DEFICIENCY SEVERITY MATRIX for EL(97)52 AUDITS

3 Minimising Risk with Injectable Medicines

Deviation from Standard –		
Complies / Negligible		**Severity Score (S)**
Current Injectables Medicines Policy (3.1.1) Organisational policies and SOPs for all items listed in 4.1.3, and associated roles and responsibilities (4.1.3)		
Risk assessments for the sites of preparation for all injectable medicines (3.1.2)		
No vial sharing for single use vials outside pharmacy (13.1.11)		
Location of preparation appropriate, with pharmacy involvement (level of risk determined by NPSA 2007)(3.1.3) System for communicating decisions on location of preparation – aseptic units / clinical areas (3.3.2)		
Current high risk (minimum) list of NPSA 'red' injectables (3.1.4)		
Risk assessment for new injectables e.g. D &T (3.1.5)		
Pharmacy strategy to reduce risk for all injectables (pharmacy prepared, out sourced, clinical areas) (3.2.1)		
Appropriate pharmacy catalogue (prepared and outsourced) available in clinical areas (3.2.2)		
Robust arrangements to specify the quality of outsourced aseptic products (3.2.3)		
Additions to PN only in pharmacy (3.2.4)		
Arrangements for PN out of hours satisfactory (3.2.5)		

Document Number: 004/06 Lead Authors: David Cope Martin Knowles Issued 31/01/2017
Replaces April 2015 Issue **FINAL**

3 Minimising Risk with Injectable Medicines continued

Arrangements for intrathecal chemotherapy comply with national guidance (see separate aide memoire) (3.2.6, 3.2.7)		
Vinca alkaloids labelled 'Fatal if given by any other route' (8.8.5)		
Intrathecal products labelled 'For intrathecal use only' (8.8.6)		
Handling of concentrated potassium complies with NPSA 2002 Alert and R-T-A products provided if possible (3.2.8)		
Preparation uses closed systems only (3.2.9) Ampoules only ever used for single withdrawal immediately after opening (13.1.9)		
Shortest practical expiry allocated to all products (maximum 7 days) (3.2.10)		
Residual risks recognised e.g. risk register (3.3.1)		
System for communicating heightened risks e.g. initiating contingency (3.3.3)		
All risks regularly reviewed e.g. risk register (3.4.1)		
System to review errors and incident organisation-wide and respond (3.4.2)		
System to learn from external events and respond to national alerts (3.4.3)		

4 Prescribing, Clinical Pharmacy and Aseptic Services Verification

Deviation from Standard –		
Complies / Negligible		**Severity Score (S)**
Prescription signed by approved prescriber (4.1.1)		
Current approved list of non-medical prescribers (4.1.2)		
Access to references e.g. BNF, Medusa , for all staff involved in prescribing and verification (4.1.4)		
Specialist references available for paediatrics and neonates, e.g. BNF for children (4.1.5)		
Chemotherapy regimes authorised by MDT, consultant or follow a CT protocol (4.1.6) Documentation includes details listed in 4.1.6.1 (4.1.6.1) Procedure for recording deviations from algorithms (4.1.6.2) Documentation control system for regimens (4.1.6.3)		
Conditions for supply of diagnostic radiopharmaceuticals against Nuclear Medicine requests comply with conditions listed in (4.1.7.1)		
Pharmacist verifying Nuclear Medicines request familiar with procedure (4.1.7.2)		
Protocol states clearly use of adjuncts (4.1.7.3)		
Clinical trials protocols authorised. Activities comply with CT legislation (4.1.8)		
All prescriptions (generated manually or electronically) clear, unambiguous, accurate (4.1.9)		
Standardised prescription format for each product type (4.1.10) Trust approved for paper or electronic prescriptions		
Computerised systems for prescribing or dose calculations fully validated. Roles and responsibilities, security and audit trails clear (4.1.11.a,b,c)		

4 Prescribing, Clinical Pharmacy and Aseptic Services Verification continued

Suitable arrangements and responsibilities documented for clinical pharmacy and aseptic service verification (4.2.1, 4.2.2) Clinical pharmacy verification of the original prescription covers all items listed in 4.3.1 (procedure is in place) (4.3.1) Patient details and dose checks for worksheets linked to electronic prescribing should be verified initially (8.7.4)		
Additional check carried out for chemotherapy (4.3.2)		
Suitable arrangements for checking full blood counts and monitoring toxicities (4.3.3)		
Additional checks carried out for PN (4.3.4)		
Maximum glucose concentration/osmolarity for use peripherally agreed. For greater concentrations of glucose, PN is labelled for central line only (8.8.4)		
London & SE Multidisciplinary team for PN5		
Any modifications to prescription are suitably verified and recorded (4.3.5)		
Additional checks carried out for radiopharmaceuticals (4.3.6)		
Robust systems if original prescription not present during preparations (4.3.7)		
Authorised Pharmacists carries out aseptic services verification and ensures clinical verification product is correct for intended route (4.4.1, 4.4.2)		
Prescription verification recorded on worksheet (4.4.3)		

5 Management

Deviation from Standard –		
Complies / Negligible		Severity Score (S)
Appropriate organisational Structure indicates clearly responsibilities and accountability of each member of staff (5.1.1) All accredited product approvers accountable directly to Accountable Pharmacist and in job descriptions (5.1.13) Where delegated product approval, management structure complies with national competency framework (5.1.14) All staff professionally accountable to Accountable Pharmacist (5.1.3) Accountable Pharmacist directly responsible to Chief Pharmacist (CP) (5.1.4) Accountable Pharmacist has title and responsibilities in their job description (9.1.2) Quality Management (QA) duties in job descriptions (8.1.4)		
Aseptic unit is managed by Accountable Pharmacist (AcP) who implements QA system (5.1.2)		
System for capturing staff suggestions for improvements and implementing regulatory changes (5.1.5)		
Supervision by an Authorised Pharmacist, including out of hours (5.1.6)		
Accountable Pharmacist authorises SOPs. Deviations approved and documented (5.1.8)		
Chief Pharmacist has effective governance arrangements for all injectable medicines (pharmacy, clinical areas, outsourced) (5.1.10)		
Chief Pharmacist responsibility for adequate resourcing documented in a policy (5.1.11)		

5 Management continued

Policy for aseptic preparation present. If delegated product approval, has board-level agreement (5.1.12)		
Regular quality management meetings. Chief Pharmacist aware PQS functioning correctly (5.2.4)		
PQS reviewed and Chief Pharmacist takes a risk management approach if quality is reduced (5.2.5)		
Culture of continuous quality improvement, e.g. learning from errors (5.2.6)		
Accountable Pharmacist authorises SOPs for product preparation. (If no evaluated data, patient-based decision made on clinical need and risks.) (5.2.7)		
Authorised Pharmacist risk-benefit decision for non-catalogue requests (5.2.8)		
Rationale for non-catalogue preparation recorded and AP informed (5.2.9)		
CP ensures QA system and off-site testing regularly reviewed (5.3.4)		
CP ensures regulatory compliance, e.g. for trials (5.3.5)		
Detailed contingency plan available (5.4.1)		
Current and effective capacity plan implemented (5.5.1)		
CP ensures capacity plan accepted outside pharmacy e.g. by Board (5.5.2)		
Workload figures regularly reviewed against capacity plan and action taken if necessary (5.5.3)		
Capacity plan ensures adequate resourcing, timely action if needed, and is comprehensive (includes QA and outsourcing workload) (5.5.4)		
Capacity plan reviewed at least annually and change control used if needed (5.5.5)		
London & SE Networking at all levels can be demonstrated both internally and externally		

6 Formulation, Stability and Shelf Life

Deviation from Standard –		
Complies / Negligible		**Severity Score (S)**
National (yellow-covered) standards used for stability studies (6.1.1)		
End of shelf-life testing used to provide additional assurance (6.1.2)		
Authorised Pharmacist ensures stability information valid and relevant (6.2.1) (Responsibility may be with the Accountable Pharmacist)		
References available and applicability carefully assessed, e.g. brands (6.2.2)		
PN stability assessed by matrix approach (6.2.3)		
Computerised systems used for stability calculations are validated (6.2.4)		
Stability data and stability assessments held on file (6.2.5) Controlled system for stability data (paper or electronic) (6.9.1)		
Documented risk assessment if no stability data (exceptional only) (6.2.6)		
Stability data obtained if (above) become routine products (6.2.7)		
Data interpreted and specifically applies, e.g. brands, concentrations (6.3.1) Extrapolation and interpolation used appropriately. (No extrapolation for biopharmaceuticals.) (6.3.2, 6.3.3) Identical practices used for biopharmaceuticals if expiry beyond SmPC (6.3.4) Degradation products considered for shelf-life (6.3.5)		
Factors which may impact on stability are considered, including nature of container, particularly for biopharmaceuticals (6.4)		

6 Formulation, Stability and Shelf Life continued

Integrity of final container assessed up to shelf-life (6.6.1)		
In-house integrity data or national data assessed as applicable is available (6.6.2)		
Infusion bags not spiked ahead of the time of their use in clinical areas (6.6.3)		
Expiry period based on all information available (microbiological and physio-chemical) (6.7.1)		
For biopharmaceuticals external data considered alongside in-house data (6.7.2)		
Expiry period reassessed if new data available (6.7.3)		
Maximum 7 day expiry (6.7.4)		
Starting materials and key components subject to formal change control (6.8)		
Data and assessments referenced on worksheets (6.9.2)		
Problems with products or patient adverse reactions investigated (6.10)		

7 Facilities and Equipment

Deviation from Standard –		
Complies / Negligible		Severity Score (S)
Design of new or refurbished facilities and equipment complies with the principles listed in section 7.1 (see standards) (7.1) London & SE Finishes and condition of facilities satisfactory London & SE Note: Will apply also to existing facilities with mitigation with design and age.		
Gaseous biodecontamination considered for new units/isolators (12.4.1)		
Validation included in Validation Master Plan that is authorised and subject to deviation and change control systems (7.1.3, 7.1.4)		
Clean rooms and clean air devices normally run continuously with no setback (7.2.1)		
Critical equipment including AHUs have been commissioned and have PPM are re-qualified and are operated according to SOPs (7.2.3)		
London & SE Workstation clean-up time validated.		
Technical Agreements (TA) for PPM of all critical equipment (11.10.1)		
Loss of environmental control subject to CAPA (7.2.4)		
Reports from visits reviewed, assessed against the TA and accepted by Accountable Pharmacist (7.2.6) (11.10.2)		
Access controlled and permit to work in place and appropriately signed off (7.2.7, 7.2.8) Normal operation confirmed after any maintenance (7.2.5)		

7 Facilities and Equipment continued

Unidirectional air flow cabinets (UAFC) and isolators appropriately sited (7.3.1, 7.3.2)		
Change rooms suitable design (7.3.3-7.3.5)		
Support rooms suitable design (7.3.7, 7.3.8)		
Materials transferred via dedicated hatches of suitable design (7.3.8-7.3.11)		
Additional considerations taken into account for specialist clean-room applications, e.g. ATMPs, blood labelling, cyclotrons (7.4.1-7.4.5)		
QC facilities physically separated from aseptic preparation and under suitable managerial control (7.5.1)		
UAFCs suitably sited and used to prevent disruption to airflow (7.6.1)		
Isolators suitably designed for products prepared, for both operator and product protection (7.6.2)		
Impact of equipment, e.g. auto-compounders, dose calibrators, on air flow is assessed (7.6.3.1)		
Suitable clothing and changing process (7.7.1-7.7.7) Entry and exit of personnel, gowning and gloving procedures acceptable (10.1.1.1 to 10.1.1.4)		
Clean room garments reviewed and subject to validated laundering (7.7.8)		
SOP details suitable changing frequency for garments (7.7.9, 7.7.10)		

7. 2 Facilities and Equipment Parenteral Nutrition Compounders

Deviation from Standard –		
Complies / Negligible		Severity Score (S)
Adequate Validation Master Plan, Installation and Operational Qualifications including draft SOPs		
Risk Assessment of general and local operational characteristics and health and safety issues including summary of all the critical control points		
Change Control for newly installed compounders		
Adequate Performance qualification including calibration and cleaning Final version of SOPs		
Robust IT protection and procedures including adequate back up systems and secure interface		
Adequate training and competency assessment records for all aspects including high level operations		
Manufacturer's recommendations followed for all operational aspects		
PPM schedule or manufacturer's support package		
Impact of auto-compounders on air flow is assessed (7.6.3.1)		
Controlled use of bar code identification system. Controls in place where bar code labels are printed and applied3		
Adequate control of source solutions drawn into syringes and connected to compounder		

7. 2 Facilities and Equipment Parenteral Nutrition Compounders continued

Documented evidence of critical checks and controls including set up and in process checks Correct starting material connected to correct line. Volume delivery check (10.1.4.4) Independent check on the required volume for each solution (10.1.4.4) These checks should be independent of set-up and may be either a second operator or automated verification e.g. barcode linking). Replenishment of starting solutions throughput the process should be similarly verified (10.1.4.4)		
Process and operator validations		
Sterility testing and accuracy testing ongoing		
Validated use of peripheral equipment e.g. scales		
Release specification based on documented evidence of satisfactory preparation All printed reports available for checking and final release3		
Controlled use of tubing and consumables associated with the compounder Tubing clamped before removal (10.1.3.19)		
Details of remaining manual additions (10.1.4.4) SOP for manual additions to part prepared bags and the attachment of lipid phase via lines and filters		
Reconciliation of starting solutions at the end of the session (10.1.4.4) Reconciliation of starting materials to ensure the correct quantity and strength Reconciliation of components3		

8 Pharmaceutical Quality System

Deviation from Standard –		
Complies / Negligible		Severity Score (S)
Robust PQS fully documented, e.g. in a quality manual (8.1.1, 8.1.2) PQS fully documented and effectiveness monitored (5.2.1)		
PQS adequately resourced (8.1.3)		
SOPs for product initiation, regular preparation, product discontinuation (8.2.1.1)		
SOP for documentation control covering, e.g. approval, archiving (8.2.2.1)		
Comprehensive and current VMP, including computerised systems (8.2.4)		
Suitable system for deviation management, including trending (8.2.5.1) Quality indicators, e.g. complaints etc recorded, investigated and trended (5.2.3)		
Appropriate level of investigation of deviations, e.g. RCA, CAPA (8.2.5.2)		
Suitable change control (CC) system, including impact assessment on product quality (8.2.6.1) Implementation of changes tracked and reviewed (8.2.6.2) Formal system for assessment of any proposed change (10.3.7)		
Periodic management review of PQS (8.2.7.1)		
Robust arrangements to specify the quality of outsourced aseptic products (3.2.3) Suitable TAs for any outsourcing (8.2.9.1)		
Sufficient resource to monitor TAs (products and services) (8.2.9.2)		
Comprehensive internal audit programme undertaken (8.2.10)		

8 Pharmaceutical Quality System continued

System for complaints (8.2.11.1)		
Complaints have timely close out and are reviewed (8.2.11.2)		
Comprehensive independently approved documentation process (8.3.1)		
Document controls in place (8.3.2)		
Worksheets and labels have standardised style for product type (8.3.3) London & SE Note: Where worksheets cannot be produced from an e-prescribing system e.g. multiple dilutions check if a second system is in use.		
Documents regularly reviewed. Superseded documents clearly identified and archived. Draft documents identified (8.3.4, 8.3.5)		
SOPs clearly written and include those listed in 8.4 SOPs for all equipment in use for aseptic processing (10.3.9)		
Individual worksheet from approved master (8.5.1)		
Worksheet enables traceability of starting materials and appropriate components (8.5.2)		
Completed worksheets appropriately retained (8.5.3) London & SE Note: Apply to all records		
Worksheets suitably designed and include items listed in 8.5.4 (8.5.4)		
London & SE Worksheets correctly completed SOP must include independent calculation check and method to be used1		
Clear differentiation of paediatric worksheets (8.5.5)		
Operation, cleaning, maintenance and fault logs for all facilities and equipment (8.6.1)		

8 Pharmaceutical Quality System continued

Planned deviation/temporary change control used for any products made outside SOPs (8.6.2)		
Records and trending of errors, near misses and investigations (8.6.3)		
Errors recorded via national reporting schemes (PASG/UKRG), trended and investigated (14.12)		
Units participate in national error monitoring schemes (PASG/UKRG) (8.6.4)		
Risk analysis, trending and CAPA in use (8.6.5)		
Record of Authorised Pharmacist supervising each session (8.6.6)		
Computerised systems (CS) have restricted access (8.7.1)		
CS used for document control, fully validated and as accurate as paper system (8.7.2)		
Back-ups for computer held masters and fall-back system (8.7.3) Moved from below Back-up of critical CS, tested periodically (8.7.8)		
Updates or changes to CS via change control only (8.7.5)		
Revalidation of critical CS (8.7.6)		
Purely electronically-held records available for life of document (8.7.7)		
Labels clear, unambiguous, no overtyping (8.8.2)		
Labels include all items listed in 8.8.3 (8.8.3) Labels comply with legal and professional requirements (8.8.1)		
Maximum glucose concentration/osmolarity for use peripherally agreed. Greater concentrations, PN is labelled for central line only (8.8.4)		

9 Personnel Training and Competency Assessment

Deviation from Standard –		
Complies / Negligible		Severity Score (S)
Service managed by Accountable Pharmacist (AcP) with appropriate knowledge and experience (9.1.1)		
Accountable Pharmacist assured facilities and systems suitable each day (9.1.3)		
Deputy for Accountable Pharmacist trained, limits agreed and responsibilities clear (9.1.4)		
Any accredited product approvers trained, limits agreed and responsibilities clear (9.1.5)		
Radiopharmacy preparation staff are 'adequately' trained as in IR(ME)R (9.1.6)		
Simplified training for visitors, engineers, etc. (9.1.7)		
SOP for acceptable hygiene expected (9.2.1)		
Reporting of skin lesions, infections etc (9.2.2)		
Management of tattoos, piercings, religious clothing etc (9.2.3, 9.2.4)		
No watches, jewellery, cosmetics, false nails etc in unit (9.2.5, 9.2.6)		
All staff trained and assessed as competent for their role (9.3.1)		
Approved current training programme, documented completion and system for evaluation (9.3.2) Individual training records, available and acceptable (9.3.3) Current approved training programme and completion documented (8.2.8.1) System for evaluation of training programme (8.2.8.2)		
Staff preparing or supplying aseptic products competent and understand responsibilities(5.1.9)		
Competency assessment and sign off of initial training (9.4.1)		

9 Personnel Training and Competency Assessment continued

Competency regularly reassessed. Retraining where necessary (9.4.2) Effectiveness of additional training checked and rechecked after a further time interval (9.4.3)		
Regular testing of operator technique with broth and observation (9.4.4) Operator validations up-to-date and cover range of techniques and clean air devices in use (10.2.2)		
Initial competency requires three successful Universal tests. Reassessment six-monthly minimum (9.4.5)		
Hand hygiene acceptable (12.8.1) Effective hand sanitisation agent and techniques and effectiveness assessed (12.8.2, 12.8.3)		
Competency assessment for calculations (9.4.6) and worksheet accuracy		
Commitment to a staff development programme. (Use should be made of the TSET portal) (9.4.9)		

10 Aseptic Processing

Deviation from Standard –		
Complies / Negligible		Severity Score (S)
London & SE A separate room or space in a quiet environment for the preparation of worksheets; minimum interruptions allowed1		
Appropriate disposal of waste (10.1.1) Waste disposal avoids cross-contamination and risks to staff (10.1.4.5)		
Choice of clean air device risk-based (10.1.2.1)		
Vials used in preference to ampoules (10.1.2.3)		
Use of sharps minimised. No manual re-sheathing. Risk assessment if re-sheathing used (10.1.2.4)		
Processes use minimum manipulations (summary available) (10.1.3.1)		
London & SE Preparation activities requiring pooling of solutions are risk assessed and will reduce the risk to the finished product when compared to a non pooling method of preparation 4		

10 Aseptic Processing continued

London & SE Comprehensive SOPs for all key elements and staff are aware of them London & SE Principles of good aseptic technique adhered to. All operators are mindful of the patient and severities of inappropriate behavior (by auditor observation) Strips of components separated before transfer into critical zone (10.1.3.4) Starting materials allowed to dry before manipulation (10.1.3.5) Critical zone uncluttered. No storage. Positioning to avoid obstruction of air flow (10.1.3.6) Operators don't reach over product (10.1.3.7) No touch of critical surfaces (10.1.3.8) Over-wrapped items peeled open in air stream. Paper-backed items not torn (10.1.3.9) Re-sheathing aid used if re-sheathing justified (10.1.3.10) 70% alcohol used to wipe vial bungs and ampoule necks (10.1.3.11) Ampoules opened in air stream (10.1.3.12) Filter used for glass ampoules (10.1.3.13) Ampoules used for immediate single withdrawal (10.1.3.14) Pressure equalisation used for vials (10.2.3.15) Additive port of bags in airstream for additions (10.1.3.16) Appropriate gauges of needles used (10.1.3.17) Needles inserted in centre of additive port (10.1.3.18) Tubing clamped before removal (10.1.3.19) Work surface and gloves sanitised between products or on contact (10.1.3.20) Spills wiped immediately, then glove change and cleaning (10.1.3.21)		

10 Aseptic Processing continued

Processes designed to avoid mix-up (10.1.4.1)		
Pre- and in-process checks appropriate and recorded (10.1.4.2)		
Vial sharing only on a campaign basis with appropriate in-process checking. (10.1.4.3) Any vial sharing is risk assessed and done on a campaign basis (13.1.10) London & SE Worksheets reflect the campaign process (No sharing of ingredients unless accurate reconciliation assured		
Aseptic process appropriately validated; Facility and equipment validation, process validation and operator validation (10.2) Process validations done initially and 6 monthly (minimum) (11.3.5)		
Process validations are worst case and cover range of processes in use (10.2.1)		
Comprehensive SOPs for all key elements and manipulative steps (10.3.1)		
Aseptic processing only uses validated staff (10.3.2)		
Staff understand all relevant SOPs before work in unit.10.3.4		
Pre- and in-process checks only by accredited staff (10.3.5)		
All staff aware of consequences of deviations and report errors and deviations to supervising pharmacist (10.3.6)		
Techniques to minimise RSI in use and staff trained to recognise symptoms (10.3.8)		

11 Monitoring

Deviation from Standard –		
Complies / Negligible		Severity Score (S)
Monitoring and testing programme complies with Tables 11.1, 11.2.1, 11.2.2, 11.2.3, 11.2.4 (11.1.1)		
Action and alerts level appropriately set (11.1.2) Action limits for microbiology comply with Table 11.3 (11.4.2)		
A monthly and annual review of trends and types of micro-organisms made. Trend data available for each workstation, operator, disinfectant transfer personnel and for each clean room (11.1.2) Alert limits reassessed during annual review (11.4.1) London & SE Review of organisms detected with those previously found		
Validity of result checked if action level exceeded and out-of-specification raised if appropriate (11.4.3) London & SE Written reports satisfactorily filed and actions noted		
Monitoring equipment calibrated annually. (11.2.1) Equipment used in testing serviced annually (11.5.1)		
Storage temperature of media monitored (11.2.1)		
Evidence to demonstrate media fit for purpose (positive control) (11.2..2)		
Media residues removed after sampling (11.2.3)		
Plates labeled and bagged/wrapped soon after exposure (11.2.4)		
Negative control plate used weekly (11.2.5)		
Incubation within 7 days of exposure (11.2.6)		
Liquid media fertility tested after use (11.2.7)		

11 Monitoring continued

Record of checks of equipment functionality available daily/sessionally (11.3.1) Operation, cleaning, maintenance and fault logs for all facilities and equipment (8.6.1) London & SE e.g. pressure and airflow logs, leak testing, alarm functions, glove changing, cleaning logs, temperature logs		
Sessional monitoring of critical zone with settle plates and finger dabs with satisfactory results 11.3.2)		
Settle plates exposed for full session (max 4 hours) (11.3.3)		
Surface monitoring results trended and linked to cleaning (12.1.14)		
Rooms and isolator hatches monitored weekly. Plates correctly exposed (11.3.4)		
Any growth in a gaseous biodecontamination isolator identified to species level and urgently investigated (11.4.4)		
Routine identification of contaminants to genus level. Routine species I.D. for grade A and where action limits exceeded. (11.4.5) London & SE By trained competent staff in an audited laboratory Incubation temp TSA / SDA dual temp incubation		
In-use testing carried out for viables and no-viables (11.5.2)		
DOP test on all HEPA supply filters (11.5.3)		
Senior staff understand design of unit eg ventilation (11.6.1)		
Sterility test programme (1/workstation/week). Failures identified to species (strain) level and investigated. (End of sessions (EOS) broth test can be alternative) (11.7.1, 11.7.2)		
Investigation/CAPA for EOS fail (11.7.3)		

11 Monitoring continued

Planned programme of physical, chemical and microbiological analysis of the finished product as appropriate (11.8.1)		
Samples suitably obtained avoiding threat to the integrity of the finished product (11.8.2, 11.8.3)		
Accountable Pharmacist ensures testing laboratory understands pharmaceutical microbiology (11.8.4)		
TA with all external testing services and monitored (11.8.5)		
All sinks hand-wash stations and drains monitored for TVC (11.9)		

12 Cleaning, Sanitisation and Biodecontamination

Deviation from Standard –		
Complies / Negligible		Severity Score (S)
SOP and programme for sanitisation (12.1.1) London & SE Areas are clean by observation		
Cleaning and disinfecting agents approved, and more than one type used (12.1.2, 12.1.3)		
Cleaning and disinfecting agents sterile for Grades A and B. Sterile water used if needed (all grades) (12.1.4)		
Any in-use dilutions freshly prepared. Six monthly microbiological monitoring (minimum) (12.1.5)		
Wet cleaning with detergents used. Vacuum cleaners dedicated, with HEPAs (12.1.6)		
Sanitisation process considers factors in 12.1.7 (12.1.7)		
Sanitisation SOP includes factors in 12.1.8 (12.1.8)		
Sterile water used periodically to remove residues (12.1.9)		
Logs show agent(s) used and are checked before unit used (12.1.10)		
Staff cleaning are trained and competent (12.1.11)		
Continuity of cleaning staff. Monitored TA for contract cleaners (12.1.12)		
Microbiological and chemical testing programme for surfaces present and reviewed to test the effectiveness of cleaning (12.1.13)		
Surface monitoring of residues, e.g. cytotoxics (minimum annually) (12.1.15)		
All areas of facility regularly cleaned and, when necessary, disinfected (minimum frequency as in Table 12.1) (12.2.1)		
Appropriate dedicated cleaning equipment (12.2.2)		
Cleaning equipment stored separately (12.2.3)		
Facility cleaned cleanest to least clean (12.2.4)		

12 Cleaning, Sanitisation and Biodecontamination continued

Sterile disposable low-linting mops for Grade B (12.2.5)		
Sufficient agent delivered for effective cleaning (12.2.6)		
Adhesive flooring included in cleaning schedule (12.2.7)		
Clean air devices cleaned and disinfected before and after each session with sterile agents (12.3.1)		
Internal surfaces of clean air devices have (minimum) monthly clean with sporicide (12.3.2)		
All surfaces cleaned (minimum) quarterly to remove chemical residues (12.3.3)		
All equipment included in cleaning schedule (12.3.4)		
Biodecontamination cycles acceptable and physical cleaning carried out (12.4.2, 12.4.3)		
Validated SOP for transfer process (12.5.1)		
Sterile agents used in Grades A and B and last sanitisation stages of the transfer disinfection process (12.5.2)		
Contact time stated, validated and maintained in practice (12.5.3)		
Storage of paper and cardboard minimised in support room but products protected (12.5.4)		
Spray and wipe with sporicide before transfer to clean room (12.5.5) (10.1.3.3)		
Spray and wipe with disinfectant before transfer to working zone (12.5.6)		
Spraying during transfer disinfection is carried out into the transfer hatch it is not remote from the hatch (12.5.7)		
Justification for any circumstances not using a sporicide, e.g. radiopharmacy (12.5.8)		
All surfaces subjected to all steps, e.g. flip caps removed at start of process (12.5.9)		
Evidence available for effective contact time for sanitising agents (12.5.10)		

12 Cleaning, Sanitisation and Biodecontamination continued

Transfer SOP considers factors in 12.5.11, e.g. bioburden (12.5.11)		
Use made of triple- and double-wrapped packs. Consideration given to other methods of minimising transfer of bacteria and fugal spores (12.5.12) (10.1.2.2)		
Sterile/disinfected gloves worn for transfer (12.6.1)		
Routine supervision of transfer technique (12.6.2)		
Wipes impregnated, low-linting and sterile for last step (12.6.3, 12.6.4)		
Wiping technique satisfactory, e.g. fresh surface, attention to folds, septa etc (12.6.5, 12.6.6)		
Initial bioburden controlled and monitored (annually minimum) (12.6.7)		
Health and safety considered, e.g. sporicides (12.6.8)		
Trays appropriate design and washed and decontaminated regularly (12.7.1)		
Tray cleaning done outside unit (12.7.2) Trays dried and disinfected (not 'drained') (12.7.3) Tray cleaning validated (annually) (12.7.4)		
Hand washing facilities appropriately located and water regularly monitored (12.8.4, 12.8.5)		
Cleaning validation frequencies comply with Table 12.2 (12.9.1)		
Limits based on both microbiological and chemical residue analysis (12.9.2)		

13 Starting Materials, Components and Consumables

Deviation from Standard –		
Complies / Negligible		Severity Score (S)
Starting materials (SM) sterile and MA when available (13.1.1)		
Any unlicensed medicines have documented quality assessment (13.1.2)		
Unlicensed starting materials from appropriate licensed supplier (13.1.3)		
London & SE The chief Pharmacist (delegated senior manager - RQA interpretation) must ensure that the unit reviews range of materials stocked. If use of more than one strength or salt of the same electrolyte is justified, risk assessment needed2		
Systems for receipt include that SmPC or technical data not changed since previous receipt; invoke change control if required. (13.1.4)		
One session only for unpreserved starting materials and they remain in critical zone (13.1.5)		
Starting materials from same manufacturer if different strengths mixed in product (13.1.6)		
No non-sterile starting materials (13.1.7)		
Re-worked material assess as a starting material (13.1.8) London & SE If prepared in an unlicensed facility cannot be re-worked. If unlicensed product prepared in a licensed facility re-working will increase the number of manipulations		
Components pre-sterilised and either CE marked devices or documented assessment. Appropriate packaging (13.2.1)		
Filters pre-assembled, CE marked and sterile (13.2.2)		
Batch numbers of critical components are on worksheets (13.2.3)		
Audit trail for other components e.g. using logs to record batch numbers (13.2.4)		

13 Starting Materials, Components and Consumables continued

Local sterilisation of non-sterile consumables validated and monitored. TA and audit of sterilising site available (13.2.5)		
Filing systems not modified (13.2.6)		
All items appropriately stored to minimise bioburden and prevent damage (13.2.7)		
One working session only for sterile components (13.2.8)		
Components and consumables used in Grades A and B are sterile (13.2.9)		
No storage of paper-backed components in clean room after transfer sanitisation (13.2.10)		

14 Product Approval

Deviation from Standard –		
Complies / Negligible		Severity Score (S)
Formal recorded decision (product approval) by Accredited Product Approver (APA – includes Authorised Pharmacist (5.1.7) (14.1) Term Accredited Product Approver (APA) includes previously used 'Releasing Pharmacist'		
Robust systems for 'release' training. Non-pharmacist by Accredited Product Approver comply with national competency framework. List of APAs (14.2)		
Accountable Pharmacist ensures effective and comprehensive PQS in place (14.3)		
Accredited Product Approver directly accountable to Accountable Pharmacist and in their job descriptions (14.4)		
Accredited Product Approver or Authorised Pharmacist has not prepared the product (check out-of-hours supervision) (14.5)		
SOPs for final accuracy checking and release give roles and responsibilities (14.6)		
Authorised Pharmacist identifiable and contactable (14.7)		
Accredited Product Approvers authorised for product type involved, e.g. PN (I/T needs pharmacist on I/T register) (14.8)		
All who release are competent and comply with Code of Ethics (14.9)		
After preparation and before release the Accredited Product Approver completes all actions in 14.10 London & SE All actions are in the SOP Dose and patient details checked at Product Approval against the prescription (on the screen when necessary to ensure the most up to date prescription is used)		

14 Product Approval continued

Authorised Pharmacist makes release decision if unplanned deviation (14.11)		
Authorised Pharmacist aware of any errors and acts on them (14.13)		
SOP for failures. Investigated, CAPA and trending. Chief Pharmacist aware of adverse trends/major failures (14.14)		

15 Storage and Distribution

Deviation from Standard –		
Complies / Negligible		Severity Score (S)
Storage and distribution staff trained (documented) and aware of responsibilities, e.g. product integrity, supply, etc,(15.1.1)		
Product quality not compromised between release and use (15.1.2) London & SE Adequate facilities / space for safe and secure storage and distribution; organised and clean.		
Products needing specific handling and storage comply with legislation, e.g. COSHH, Radiation Regulations (15.2.1)		
Products refrigerated unless detrimental or suitably stored (15.2.2) Products stored in a refrigerator if this does not negatively impact on quality (6.5)		
All storage areas temperature mapped (15.2.3)		
All storage areas continually temperature monitored (2-8℃ fridges, ≤ 25℃ ambient (15.2.4)		
SOP for temperature monitoring includes action for out of specification temperatures. Actions recorded and trends monitored (15.2.5)		
Annual two-point (minimum) calibration of temperature monitoring equipment traceable to a recognised measurement standard (15.2.6)		
Validation of automatic temperature monitoring equipment (15.2.7)		
Product quality not impaired by repair, maintenance, calibration (15.2.8)		
Alarms appropriate limits and tested regularly. Authorised Pharmacist aware of any alarms (15.2.9)		
Knowledgeable decision made if storage temperature failure (15.2.10)		
Transit containers offer adequate protection (15.3.2)		

15 Storage and Distribution continued

Transit containers comply with appropriate regulations, e.g. radiopharmacy or chemotherapy (15.3.3)		
Compliance with all health and safety regulations, e.g. COSHH (15.3.4)		
Transit containers suitably labelled, e.g. identity, handling. Includes – source, emergency contacts for hazardous products (15.3.5, 15.3.6)		
Prevention of movement, e.g. syringe barrel and plunger (15.3.7)		
Cold/ambient chain assessed if appropriate (15.3.8) Distribution maintains product quality, security and integrity (15.3.1)		
Documented training of staff involved (15.3.9)		
Records of destination of products. (Additional system for CDs and radioactive products.) (15.3.10)		
Policy for returned/unused products, including outsourced and environmental factors(15.3.11) Returned/unused products clearly marked and segregated (15.2.11)		
Complaints recorded. Distinction between quality and service complaints (15.4.1)		
Specific person for complaints. Thorough investigation of cause (15.4.2)		
CAPA if necessary after complaint evaluation (15.4.3)		
Procedure for recall (covers own products, and starting materials or components used) (15.4.4)		
Annual testing of recall system (if no actual), and report produced (15.4.5) Recall SOPs tested annually (8.2.12.1)		

16 Internal and External Audit

Deviation from Standard –		
Complies / Negligible		Severity Score (S)
Chief Pharmacist and Regional QA (RQA) ensure regular external audits (5.3.2) Chief Pharmacist sends action plan to RQA on time and communicates major changes to RQA, e.g. staffing etc (5.3.3)		
Chief Pharmacist ensures regular internal audits carried out (5.3.1) Audit of all aseptic areas on a regular, planned basis (16.1) Detailed quality review of PQS (16.2) Audit programme documented and adhered to (16.3) Audits include review of capacity planning (16.4)		
Internal audit carried out by designated competent staff in independent way (16.5)		
Observations recorded with proposals for corrective actions (16.6)		
Suitable action plan, with timescales and persons responsible produced (16.7)		
SOP for management and review of action plan and the effectiveness of these procedures should be verified (16.8)		
Corrective actions reviewed (16.9)		
Chief Pharmacist ensures QA system and off-site testing regularly reviewed (5.3.4)		
Audit report submitted to senior management. Escalation procedures in place to communicate risks to hospital management (16.10) Response to external audit is realistic and timely (16.11)		
Subject to additional audit if preparing intrathecal chemotherapy (16.12)		

Deficiency Action Times

Deficiencies	Severity Score	Action
Critical	4	Critical deficiencies that require immediate action (within 24 hours)
Major	3	Major deficiencies that require action within three months
Moderate	2	Moderate deficiencies that require action within six months
Minor	1	Minor deficiencies that need to be addressed within twelve months

Notes:

- Audit categories e.g. 'Risk Management Arrangements', Internal and External Audit are chapter titles from Reference 1 below
- In the Matrix the 'Complies / Negligible' column is the compliance statement. Compliance statements have been developed from the audit aide-memoir written by Alison Beaney which is based on Reference 1
- The Matrix has been constructed using the references cited below and auditor's experience. Where a Pharmacy Quality Audit Guideline states a deficiency severity then this has been referenced in the Matrix

Abbreviations:

AHU	Air Handling Unit
ARSAC	Administration of Radioactive Substances Advisory Committee
BMS	Building Management System or Building Maintenance System
BNF	British National formulary
CE	*Conformité Européenne* (possible interpretation of the abbreviation) meets all the essential requirements of the relevant European Directive(s).
CIVAS	Centralised Intravenous Additive Service
CPD	Continued Professional Development
CT	Chemotherapy
DOP	Dispersed Oil
GAMP	Good Altermated Manufacturing Practice
GMP	Good Manufacturing Practice
HEPA filter	High Efficiency Particulate Air filter
HVAC	High Velocity Air Conditioning
IMS	Industrial Methylated Spirit
IP	Ingress Protection
IV	Intravenous
LAF	Laminar Air Flow
LAFC	Laminar Air Flow Cabinet
LFC	Laminar Flow Cabinet
MA	Marketing Authorisation
MHRA	Medicines and Healthcare products Regulatory Agency
PN	Parenteral Nutrition
NPSA	National Patient Safety Agency
PL	Product Licence
PPM	Planned Preventative Maintenance
PQAG	Pharmacy Quality Audit Guideline
QA	Quality Assurance
QE	Quality Exception
QER	Quality Exception Report
QC	Quality Control
SLA	Service Level Agreement
SOP	Standard Operating Procedure
TSE	Transmissible Spongiform Encephalopathies

References:

All standards are:

Beaney, Alison, M, D Prof, MSc, FRPharmS , Editor, Quality Assurance of Aseptic Preparation Services: Standards Handbook, 5th Ed. Royal Pharmaceutical Society 2016. ISBN0- 978-0-85711-307-8

unless otherwise stated. Alternative references will be from the documents listed below or from the London & SE audit team which will be stated in the document.

1 Professor Brian Toft OBE, Independent review of the circumstances surrounding a serious untoward incident that occurred in the Aseptic Manufacturing Unit, Royal Surrey County Hospital on Monday, 18th June 2012

2 Paediatric Chief Pharmacists Group. Improving Practice and Reducing Risk in the Provision of Parenteral Nutrition for Neonates & Children 11/2011

3 Good Manufacturing Practice Question and Answers for Manufacturing Specials (MS) Licence Holders, MHRA, 2013

4 Good Manufacturing Practice Question and Answers for Manufacturing Specials (MS) Licence Holders, MHRA, 2015

5 Report of the Mid Staffordshire NHS Foundation Trust Public Enquiry, Robert Francis QC, HC 947, February, 2013