agreements, between the two parties and will last for the duration of the agreement. The technical agreement shall be reviewed every 24 months or earlier if requested by either party.

This Technical Agreement is executed in duplicate, all of which shall be deemed to be originals, and all of which shall constitute one and the same Agreement binding upon both parties.

This Quality Technical Agreement shall be effective as of the date of the final signature and shall remain in effect until review or termination.

1. Scope

This agreement defines the roles and responsibilities between CG and CA relating to the manufacture and delivery of unlicensed supplemental parenteral nutrition (PN) for patients under the care of CG.

All parties agree as follows:-

2. Subject of the Agreement

1. CA is a provider of ready-to-administer supplemented PN which is manufactured according to an agreed specification and delivered CG.

2. CA shall manufacture and deliver the products in accordance with this technical agreement and in addition to other financial agreements.

3. CA is subject to registration and inspection by the competent national authorities and holds the necessary manufacturing licence according to the respective legislation.

CA hereby acknowledges that CG is relying on the skill and experience of CA in the proper manufacture and delivery of the contractual products under this Agreement and CA accordingly warrants to CG that:

- The product shall be of satisfactory quality and fit for purpose.

- The product shall comply in all respects with order provided by CG

Both parties will strictly observe the detailed pharmaceutical responsibilities which are specified in Appendix 1 (“Responsibilities”).

CG and CA must appoint Contact Persons as named in Appendix 2 (“Contact Persons”).

3. Regulatory Information

CA is responsible for ensuring that manufacture and distribution of products meets all current legislation and best practice guidelines.

For the period of the contract CG will ensure that they hold suitable MHRA approval for the supply of unlicensed supplemented PN.

4. Starting Materials

CA shall source starting materials which possess a UK marketing authorisation or which have been manufactured under a ‘manufacturers specials’ licence. Materials must be sourced from a bona fide Manufacturer or Wholesaler holding a UK Wholesale Dealer’s Authorisation.

5. Manufacture

CA shall provide adequate premises, equipment and staff to satisfactorily carry out the work undertaken. CA shall perform all operations in accordance with Good Manufacturing Practice.

CA shall manufacture the PN in accordance with the specification provided by CG.

CA shall refrain from performing any activities that could adversely affect the quality of the service provided

6. Quality Control / Assurance

CA must provide sterility assurance of all products purchased by CG. The method to determine sterility assurance must be in line with current pharmacopoeial requirements and be compliant with current guidance e.g. MHRA Q&A’s.

CA shall obtain satisfactory stability information for each supplemented PN bag before allocation of an expiry date. This data shall be provided to CG upon request.

Release of each batch of product shall be under the authority of an authorised releasing officer.

CA shall maintain a suitable Pharmaceutical Quality System.

CA acknowledges that CG will perform sample inspection on batches received. Any deficiencies found during sample inspection which relates in some way to the Product supplied by CA will be notified back to CA at the earliest opportunity this may lead to a formal complaint.

CA shall provide Certificates of Conformance for each batch supplied. The Certificate of Conformance shall at a minimum specify:

a. Name and site of manufacture.
b. Name or description of PRODUCT
c. PRODUCT Batch or Lot number
d. Batch size
e. Storage conditions

f. Expiry date
g. Date of manufacture
h. Statement that the product has been manufactured in compliance to applicable GMP requirements
i. Name and Title of person responsible for the validity of the certificate and the data it contains.

7. Storage and Distribution

CA shall adhere to Good Distribution Practice.

CA shall ensure that product shall be delivered in accordance with agreed procedures and records of delivery and receipt shall be retained by each party to affect a satisfactory audit trail in the event of recall.

CA shall store, handle and distribute the product according to its defined storage conditions.

CA shall be required to provide evidence that the appropriate storage temperatures have been maintained and that all systems have been validated upon request.

CA shall ensure all products are packaged in such a way as to give them adequate protection from damage during transit.

8. Documentation

CA will archive completed documentation according to current regulatory guidance.

9. Change Control

Information related to any planned change to the product, overall process or specification for the product(s) by CA is to be notified to CG in writing at the earliest opportunity and authorised by CG prior to the change being in effect.

It is recognised that problems relating to the supply of starting materials may require urgent action. The substitution of any starting material with an equivalent material that holds a UK marketing authorisation should be notified to CG at the earliest opportunity prior to implementation.

In the event of merger, acquisition or facility closure of CA or any of its agreed subcontractors, CA shall notify CG at least 3 months before the change is implemented.

CA shall not delegate or sub-contract any of the work entrusted to it under the Contract Agreement without prior evaluation and approval of the arrangements by CG. Any such arrangements made between CA and any approved third party shall ensure that the information relating to this contract is made available and remains confidential in the same way as between CG and CA.

CA shall be responsible for inherent responsibilities of their sub-contractors. Terms of this TA must be adhered to by any approved subcontractor.

10. Unplanned Deviations

Information relating to any major or critical unplanned deviation associated with the individual batch supplied or overall process by CA is to be notified to CG in writing at the earliest opportunity e.g. prior to the product being delivered.

Unplanned deviations which do not directly relate to a contractual product but could impact on the quality of a product purchased by CG should also be reported at the earliest opportunity.

11. Complaints

Any complaint from CG concerning quality of supplied product shall be acknowledged by CA within 24 hours.

A report containing details of the investigation with corrective and preventative actions as appropriate shall be forwarded to the CG within 10 working days; this may take the form of an interim report if the investigation has not been completed within this timeframe. The CA shall make every effort to complete investigations and provide feedback including actions assigned to CG in a timely manner.

Any complaint regarding non-adherence to this TA by either party should be escalated to the line manager of the relevant signatory for this agreement if a satisfactory outcome cannot be achieved by discussion. Ultimately if a satisfactory outcome still cannot be achieved, financial penalties or termination of the contract may be considered.

12. Recalls and Returns

CA shall notify CG of any recall or near miss (company or MHRA led) relating to contracted products manufactured by CA or starting materials / components which were used in their manufacture.

Recalls and near misses which do not directly relate to a contractual product but could impact on the quality of a product purchased by CG should also be reported at the earliest opportunity.

CA shall co-coordinate and document the recall process. CA is responsible for coordination and disposal of all products returned by CG patients. CA will co-operate with the collection, logging, storage and segregation of any recalled and returned product as required.

13. Audit

CG is responsible for assessing the competence of CA to carry out successfully the work required, this may be through review of a relevant audit performed on behalf of the NHS.

CA shall perform internal audits and perform audits of any outsourced activities.

CG is entitled to audit CA facilities relevant for the manufacture of the contractual products on a bi-annual basis and on specific occasions, e.g. “For-Cause-Audits”. Dates for bi-annual audits shall be mutually agreed at least 4 weeks in advance, For-Cause-Audits one working day in advance.

14. Confidentiality

The information contained in this agreement is confidential and must not be divulged to any other party without the permission of all signatories.

15. Contingency

CA must ensure a robust contingency plan has been arranged to ensure continuity of service in the event that they cannot provide the pre-defined quantities of PN as defined by CG. The use of any sub-contractors must be agreed by CG prior to implementation (see above). Any contingency partner must agree to the terms within this technical agreement.

Final Provision

Amendments of this Quality Technical Agreement and its Appendices may only be carried out by mutual consent and shall be made in writing. Any amendments to the appendices 1-5 may be signed for CG by a responsible Quality representative and together with the signature of CA the appendix will be binding upon the parties.

Appendices

Appendix 1 Responsibilities
Appendix 2 List of Sub-contractors
Appendix 3 Technical Agreement Approval
Appendix 4 Key Contact Persons
Appendix 5 Version History

Appendix 1
Responsibilities

	CG	CA	Comments
1. Regulatory Processes			
Hold appropriate 'specials' manufacturing licence of relevant national authority in order to manufacture products as agreed by CG. Comply with any and all EU and other local current applicable laws, regulations and guidelines relating to GMP and GDP. CG is to be informed of any changes to licence, outcome of regulatory inspection and any pending regulatory action. Actions to remedy any deficiencies identified by regulatory inspection shall be made available to CG upon request.		✓	
Ensure pharmacovigilance systems are in place to collect and collate information concerning all suspected adverse events / reactions reported to CG.	✓	✓	
Report pharmacovigilance events to CA.	✓		
Ensure competent authorities are notified of all complaints concerning suspected adverse events / reactions / lack of effect according to existing regulations and requirements.	✓	✓	

	CG	*CA*	Comments
2. Starting / Raw Materials and Excipients			
Purchase sterile materials from bona fide suppliers.		✓	
Assessing the quality of starting materials for use		✓	
All starting materials are TSE/BSE free		✓	
Maintain a supplier qualification program.		✓	
Check that the condition of all containers, closures, seals and labelling of delivered starting materials are satisfactory for use.		✓	
Approval of materials for use.		✓	

	CG	CA	Comments
3. Packaging Material			
Only purchase primary packaging materials from approved suppliers in accordance with a specification.		✓	

	CG	CA	Comments
Maintain a supplier qualification programme.		✓	
Check that the condition of all packaging material is satisfactory for use.		✓	
Approval of packaging for use.		✓	

	CG	*CA*	Comments
4. Processing			
Qualification / Validation according to applicable GMP requirements for production equipment, utilities and processes.		✓	
Maintain a suitable environment		✓	
Maintain a specific batch number system to identify individual products.		✓	
Manufacturing process including all necessary activities.		✓	
In-process checks are performed and are deemed satisfactory.		✓	
Appropriate design and use of manufacturing batch documentation.		✓	
All critical automated processes are fully validated and appropriate for use and meet the requirements of GAMP.		✓	
Ensure that all products are manufactured in accordance with the agreed specification and current legislation.		✓	
Medicines will be handled with appropriate safety measures.		✓	
Ensure all labelling of products is in compliance with all laws, regulations and guidelines associated with the labelling of unlicensed specials.		✓	

	CG	CA	Comments
5. Stability			
Provide stability data to support the allocated expiry of the products. Methods to determine product stability shall be in line with current regulatory requirements.		✓	This data shall be made available to CG upon request.

	CG	CA	Comments
6. Sterility			
Provide sterility assurance using methods defined in current guidelines.		✓	
Maintain a suitable system to record, investigate and risk assess all microbiological non-conformances (out of limit) results. Implement appropriate corrective and preventative actions following the investigation and root cause analysis.		✓	
Assess the potential impact a microbiological non-conformance (isolated result or 'trend') could have on product quality and patient risk and act accordingly.		✓	
Trend microbiological non-conformances.		✓	
An annual summary of all microbiological non-conformances should be made available to CG on request.		✓	
Inform CG of any microbiological non-conformances relating to products received by CG within 48 hours of receipt		✓	It is recognised that this may be in retrospect. Microbiological non-conformances which do not directly relate to a contractual product but could impact on the quality of a product used by a patient of CG should also be reported. The investigation and any associated corrective and preventative actions shall be made available upon request by CG.

	CG	*CA*	Comments
7. Product release			
Product release according to agreed criteria.		✓	
Preparation of documentation for release.		✓	
Have satisfactory systems in place that ensures patients only receive released products.		✓	
Released product conforms to order placed by CG.		✓	

	CG	CA	Comments
8. Storage / Distribution			
Qualification / Validation of storage sites for starting materials and products as appropriate.		✓	
Qualification / Validation of transport of the products from place of manufacture to the CG.		✓	
Store all Products and/or starting materials / other ingredients / excipients / auxiliary materials under appropriate conditions in compliance with GMP/GDP requirements and any licence requirements.		✓	
Maintain an audit trail to the patient.	✓	✓	
Delivery containers ensure the product is protected during delivery and complies with health and safety standards.		✓	
Distribute to the CG in a timely way as described in this technical agreement and other financial agreements.		✓	

	CG	CA	Comments
9. Documentation			
Ensure that prescription forms as well as records of manufacture and distribution are clear, readily available and retained for the period required by current legislation. Records shall ensure the traceability of the origin and destination of Products.		✓	
Archive documents for according to current regulatory guidance.			
Ensure written procedures are available to describe all operations that may affect the quality of the products.		✓	
Maintain complete and accurate records relating to the manufacture, packaging and storage of products supplied.		✓	
Store all documents and records so that they are easily retrievable and stored protected from loss and damage.		✓	
Maintain a record of batch numbers of all starting materials and products manufactured, supplied or returned in the event of a recall.		✓	

	CG	CA	Comments
10. Changes			
Maintain a suitable change control system and communicate all information relating to planned changes with quality implications in writing before implementation.		✓	See above for timelines.
Maintain a suitable unplanned deviation system and communicate all unplanned changes (unplanned deviation excluding microbiological results) deemed to be major or critical. Events shall be reported at the earliest possible opportunity e.g. before delivery of the product.		✓	Unplanned deviations which do not directly relate to a contractual product but could impact on the quality of a product used by a CG patient should also be reported. The investigation and any associated corrective and preventative actions shall be made available upon request by CG.
Results of any investigation relating to a major or critical unplanned deviation for a contracted product shall be provided in written format to CG within 72 hours of completion.		✓	This investigation must include proposed corrective and preventative actions.
No work should be sub-contracted without the prior written agreement of CG.		✓	

	CG	CA	Comments
11. Complaints			
Acknowledge any complaints from CG or patients of CG with quality implications within working 24 working hours.		✓	
Investigate and document any complaint relating to the quality of contracted products within 10 days, feedback may be in the form of an interim or final report. This document should include details of all corrective and preventative actions as appropriate.		✓	

	CG	CA	Comments
12. Recalls			
In the event of product or any starting materials or components being recalled, arrange for the collection, stocking and segregation of products affected. This also includes products which were manufactured using a recalled starting material or component.		✓	Must comply with timelines as specified in regulations

	CG	CA	Comments
Maintain a product recall procedure for use when it is necessary to recall a defective product from market, and test the procedure at least annually.		✓	This also includes products which were manufactured using a recalled starting material or component.
Advise CG if they have received products which are / contain starting materials which are subject to MHRA Drug Alert or Recall.		✓	Must comply with timelines as specified in regulations
Inform prescribers of any recalls concerning products supplied to patients.	✓		

	CG	*CA*	Comments
13. Audit			
Provide reasonable access, at agreed pre-determined times, to permit audits of the relevant facilities and documents by CG or the regulatory authorities.		✓	
Undertake the necessary quality audits of CA	✓		
Undertake the necessary quality audits of subcontractors as required for assurance of this agreement.		✓	
Conduct internal audit in order to monitor the implementation of and compliance with GMP and GDP.		✓	
Propose necessary corrective measures following internal audit.		✓	
Make available evidence of adherence to internal audit schedules.		✓	
Make available evidence of closure of external audits and inspections, and the anticipated date of the next MHRA inspection.		✓	
Conduct inspections of all subcontractors in order to monitor the implementation of and compliance with GMP and /or GDP.		✓	

	CG	*CA*	Comments
14. Training			
Staff involved in all aspects of the service will be adequately trained as appropriate to their role.	✓	✓	This includes training to outsourced contractors
Staff will comply with relevant legislation and NHS requirements concerning both patient and commercial confidentiality e.g. Data Protection Act.	✓	✓	

Appendix 2
List of Subcontractors

e.g. Couriers, Contingency partners and Contract Laboratories

Appendix 3
Technical Agreement Approval

Agreed on behalf of the Contract Giver

Name:	Name:
Title:	Title:
Signature: _____	Signature: _____
Date:_____	Date:_____

Agreed on behalf of the Contract Acceptor

Name:	Name:
Title: (QA Representative)	Title:
Signature: _____	Signature: _____
Date:_____	Date:_____

Appendix 4

Key Contact Persons

Contract Giver

Name	Designation	Contact number	E-mail

Contract Acceptor

Name	Designation	Contact Number	E-mail

Appendix 5
Version History

Version Number	Date of Amendment	Amendment(s) Made