

MHRA Guidance for Specials manufacturers

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1 INTRODUCTION & PURPOSE

The purpose of this document is to provide guidance for Manufacturing Specials (MS) licence holders in the interpretation of the GMP requirements to be applied when manufacturing unlicensed medicines. Questions and Answers have been used to promote easy updates when further clarification on specific topics is required.

The document includes guidance on the appropriate standards for the manufacture of aseptically prepared products under an MS licence using essentially closed systems. However it is important to recognise that all aseptically prepared products where open systems are used, should be manufactured in accordance with the standards outlined in the EU Guide, specifically Annex 1.

This Q&A does not replace any of the requirements for unlicensed medicines already contained in Guidance Note 14 (GN 14).

2 SCOPE

The guidance in this document is for the manufacture of products under an MS licence. It is not intended to cover the importation of unlicensed products although many of the expectations are common. The general guidance within this document will also apply to radiopharmaceuticals.

This document does not contain any guidance relating to Advanced Therapy Medicinal Products which came into operation in December 2008 in accordance with European regulation No 1394/2007.

3 Q & As

3.1 Quality Management

3.1.1 What is the expectation for the preparation of a Product Quality Review (PQR) for MS manufacturers?

- Given the range of products produced, the absence of a Marketing Authorisation and, in general, the limited batch sizes manufactured there is no mandatory requirement for MS manufacturers to produce a PQR.

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- However there are benefits in conducting a regular periodic quality review at a justified frequency incorporating the relevant PQR elements in Chapter 1 of the EU GMP guide. This approach is strongly recommended where numerous batches of the same product are manufactured.

3.1.2 What are expectations regarding data trending?

- The minimum expectation is that trending will be conducted for environmental monitoring, complaints and deviations.
- Trending for environmental monitoring should be carried out monthly to indicate whether organisms detected are in line with those previously found or whether there has been a shift in the type of organisms detected. An annual summary review should also be undertaken

3.1.3 What is the minimum expectation for capacity planning?

- A capacity plan should be in place, to ensure adequate resourcing for the expected demand. Note: The expected utilisation in a manufacturing facility is around 70 - 80% to allow adequate resource for the associated ancillary tasks outlined below. Utilisations greater than this will be viewed as increasing the risk profile of the site.
- There should be a thorough understanding of production demand and supply constraints, and appropriate strategies to highlight imbalances in a timely manner to ensure appropriate action is taken.
- Capacity plans should also address associated essential tasks such as maintenance of the quality management system, order entry, surface sanitisation, preparation activities, and product release and any other relevant activities so that a company clearly understands any bottlenecks in its process.
- A unit's defined capacity should only be exceeded infrequently. If it is exceeded, approval from QA must be sought through the use of the planned deviation system.
- Compliance with the capacity plan should be assessed at a minimum monthly during management review and reviewed at least annually. Any changes should be evaluated through the change control system.

3.1.4 What is the basis for the formulation of an unlicensed medicine?

- See Human Medicines Regulations section 167 for full details.
- The product formulation must be in line with the order supplied.

- In cases where the order does not adequately describe the formulation, this may be determined by the manufacturer, and where necessary, should be confirmed with the customer.
- The product formulation should be derived by personnel appropriately qualified and experienced to do so. Typically, this would be a scientist who meets similar education criteria for the person responsible for QC [i.e. a relevant life sciences degree and relevant post-qualification experience in formulation (typically 3 years) although an applicant does not have to be eligible to be a QP]
- The formulation must be independently checked against the requirements of the order, and must verify that the formulation is suitable for the intended route of administration.
- The formulation check may incorporate a clinical check; however there is no GMP requirement to do so.
- The product should comply with the requirements of the British Pharmacopoeia (BP) in cases where there is a published monograph.

3.1.5 What format is allowable for the order received?

- Initiation of the order may be by telephone, however this should be followed up by a written (faxed or email) confirmation from the customer to be used as part of the final release check. Computer ordering systems providing the same level of assurance are also acceptable.
- Manufacture of a product may be carried out in anticipation of an order. i.e. batches are manufactured based on the known future demand for a product.
- The product must be in compliance with the original order. Any proposed changes from the requirement of the original order must result in receipt of a new order.

3.1.6 Batch Release (see also 3.2.1 for persons who can perform release)

- The order must be available in a written format (fax, mail, email) at the time of product release. An order can be received externally for an individual patient or internally to manufacture a batch for stock replenishment.
- **For external orders:** Batch release must include an independent check against the original order (or prescription if manufactured as a bespoke product for an individual patient). It is essential that the final product release includes a physical check against the product to be dispatched including any secondary labelling that is applied.

- **For internal orders:** (batches manufactured in advance): release may be against a specification or equivalent document in anticipation of supply. In this case the release should include verification that the QC testing results comply with the specification for those batches which are manufactured from API and excipients.

3.1.7 Is retrospective product release acceptable?

- Product release is a real-time activity; any subsequent review of batch documentation should be viewed as a quality review tool, but not considered to be a component of the release process for a given batch.

3.1.8 Pharmacovigilance

3.1.8.1 The requirements relating to suspected adverse reactions are such that:

- Any person who sells or supplies a relevant medicinal product shall maintain, and keep for a period of at least five years; a record showing details of any suspected adverse reaction to the product sold or supplied. This applies to not only manufacturers, importers and distributors but also pharmacists, doctors, dentists, independent prescribers etc.
- The person required to maintain the records mentioned in the above paragraph shall:-
- Notify the licensing authority of any suspected or serious adverse reaction;
- And make available for inspection at all reasonable times by the licensing authority, records mentioned in the above paragraph.

See section 3.7 of the Good Pharmacovigilance Practice Guide.

3.1.9 What impact will the revised chapter 1 have on MHRA expectations?

- The revised chapter 1 provides more detail on expectations for deviations. As per 1.4 xv and 1.8vii, it is expected that there is a robust deviation process in place which documents the issue, applies immediate corrective action but also in addition, identifies the most likely or probable root cause to prevent re-occurrence. Once the root cause is identified, it is expected that there is a CAPA system in place which can be either included or separate from the deviation itself. Deviations where the same issue reoccurs over a period of time and are not addressed are indicative of a weak deviation process and will be cited under chapter 1.

- The role and responsibility of senior management to ensure that the quality system is effective is defined in section 1.5 and evidence of their involvement e.g. through attendance at quality meetings would be expected during inspections. Senior management would include those who are named on a manufacturing authorisation and the head of the Pharmacy unit. Any serious quality issues would also be expected to be notified to the Chief Executive of the Trust.

3.2 Personnel

3.2.1 Who can perform delegated batch release? – What should be their qualifications?

- A releasing officer should typically have at least 2 years post-qualification relevant GMP experience.
- Anyone who has received appropriate training (relevant to the manufactured dosage forms) may perform batch release, provided they are approved by the person responsible for QC. Typically, these persons will hold a recognised qualification in a Pharmacy or related subject and have the appropriate experience.
- Releasing officers should be named within the Quality System, and be approved for batch release activities by the person named on the license for QC. There is no requirement for all releasing officers to be named on the MS license.

3.2.2 What are our expectations regarding the independence of QA/QC and production?

- Ideally, QC and production functions should be separate, and staffed by separate personnel.
- Where staffing levels do not permit this organisational structure, an authorised releasing officer must be demonstrably independent of production when performing releasing duties, and should not release batches which they have manufactured.
- Systems should be in place to demonstrate an effective oversight of this system by the person named as responsible for QC on the licence. This should include details of the process required to authorise individuals to be able to perform batch release. The department should hold a current list of individuals authorised to perform batch release.

3.2.3 What are the minimum requirements for someone to be named on MS as responsible for QC?

- These requirements should be aligned with those for a Qualified Person (i.e. a relevant life sciences degree, although the person does not have to be eligible to be a QP).
- The person responsible for QC should typically have at least 5 years post qualification relevant GMP experience but each case will be reviewed on merit.

Note: There may be specific cases where such requirements cannot be met and these cases may require further review by the MHRA Inspection Action Group (IAG)

3.3 Premises and Equipment

3.3.1 I am planning a new unit and I am considering gassed isolators versus “spray and wipe” – what are the MHRA expectations?

- Currently the majority of units inspected in the UK use liquid disinfectants to sanitise items being transferred to processing zones i.e. spray and wipe. We accept this approach provided that there is evidence that the process is controlled within the boundaries of capability. However due to the reliance of this approach on human factors, it is not possible to validate it. Verification (a better term) shows that, on the day the exercise was performed, processes were capable to produce items with an acceptable bioburden profile. This is important as the evidence suggests that the majority of contaminants within Grade A processing zones arise from the transfer of items.
- On inspection we see examples of poor practise using spray and wipe as a result of inadequate training, time pressures and difficulty in ensuring proper surface coverage. When a contamination has been detected within the processing zone there is always a suspicion that sanitisation processes have failed but investigations, particularly as there are likely to be several days after the event, are rarely conclusive. The lack of any independent processing record, such as that provided by a gassing unit, is obviously a disadvantage for such investigations.
- Disinfectants, provided there is adequate contact including residence time, generally are effective as bactericides, fungicides **and sporicides**. Hydrogen peroxide has a good profile as a bactericide, fungicide and importantly as a sporicide.
- Therefore based on the above, the use of VHP has a number of key advantages, assuming that it is performed in a controlled manner, i.e. Reproducible, has a defined microbiological kill profile and an independent processing record.
- Currently our guidelines still support the use of spray and wipe as there would appear to be a number of factors that limit the widespread introduction of gassing

isolators:

- Time of cycle - although we are seeing a reduction in cycle times with rapid gassing units, this is still seen to be a major disadvantage.
- Commonality of load. Validation usually involves for commercial operations either fixed loads or use of min/ max cycles. Due to the nature of work in a number of units, the predictability of requirements is sometimes difficult and therefore the flexibility of manual sanitisation has advantages.
- Experience - people are used to spray and wipe and there is a lack of familiarity with gassing technology. In addition a number of units, including some new ones, still prefer LAF cabinets over isolators (ergonomics is often quoted as a justification), and therefore the integration benefits of gassing isolators via transfer ports is limited.
- Perceived validation requirements. Within the Inspectorate we try to be realistic regarding validation of such units but there is a requirement to provide evidence of the effectiveness of operation both now and in the future. In enforcing such requirements we are mindful that the alternative is spray and wipe but a badly run gassing unit could generate a false degree of assurance about the effectiveness of the process.
- Finally it is difficult to quantify the benefit in risk reduction to the patient from using VHP as opposed to the traditional sanitisation methods. There is little doubt from the points raised above, that in absolute terms VHP is a more robust process but the difficulty in quantifying this advantage, particularly for closed techniques, may be a limiting factor.
- For these reasons when approached by new units we would encourage them to consider the use of gassing technology but at present this is only guidance and there is no mandatory requirement in place.

3.3.2 Can a Specials Manufacturer use shared facilities and equipment for Biological Products?

- This will depend on the nature of the products being processed and the processes conducted. A definition of Biologicals manufacture is included as part of the glossary. It is unlikely that traditional aseptic 'Specials' may be manufactured using the same facilities and equipment as biologicals and a risk assessment should be performed as the basis for any justification. Factors to consider include the potential for transfer of viable cellular, viral or genetic contaminants, including adventitious human pathogens, and the control strategies in place to address these risks. There should be awareness of the type of technologies and starting materials used in biological product manufacture (live cells, viral vectors, and human blood and tissues) which each present a different challenge to the prevention of cross contamination.

- There are in addition to the above a number of biologically derived products such as Monoclonal Antibodies (MABs), enzyme replacement therapies and peptide hormones which are commonly seen in aseptic MS operations as starting materials for reconstitution. These products should be treated as per 3.3.4

3.3.3 Is Blood labelling an activity inspected by the GMP Inspectors and can it be used in the same facility as for 'Specials' manufacture?

- The labelling of blood and cell components (e.g. in radiopharmacies with Tc-99m) is not considered to be a 'specials' manufacturing operation, and is also outside the scope of the Blood Safety and Quality Regulations. These activities are only inspected to assess their potential impact upon adjacent licensed activities.
- For new facilities, the expectation is that dedicated facilities will be provided for changing, preparation and manipulation to minimise the risks of contamination. Existing facilities should have dedicated areas for manipulation but may rely on procedural controls for preparation and changing areas, for example different coloured garments.

3.3.4 What is the requirement for dedicated facilities for small scale production?

- It is common to see antibiotics, cytotoxics and other sensitising agents being used as starting materials in aseptic MS operations. Although dedicated equipment is recommended for handling these substances there are examples where common equipment is used, particularly in the case of antibiotics. The rationale for this approach is based on the essentially closed nature of the processes employed. Under these circumstances a risk assessment should be undertaken to determine suitable control measures to minimise the potential for cross contamination of other products. Such control measures should include a consideration of spillage.

3.3.5 What is the required frequency for HEPA filter integrity checks for MS units manufacturing aseptically prepared products?

- There has been a long established practice in some NHS MS units of a requirement for an annual check on such filters. Given the closed nature of the process this is accepted as a minimum standard; obviously known faults will require immediate correction.

3.3.6 What would be expected in terms of cleaning validation for the manufacture of Specials?

- We would generally expect the same level of cleaning validation found in any manufacturing facility for pharmaceuticals and should be based on the principles in Annex 15 of the EU GMP guide.
- In general terms, product contact equipment e.g. beakers, vessels etc. used for external and internal product preparation should be separated. Substances which stain and potent substances such as Digoxin, antibiotics, cytotoxics, hormones etc. should use dedicated equipment. Cleaning should be based on a risk assessment and cleaning verification or validation performed where appropriate. The use of verification or validation will be dependent on the frequency of batches prepared.

3.4 Documentation

3.4.1 Is a Site Master File (SMF) expected for MS license holders?

- The expectation is that units will have a SMF unless they can present a justification for not having one, e.g. size of site, simple operation, which will apply to only a small number of MS manufacturing sites.

3.4.2 What is the expectation for a document retention period?

- Batch documents should be retained for at least one year after expiry or 5 years after release whatever is longer. In practice many sites will keep records for much longer periods based on legal advice. Specials manufactured using blood or ATPM should be retained in accordance with the relevant requirements in the EU GMP guide

3.5 Production

3.5.1 What checks are required for a supplier/manufacturer of licensed products used as starting materials?

- No additional checks of compliance status is required if:
 - I) A licensed product with either a UK, centrally approved or EU national licence is used.
 - II) The product is supplied by a UK Specials manufacturer under the terms of their MS licence.
 - III) The product is supplied by the holder of a WL under the terms of their WL licence for unlicensed products.

IV) The relevant bona fide checks of the supplier/wholesaler should be included as part of the order /receipt process.

Note: These guidelines reflect the fact that the above products can be used in patients without any additional testing.

3.5.2 What checks are required for a supplier/manufacturer supplying materials with a CE mark e.g. Water for irrigation?

- No additional checks of compliance are required.

3.5.3 What checks are required of a supplier/manufacturer supplying Active Substances and excipients used for the manufacture of unlicensed medicines?

- The Falsified Medicines Directive (FMD) transposed in to UK law via SI 2013:1855 will not apply to the materials used to manufacture products under an MS licence. The only exception being registration of manufacturers/importers of Active Substances. MS holders should therefore ensure they purchase only from registered agents/distributors.
- The guidance below is intended to support the assurance of supply of a safe product to the patient while at the same time recognising the logistical challenges faced by MS manufacturers when obtaining starting materials for use in the manufacturing process. Typically these challenges will be greater for manufacturers of non sterile products as the vast majority of sterile products are made using licensed starting materials.
- The manufacturer should have a vendor/starting material qualification programme based on the principles of risk assessment. This risk assessment should consider all known evidence related to the manufacturer/ supply chain and also to the route of administration of the medicine as well as the nature of the medical condition. There should be a greater level of evidence of suitability of sources of starting materials where injectable products are manufactured
- The MS license holder must record evidence that the materials to be used are fit for purpose and justification that they are safe for patient use. This can be achieved by obtaining materials from manufacturing and supply sources operating to EU GMP part II requirements or IPEC-PQG GMP Guide for Pharmaceutical Excipients 2006. However it is accepted that this may not always be practicable and factors relating to availability may need to be considered.

3.5.4 What evidence to support the assurance of Active Substance GMP compliance could be used?

- An audit conducted against EU GMP Part II requirements at the actual manufacturing site address covering specific products of interest as well as quality systems of the site and security of packing/shipping. The auditor must be independent of the manufacturer with reasonable experience for auditing against EU GMP Part II. The audit should have been conducted within the last 3 years and any significant (generally equivalent to major or critical) deficiencies must have been corrected since the audit (confirmation of successful closure of actions must be available). Audits should confirm access to all relevant facilities/equipment and systems and be specific to the materials in question.
- A GMP compliance certificate issued by an EU Competent Authority based on an inspection conducted within the last 3 years specific to the material of interest and to the actual manufacturing site address. Certificates of European Pharmacopoeia (CEP), although supporting evidence, cannot be used as evidence of GMP suitability of the manufacturer as these are issued on a desk top assessment basis only. Any sites named on CEPs that have been inspected as part of the EDQM surveillance program that have been found to be GMP compliant should have been issued with a GMP certificate by an EU Competent Authority (EDQM conduct some inspections with Swissmedic and TGA).
- Evidence of conduct and successful closure and acceptance of an inspection conducted at the actual manufacturing site in the last 3 years by an EU Mutual Recognition Agreement partner or other PIC/S member.

Additional contributing information:

- Supplier/manufacturer questionnaires can provide contributing information about the facility and the quality system in place at the site. This information is unlikely to be obtained through the use of questions which only result in an answer of yes or no.
- Testing of the material against a specification. However a note of caution: some of the biggest risks of using APIs not manufactured to GMP standards are unknown/ unexpected impurities caused by synthesis or contamination from other products/chemicals/extraneous matter/microbiological contamination. Such impurities or contaminants may not necessarily be detected by the analysis of the Active Substance.
- Certificate of analysis supplied with the Active Substance. Processes in place should establish the validity of any supplied certificates of analysis used as the basis for reduced testing. This should include an understanding of whether testing has occurred or if the statement relates to compliance 'in the event of testing' being carried out.
- Information regarding supply site held on centralised databases e.g. NHS QA.

3.5.5 What evidence to support the use of non API starting materials (excipients) could be used?

- In the first instance the risks posed by the excipient and nature of the product it will be used in should be considered in order to determine the supporting information required to provide adequate justification.
- Where there is evidence of GMP compliance of manufacture and through the supply chain e.g. audit against the joint IPEC-PQG GMP Guide for Pharmaceutical Excipients 2006. Evidence of GMP compliance from suitable audit may be best practice for high risk excipients while those of lesser risk may be more suitable to determine compliance through remote assessment, C of A and analysis on receipt.
- Suppliers should be working to an appropriate standard e.g. WHO Good Trade and Distribution Practices for Pharmaceutical Starting Materials. Suppliers of such materials should be assessed to ensure that the materials supplied are of a quality appropriate to their intended use. Approval of manufacturers/brokers should be based on the combination of material and vendor rather than purely on vendor history.
- It is important that the manufacturer (MS holder) documents any starting materials that do not meet the requirements. The outcome of the investigation will indicate whether the material can continue to be used and if any relevant action is required for previously supplied or stored material.

3.5.6 What do I do if I cannot find any evidence to confirm the quality of the starting materials (Active Substance or Excipient)?

- If the risk of use of starting materials from unproven sources is outweighed by the risk of patient harm of not supplying the medicine then such starting materials may be used based on a recorded/justified risk/benefit analysis. Alternative sources should always be considered in the first instance.
- The evidence and justification for use of any materials not meeting the criteria for manufacture to GMP standards should be recorded. Under these circumstances there should be a written confirmation by the relevant Medical Practitioner that the risks associated with this approach are understood and accepted.
- For both sterile and non-sterile manufacturing, a periodic re-assessment process is expected to confirm the GMP compliance of the manufacturing site for starting materials.

3.5.7 Can I use starting materials which do not have key information recorded in English on the containers?

- If non English language labels are accepted, in-house specifications for starting materials must clearly define the material details in the language expected before receipt of the material. The risk of error through handling non English labelled materials must be assessed and the risk minimised before use. C of A's received must include both the non English and English equivalent names. Staff should be trained in translation of terms used where non English language details are accepted. However MS holders should be encouraged to request English language labels and C of A from suppliers.

3.5.8 What is the current position on requirements for TSE compliance?

- All starting materials should have an assurance of the absence of TSE risk agents. Re-verification of TSE compliance should be confirmed for each relevant material at an appropriate frequency based on risk, unless specified on the individual batch Certificates of Analysis.

Note: The statutory instrument that covers TSE for unlicensed medicines is 2003 No. 1680 (The Unlicensed Medicinal Products for Human Use (Transmissible Spongiform Encephalopathies) (Safety) Regulations 2003), which does not amend the Medicines Act 1968, but in fact is related to the Consumer Protection Act 1987.

3.5.9 What is the expectation for the use of material reference codes in Specials manufacturing?

- The application of a unique reference or control code to each API, excipient and packaging component, and its use in documents such as specifications and manufacturing instructions, should be applied to all such materials used in bulk manufacture. Other equivalent systems are also acceptable. We would expect a different code for the same material which is of a different grade, e.g. USP and EP. In some circumstances it may also be useful to have a different grade for different suppliers.
- Each material received should have a unique lot number assigned which may be the original manufacturer's lot number or a unique generated in - house number. A separate lot number should be generated for each batch received.
- In the case where formulated medicines are used as starting materials, additional control measures, for example a physical segregation of stored materials, additional instructions on batch documentation, may be required where these are not equivalent, to ensure that the correct material is used (e.g. preserved / unpreserved, formulations of the same active injection).

- Requirements for approval of primary and secondary components including syringes etc. All items which are part of the final pack should be included in the Bill of Materials (BOM) with a batch number. Note a list of all components in the BMR could be used in place of a separate BOM. Components such as syringes which are used for transfer within the process should be traceable in the event of a notified issue.

3.5.10 What checks are expected for auto-compounders?

- Checks on the correctness of set-up should include:
 - The correct starting material is connected to the correct line. This check should be independent of set-up, and may be either a second operator or automated verification (e.g. barcode linking). Replenishment of starting solutions throughout the process should be similarly verified.
 - Volume delivery checks.
 - Independent check on the required volume for each solution.
 - Reconciliation of starting solutions at the end of the compounding session.
 - Details of remaining manual additions
- Given that there have been a number of reported adverse incidents at sites using auto compounders, the mechanism for setup and checking is extremely important. Validation of any new equipment should also include a risk assessment.

3.5.11 What is the mix check report and is it important?

- This is a report which will record when a material is changed during filling. It will aid in ensuring traceability of raw materials and for gross reconciliation and is thus an important document. There have been instances where bags have been rejected due to occlusion or weight issues and the system will not print this report. It is therefore important that this report is verified during batch review and it should raise a warning if the report is missing on multiple occasions.

3.5.12 Would you recommend the use of barcodes in auto-compounding?

- Bar coding is considered an integral part of the risk reduction strategy for compounding. It is therefore mandatory that companies use this capability if installed or move towards installing this capability within a reasonable time period.
- It is important that there is a process for generating and checking bar codes which includes line clearance and QA checks where appropriate and there is assurance that they are applied to the correct container unless previously applied by the manufacturer. The use of laminated sheets containing all the bar codes to be verified is not considered an acceptable practice.

3.5.13 What checks are required for reconciliation?

- There should be a system in place for the reconciliation of all materials and components used during any compounding operation, prior to release of batch and before destruction of the used/empty containers.
- For large volume (Macro) additions, these can be reconciled through the automated compounding systems, assuming that the validation is robust. Where manual compounding takes place then there should be checks in place to ensure the correct quantities have been used, for example by use of a weight check.
- Small volume (Micro) additions are usually made manually and often involve more critical items (API, potassium etc) and the system in place should ensure that these key/critical micro additions are checked by the compounding operator and an independent operator prior to addition and are accurately reconciled afterwards. The aim of the process should be to ensure that the correct quantity and strength have been added.
- Adequate controls should exist for the pre-dilution of multiple containers prior to use and the practice of sharing starting materials across batches. Reconciliation processes should be checked to ensure that the appropriate control exists for these operations due to the risk of mix up. **See also 3.5.19**
- During the production of many aseptically prepared specials, syringes are used to transfer reconstituted products to the final container, for addition of diluents and for the calibration of compounding devices. The unit must identify such practices as part of a risk assessment and ensure adequate control measures are in place to minimise the risk of mix-up, including a system to mark, label or otherwise identify such devices. A consideration of these syringes should be included as part of the reconciliation exercise.

3.5.14 What are the requirements regarding the key criteria for labelling systems?

- A readability check should be performed at the time of label design.
- Routine GMP requirements for label generation systems should be applied.

3.5.15 How should returned medicines be controlled?

There should be a process in place to review the suitability of reuse of any returns sent back from the ward (for example) to the manufacturing unit. The criteria should be documented in a procedure or equivalent document and include evaluation of specific issues relating to the product or formulation type, for example cold chain. They should also be a consideration regarding the product integrity as a result of time spent outside of the controlled supply chain.

3.5.16 What are requirements for the validation of unlicensed medicines?

The principles of EU GMP Annex 15 apply although there may be flexibility depending on the batch size and complexity of the products. The principles of Annex 11 also apply to unlicensed medicines.

Manufacture of Sterile Medicinal Products
3.5.17 How should aseptic processes be designed in a 'Specials' manufacturing facility?

- Production processes should be designed to minimise the number of aseptic connections/manipulations and this should be documented for all products and intermediates. A summary table indicating all the products and intermediates manufactured on site (grouping of similar products is acceptable) and the typical maximum number of aseptic connections/manipulations with any relevant comments should be included in the site master file for visibility.
- Where isolators are not used, operators assigned to Grade A aseptic connections/ manipulations should be dedicated to this activity for the duration of the work session, and remain in the Grade A environment throughout. Process design should prevent "swapping" of roles (e.g. with other Grade B operators) as this could create disturbance to the Grade A environment
- Manufacturers are reminded that even when operating a well-designed and controlled sterility assurance programme, there remains a risk of product microbial contamination with each aseptic manipulation. Additional procedural control is not a substitute for good process design

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3.5.18 How should ampoules be used in 'Specials' manufacturing units?

- Ampoules should only be used for a single withdrawal immediately after opening and then discarded.
- The use of vial presentations is preferred, as this better enables the maintenance of a 'closed system' for aseptic compounding.

3.5.19 How should pooling operations be controlled in a 'Specials' manufacturing facility?

- Pooling is defined as 'the bulk transfer of multiple original containers of a sterile starting material into a new (pre-sterilised) container without changing the formulation or concentration of the original starting material'.
- Aseptic pooling of sterile materials should be minimised and only used where this activity reduces the risk of errors in compounding. The use of aseptic pooling should be justified by a risk assessment which considers the risk to the finished product from the additional aseptic manipulations required for the production of the pool(s).
- Aseptic pooling should be treated as a batch operation, which is validated by media fill, described in company SOPs, and is recorded in a batch manufacturing record. Each batch should undergo assessment and release and in the case of pools for immediate use, this release may be concurrent with finished product release.
- Any aseptic pool should be given a maximum shelf life of 4 hours and should not be transferred between different work sessions.

3.5.20 What is the minimum expectation for the sanitisation of components and equipment being transferred into the grade A working zone?

- In this section it is assumed that components used for aseptic manufacture such as licensed products, needles, luer connections etc. are transferred into a preparation room, stored, with subsequent transfer through airlocks into the manufacturing room and then into a cabinet or isolator.
- The storage of paper and cardboard in the preparation room should also be minimised whilst at the same time ensuring that the product is protected, secure and information is still available to use the product correctly
- Before transfer to the manufacturing room, a sanitisation step using a spray and wipe technique including a sporicidal agent designed to inactivate bacterial and fungal spores must be carried out. (Step1)

- Before transfer to the working zone a second sanitisation step using a spray and wipe technique including a disinfectant must be carried out. (Step 2)
- The minimum expectation is therefore two discrete decontamination steps, with a spray and wipe performed at **both** steps and the first decontamination steps must use a sporicidal agent.
- The only exemption from using a sporicidal agent in step 1, at the current time, is for the manufacture of radiopharmaceuticals and biologicals only where evidence is available that the product performance may be affected by sporicidal residues. Justification may be possible for other medicines however documentation to support the approach taken should be available
- During sanitisation, particular attention should be paid to the rubber septa of vials and break lines of ampoules, which should be subjected to all stages of the sanitisation treatment. Over-seals should therefore be removed at the first sanitisation stage.
- An effective contact time for the sanitising agent should be used. Third party supplier data may be used, provided that this is reviewed to demonstrate its relevance to the intended use. Where contact time differs from the manufacturers recommendations, this should be supported by scientifically valid microbiological studies.
- Consideration should also be given to the air classification of the Preparation room and a risk assessment should be performed where the preparation room is unclassified to consider if any additional controls are required.

3.5.21 What factors should be considered in developing a surface sanitisation strategy?

- The bioburden challenge presented by the type of item being sanitised. i.e. number of surfaces, ease of cleaning.
- Minimum residence period post sanitisation (2 minutes are usually applied as a guidance value for a disinfectant effect with longer times required for a sporicidal effect)
- Periodic verification of sanitisation effectiveness should be carried out with frequency based on a risk assessment.
- Extended storage time of sanitised components is considered to be a risk factor, and subsequent sanitisation steps prior to use should address this risk.
- Steps should be taken to minimise the exposure of items supplied as sterile prior to entering the Grade A work zone.

- Cleaning of any folds where sealed packages are required to be sanitised.

3.5.22 What agents should be used to achieve the above sanitisation?

- Agents used typically consist of 70% ethanol or IPA and include a sporicidal agent such as Hydrogen Peroxide.
- Solutions should be sterile if used for aseptic processing at the last sanitisation step.
- Wipes used should not shed particles and be sterile when used at the last stage of transfer for aseptic products.

3.5.23 What controls are expected for sanitisation agents?

- For purchased items there should be an assurance from the manufacturer regarding the quality of the supplied item and confirmation that the product is sterile if specified. For items sterilised by irradiation there should evidence that this process has been completed satisfactorily.
- The dispensing system should minimise the potential for contamination of the supplied contents, typically this could involve a bag in bottle or some other mechanism which reduces the potential for contamination ingress as the contents are used.
- The in-use shelf life should be justified and documented for such sanitisation agents and information from manufacturers can be accepted. There should be an indication on the spray bottle as to the date of opening and processes in place should ensure that units are not used beyond the specified shelf life.
- During use steps should be in place to ensure that external surfaces of the spray unit are sanitised such that bottles do not present a risk of cross contamination.

3.5.24 What are the minimum gowning requirements in grade A/B facilities for closed aseptic operations?

- The minimum change requirement for aseptic gowns in these operations is a daily change. Precautions should be taken to ensure the risk of contamination during storage is minimised. Ideally clothing should be sterilised, although a validated biocidal wash is acceptable.
- For closed systems of manufacture and where isolators are used goggles or other face protection is not a mandatory requirement. See 3.5.27 below for open system(e.g. eye drops) manufacture

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- There is an expectation that a suitably sterilised and wrapped facemask is provided and worn. This should be changed on each entry to the area.

3.5.25 What are the requirements for sessional particle monitoring for aseptic production using closed systems?

- Many of the processes used to manufacture aseptically prepared “Specials” are manual and involve essentially closed operations as defined in the Glossary. Under these conditions the MHRA accepts a risk based assessment as to the validity and value of performing sessional particle monitoring (as defined in Annex 1) for these types of operations.
- The principles of quality risk management should be applied and the justification should identify an assignable cause for the inability to meet the routine monitoring requirement.

3.5.26 What do you mean by ‘identify an assignable cause for the inability to meet the routine monitoring requirement’ in the above?

- It is accepted that in some cases intrinsic particle generation by the process such as spraying of disinfectants, or opening packages limits the value of continuous particle monitoring in the grade A area. The rationale for not utilising continuous particle monitoring should include (where applicable):
 - Risk to product. It is accepted that for closed systems the risk of contamination from airborne contaminants is significantly reduced when compared to open operations.
 - The source(s) of particles generated.
 - Steps to minimise generation had been thoroughly investigated and appropriate actions taken.
 - Residual causes of particle generation make continuous particle monitoring during processing impractical.
 - Demonstrates that in the absence of the particle generating source(s) the remainder of the operation complies with Grade A.
 - A verification plan repeated and documented at defined intervals to demonstrate the continued validity of the prepared rationale.
- In addition in some cases the duration of processing provides insufficient time to collect a representative sample for monitoring purposes.
- In those cases where an acceptable rationale has been prepared the MHRA Inspectorate will not expect continuous particle monitoring to be performed for

closed aseptic operations in either existing or new facilities.

- Under these circumstances the expectation is that during initial validation a classification exercise will be conducted to show that in the absence of identified particle generating sources such as spraying of sanitising agents under normal operating conditions, the Grade A zone will conform to the requirements of the Annex. A periodic monitoring exercise typically 3 monthly (again in the absence of identified particle generating sources) should demonstrate continued compliance with the requirements.

3.5.27 Based on the above how should open systems (e.g. eye drops) be manufactured in 'Specials' manufacturing units?

- Open system (e.g. eye drop) manufacture can take place in isolators with a demonstration that Annex 1 requirements are met at rest and the integrity of the isolator is checked prior to eye drop operations being performed. Goggles or other face protection do not require to be worn for open system manufacture in an isolator.
- Eye drop manufacture can take place in LAFs only if full Annex 1 compliance is met. This would entail full gowning with no facial exposure and continuous particle monitoring during operations. Goggles are the preferred option but other types of protection may be used so long as they are completely sealed to the head dress to prevent any egress of contamination. Visors which are open at the side are therefore not acceptable.

3.5.28 Is vial sharing acceptable?

This situation commonly arises in sites operating a centralised intravenous additive service (CIVAS) service. Some injectable products are intended for single use only, however in some sites the full contents of a container may not be used and another patient who is to receive the same drug has an appointment later in the day and the vial is retained. This can occur if the drug is very expensive and there are pressures to make best use of resources.

This type of activity would be acceptable if the following conditions were met:

- The container is a vial and stays in a Grade A LAF cabinet or isolator at all times. Ampoules should not be reused once opened.
- The product is manufactured as a campaign with the patient doses prepared one after each other. The vial **cannot** be left in the cabinet when other different products are being manufactured.
- The batch records must reflect the actual manufacturing process carried out

with the appropriate line clearance steps between the manufacture of individual patient doses as required.

- Appropriate checks on the volume drawn up for each patient at the time of manufacture are carried out to ensure that the correct dose is supplied for each patient.
- It is recognised that new storage devices are being developed to facilitate vial sharing practices and this guidance will be updated when further experience of these have been obtained.

3.6 Quality Control

3.6.1 What problems are expected when you develop an Environmental monitoring (EM) programme for Specials?

- The environmental monitoring programme to support rapid turnaround in Specials operations is affected by a number of factors which differ from 'traditional' large scale sterile manufacturing operations however **the general monitoring requirements in Annex 1 of the EU GMP guide apply:**
- Data is retrospective, and therefore less useful for batch-specific actions. Most products will have been released before the information on colony count is available.
- Multiple batches may be compounded in a single session. This makes traceability of a contamination event to a single batch very difficult and excursions often implicate a number of batches.
- The use of closed systems of compounding reduces the risk of microbial ingress to the product.
- If, when reviewing EM data a potential problem with environmental control is identified, the basis on which the company is confident to continue with release should be documented for operations where the reporting of results is retrospective.
- Adequate Microbiology expertise either on or off site is needed to support the provision of an acceptable sterility assurance programme.

3.6.2 What is the expectation regarding the frequency and number of products used to perform retrospective sterility testing?

- A documented sterility test programme must be in place, which includes consideration of all process variables. The minimum expectation is one sterility sample per operational work station per week. Variables such as product and

operators should be cyclically covered on a rolling basis. This sterility testing frequency only applies where there is sufficient data to demonstrate that the areas are adequately controlled and therefore would not initially apply for new facilities where there is no history.

- The use of a suitably designed 'end of session media fill simulation' may be considered as an alternative to sterility testing of the finished product as part of an ongoing monitoring programme.(see 3.6.3).

3.6.3 How does the above requirement above apply when only a single unit is produced?

- The requirement for sterility testing may be off-set by the use of an 'end of session media fill simulation'. The frequency of this should be in line with the minimum requirements for sterility testing.
- End of session media fills should evaluate all types of aseptic manipulation, and variables such as product and operators cyclically covered on a rolling basis. Processes to achieve the required level of coverage should be included as part of QMS/EM programme.

3.6.4 What are the considerations to be evaluated when deciding whether to use sterility testing or end of session media fills?

- Advantages of media fill:
 - Whole unit taken, not a proportion.
 - Representative of manufacturing process (need to use same consumables wherever possible).
 - No opportunity for invalidation of a true positive due to poor technique or EM in the sterility test.
 - Greater opportunity to perform testing on site, therefore faster provision of results.
 - Facilitates testing of hazardous materials such as cytotoxics products.
 - Validation of sterility test not required.
- Disadvantages of media fill:
 - Frequent handling of media in production environments
 - Process may not reflect the actual manufacturing process.

- May not be the method of choice in cases where the manufacturing process is not from sterile (e.g. PL) starting materials – media only gives a measure of aseptic technique, not the sterilisation by filtration aspects.

Irrespective of the methodology used, we would expect each work station to be monitored weekly.

3.6.5 Is there a requirement for prospective sterility testing when an item is given an extended shelf life?

- For products (terminally sterilised or aseptically prepared) with a **shelf life of less than 90 days**, it is accepted that the results from sterility test or media simulation may not need to be available or considered as part of the product release criteria. The rationale for this must be justified, and there is an expectation that retrospective media fills and sterility tests will form part of the body of evidence for sterility assurance
- The expectation for products with a **shelf life of 90 days or more** is that a prospective acceptable sterility test or media simulation should be completed prior to product release. The sterility test or media simulation under these circumstances must relate to the batch in question i.e. a sample of the batch is part of the sterility test or the media simulation conducted includes the processing of this batch.

Note: 90 days was selected as a practical timescale for remaining product shelf life based on a 14 day incubation period. It is noted that some companies have been exploiting this situation by giving products a shelf life slightly less than 90 days to avoid doing prospective release. This approach is not acceptable and will be specifically looked for during inspections.

3.6.6 What is the minimum frequency for media fills? What type of manipulations should be simulated?

- Process simulation test should be performed as part of initial validation and repeated at six monthly intervals and should be representative of the batch sizes used. (See below)
- Operator media fills must be performed twice per year for every operator involved in aseptic manipulations. These assessments are typically separate from process simulation tests.

3.6.7 How should process validation (media fills) be performed in 'Specials' manufacturing units?

- Process validation should mimic the number and type of manipulations taking place in the worst case manufacturing process identified. It may not be possible

to mimic all manufacturing processes with a single type of media fill, and therefore a matrix approach is acceptable. New processes or changes to existing processes, including the scale of the activity, must be assessed to ensure that previous media fills remain valid.

- Batch scale “Process Simulation” exercises should not be confused with “End of session Media Fills” which are commonly used by units in lieu of a sterility test and can be an abbreviated form of a media fill.

3.6.8 How can a matrix approach be used in the Process Validation of unlicensed medicines?

Products compounded using similar processes may not require individual process simulations, provided that a single process simulation includes the worst case attributes of the products covered by the simulation. Factors to consider could include the number of compounded units, length of the manufacturing process and container type.

3.6.9 What level of identification is required when growth is observed on plates within the grade A/B area?

- The general monitoring requirements in Annex 1 of the EU GMP guide apply.
- The identification of all microorganisms in grade A areas should routinely be to species level, and the staff performing microorganism identification should be able to demonstrate adequate training and experience
- Identification of all micro-organisms in grade B areas should be to genus level. **However**, in the following circumstances identification should be to species level.
 - High individual counts (guidance: >5 cfu/session in Grade B).
 - Trends (guidance: >3 consecutive days or individual operator finger dabs) of Grade B EM showing the organism, or >5 in 2 weeks).
 - Recovery of potentially objectionable organisms (Organisms which may be hazardous/pathogenic to a specific patient or patient group)
 - The above can be addressed by retaining all Grade B plates demonstrating growth for a sufficient period that any trends, (as described above), would be identified or alternatively by identifying all grade B colonies to species level.
- It is important to ensure that sufficient information is available from the environmental monitoring programme to identify any loss of control in a timely manner to enable appropriate remedial actions.

- The identification of microorganisms should include basic laboratory tests such as Gram Stain and oxidase / catalase enzymatic tests in cases where morphology alone cannot provide identification with acceptable confidence.
- Establishment of typical local isolates should also form part of the validation for new facilities to ensure that the cleaning and the environmental monitoring programme is appropriate to local environmental risks.
- Further identification to differentiate between strains (e.g. genotyping) may be considered when actions taken in response to situations where species information is ineffective in returning the environment to a state of compliance.
- Units should ensure that the location where plates are read is suitable for the opening of plates for identification and this does not present a risk to manufacturing operations. Consideration of off-site testing by a contract laboratory may be necessary.
- The facility should have access to appropriate microbiological laboratory expertise and testing. Laboratories performing environmental monitoring for MS operations should appear on the license.
- Staff providing a microbiological service to Specials manufacturers should be able to demonstrate the required competence to perform this role.

3.6.10 What are the requirements for growth promotion for media used for environmental testing?

- We accept that the requirement for full European Pharmacopoeia (EP) growth promotion has not been a standard that has consistently been applied to MS operations and given this history and the closed nature of the processing involved we do not feel that it would be appropriate to require this level of testing going forward. Controls in place for media should however include supplier evaluation and the availability of a C of A. In addition a check on fertility for each delivery, to ensure transport conditions are considered should be conducted by dilution of some environmental isolates to confirm growth. Alternatively, as part of the regular environmental data review it could be confirmed that growth and the range of organisms found are normal for the controlled areas.

3.6.11 What are the requirements for environmental monitoring of transfer hatches on isolators?

- The purpose of isolator transfer hatches is to protect the integrity of the work zone (ref: ISO 14644 Part 7). The operation of an isolator in lower classification environments (i.e. Grade D) may result in difficulty in meeting the more stringent viable contamination limits required for the background environment for a Grade

A work zone when monitored 'in use', due to the frequent opening of outer doors onto the lower classification room environment.

- Isolator hatches should be designed to achieve compliance with Grade B air classification in the 'at rest' condition. This should be determined as part of equipment commissioning, at which stage the time required to return to compliance after opening the outer doors should be determined. In-use monitoring for viable contamination should be performed during the validation of surface sanitisation and transfer of materials into the isolator work zone, to determine the typical environmental microbial challenge to the process.
- Isolator hatches should be monitored at an appropriate frequency (e.g. weekly) to alert to changes in the environmental challenge compared to that seen during commissioning and material transfer validation. Significant changes in microbial load may challenge the effectiveness of the material transfer process, and should trigger an investigation, including consideration of re-assessment of surface material transfer capability.
- Additional 'in-use' monitoring of isolator transfer hatches may provide useful information in the event of work zone EM excursion investigations.

3.6.12 What information should be used as the basis of the designated expiry date?

Product expiry should be based on a scientific rationale, including test data. Laboratories used to generate this data should operate an appropriate quality system and be subject to the company's (contract giver) supplier's approval system. At this time such laboratories do not require to be named on the MS licence if a finished product testing/ environmental monitoring service is not provided.

- Test data may be obtained from literature searches, provided that the literature is relevant to the product formulation and container/closure system proposed.
- Expert opinion on product shelf life must be supported with a documented rationale and test data if available.
- For products manufactured from licensed starting materials the expiry of the resulting product should not be greater than the shelf life of the input product prior to reconstitution.
- For products manufactured from API and excipients it is expected that all these are within the current shelf life at the time of manufacture.
- For multiple use containers, the expiry date/time of the container starts when it is first opened. Data used to assign product expiry must be derived using stability indicating analytical methods, and be relevant to the proposed product formulation and container closure system.

- The assigned shelf life must include a margin of safety from the stability data available.
- Special attention should be given to shelf lives assigned and the methodology used for biologically derived products such as MABs.

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.

3.6.14 What testing is expected for starting materials?

- For starting materials used in **sterile products**, the default requirement will be an identity test on all containers for both the API and excipients. A review of the supplier certificate of analysis against the specification held by the manufacturer will also be required
- For starting materials used in **non-sterile products**, the default requirement will be an identity test for each container of API. Statistical sampling could be justified, together with the review of the certificate of analysis for the active and excipients against the specification held by the manufacturer.
- Additional testing requirements may be needed in the case of identified high risk materials (e.g. Glycerol) or in the case where the C of A supplied does not provide sufficient assurance of critical quality attributes (e.g. C of A states 'would comply if tested', or if C of A is different to that specified in the Purchase Order).
- Products manufactured/imported by other MS/WL suppliers should be checked for conformance against an in - house specification, using the supplied C of A prior to use.
- It is expected that during FTIR testing it should be confirmed that there are no

additional peaks present which may indicate the presence of contaminants rather than just confirming that the expected peaks are present. It is often noted that sites will only do a software comparison only where up to 10 peaks are compared for identity purposes and this would not pick up contaminants.

- See summary table 3.6.16

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.

Reference and Retention Samples

3.6.17 What is the expectation for reference/retention samples?

- Reference samples are expected for products where manufacture involves a discrete bulk manufacturing step
- Retention samples – In lieu of reference samples, samples of Finished Product labels and any other printed items used are to be included as part of batch documentation, for all products (irrespective of expiry).
- For re-packaging the requirement is a copy of the leaflet and label. Systems in place should ensure samples from each print run are collected.
- For packed down products, no retains would be expected if packing into a blank carton and a sample of the label is already retained in the packing record.

3.6.18 Summary table on expectations for testing and reference samples:- (To be used in conjunction with 3.6.14 above)

	Starting Materials Testing	Finished Product Testing	Starting Material Reference Samples	Finished Product Reference Samples	Comments
Non Sterile products using raw materials	API id + relevant testing of certain excipients based on risk e.g. Glycerol. Statistical sampling can be considered	Over 90 days shelf life would expect FP testing on identified attribute(s). Consideration should be given to batch homogeneity and validation of manufacturing process.	API and "risk" excipients	Would typically expect reference sample for product with shelf life greater than 90 days.	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.
Non Sterile product using PL + "diluent"	No testing required. If diluent is not a PL material, consider relevant testing of certain excipients based on risk e.g. Glycerol.	As above	No reference samples expected. If diluent is not a PL material, consider "risk" excipients	Would typically expect reference sample for product with shelf life greater than 90 days.	
Sterile product using raw materials	As per EU Guide	As per EU Guide	As per EU Guide	As per EU Guide	
Sterile product using PL + "diluent"	No testing required. If diluent is not a PL material, consider relevant testing of certain excipients based on risk e.g. Glycerol.	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.	No reference samples expected. If diluent is not a PL material, consider "risk" excipients	For products with shelf life of 90 days or greater	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.

3.7 Contract Manufacture and Analysis

No specific topics identified at this time.

3.8 Complaints and Product Recall

3.8.1 Should serious complaint and recall information be reported to DMRC for 'Specials'?

- DMRC should be notified of all recalls and serious product complaints, even if all product(s) has been returned, or (in the case of the NHS) was only distributed within the Trust. Such notifications may not necessarily result in further action in response to individual events, but will be used to update the Inspectorate's risk based inspection (RBI) programme.
- In order to comply with the above requirement the unit/company should document the point in the process where manufacturing activities cease and clinical governance starts. This is particularly true for units that have both manufacturing and clinical responsibilities for example some radiopharmacies and cytotoxic units. Typically this interface will be identified by the release process.

3.9 Self Inspection

No specific topics identified at this time

3.10 Distribution and storage

No specific topics identified at this time

3.11 Computerised Systems

No specific topics identified at this time

3.12 Licensing and Regulatory Advice

3.12.1 What checks should be performed to establish that there is no licensed product available (evidence of special clinical need)?

- It is essential that a manufacturer has systems in place to ensure that medicines are not supplied where a licensed alternative exists. These checks should take place where products are manufactured in response to a specific order. Where stock items are supplied, the company should maintain a system to monitor new licence approvals to ensure that supply is in compliance with Regulation 167 of the Human Medicines Regulations 2012. A 6 monthly check should suffice in this latter case.
- There is currently no definitive official list of all medicines licensed for use in the UK. Therefore a company's systems should involve a check of a number of existing publications. The expectation is that the following publications (which are available without subscription) are checked:
 - The NHS drug tariff (ppd.org.uk)

- The Electronic Medicines Compendium (medicines.org.uk/emc/) – it should be noted that not all Marketing Authorisation Holders upload their product data to this resource, and in particular checks of generic drugs can be limited using this resource.
- The British National Formulary (BNF) (bnf.org)
- Checks should ensure that there is no licensed product containing the same active in the same dosage form. Should a licensed alternative be identified, the person placing the order should be contacted for clarification of why an unlicensed medicine is required. Anyone supplying an unlicensed medicinal product, where an equivalent licensed medicinal product is available must be satisfied as to the existence of a special need for the unlicensed medicinal product. The MHRA expects that documentary evidence of this special need should be obtained by manufacturers, importers or distributors and that this evidence should be made available on request of the Licensing Authority. This may take the form of a prescriber's letter, however an alternative fully documented audit trail through the supply chain confirming special need may be acceptable. New letters would not be required for every supply if, for example, there is a continuing need for a group of individual patients, and evidence covering groups of patients, such as those who cannot swallow, may be acceptable. Acceptable justifications could include the requirements for a lactose or sugar free formulation.
- Unlicensed products may be manufactured when a shortage of the licensed product exists. There should be documented evidence of this shortage e.g. correspondence from the Marketing Authorisation Holder (MAH), Pharmaceutical Journal notice, confirmation received from the MHRA or Department of Health, commercial medicines unit.
- Under these circumstances supply may continue for a short period until licensed product becomes available in order to use up any manufactured stock.

3.12.2 What license is required for the over-labelling of individual blister strips which are removed from licensed packs which contain multiple blisters?

- a.** If this activity is done in a hospital pharmacy to supply patients in A& E departments and clinics within that Trust with a small amount of medicine until they get to their GP.

This activity can be covered by section 10 of the 1968 Medicines Act through Regulation 4 of the Human Medicines Regulations 2012 [SI 2012/1916]. If large quantities of medicines are to be assembled then the operation should be carried out under a Manufacturer's Specials Licence and GMP.

- b.** As (a) but for supply **outside the Trust**.

These cannot be supplied under via the section 10 route unless the hospital pharmacy in question is dispensing the medicine against a prescription that they have been given. Some NHS Trust hospitals that hold a Manufacturer's Specials Licence for the assembly of large quantities of medicines for use within their own legal entity have over time extended the supply to other NHS Trusts. This is because of the way the NHS has evolved with the merging and demerging of Trust sites.

- c. If this activity is done by commercial companies for NHS hospitals.

Commercial companies do not normally conduct this type of activity. This activity will require a manufacturer's licence and the Marketing Authorisation of the product concerned will have to be varied accordingly to show the company as an authorised assembler and the new pack size and presentation of the product.

3.12.3 What license is required for the over-labelling of a complete licensed pack?

- a. If this activity is done in a hospital Pharmacy to supply patients in A& E departments and clinics **within that Trust** with a small amount of medicine until they can get to their GP.

This activity can be covered by section 10 of the 1968 Medicines Act through Regulation 4 of the Human Medicines Regulations 2012 [SI 2012/1916]. If large quantities of medicines are to be prepared then the operation should be carried out under a Manufacturer's Specials Licence and GMP.

- b. As (a) but for supply **outside the Trust**.

These cannot be supplied via the section 10 route unless the hospital pharmacy in question is dispensing the medicine against a prescription that they have been given. Some NHS Trust hospitals that hold a Manufacturer's Specials Licence for the assembly of large quantities of medicines for use within their own legal entity have over time extended the supply to other NHS Trusts. This is because of the way the NHS has evolved with the merging and demerging of Trust sites.

- c. If this activity is done by commercial companies for NHS hospitals.

Commercial companies have been allowed to conduct this activity under contract with a specific hospital on the basis that:

- The company holds a MIA that authorises assembly.
- The company is under contract with the hospital concerned. A technical agreement should cover the details of what must appear on the dispensing

label.

- An over label (or dispensing label) may only be applied to a licensed original pack.
- The over label must not obscure the printed text of a licensed pack in any way.
- The over label should be applied to the blank area designated on the original pack for the dispensing label.
- In cases where an original pack does not have provision for a dispensing label, the over label should be firmly attached to the pack in a manner that is easily readable and does not obscure the licensed text nor interfere with the safe and effective use of the medicine.
- The labelled medicine should not enter any further licensed wholesale distribution chain, but should be supplied direct to hospital that has commissioned such services under contract and their details will be required on the label.

In addition it should be noted for clarity that;

- The labels should not carry any information that would normally be attributed to a dispensing operation e.g. "one tablet to be taken three times a day"
- *'Cautionary and advisory labels for dispensed medicine'* in the BNF appendix provides "words" which can be given as separate warnings, and which can be incorporated in an appropriate position in the direction for dosage or administration on a label. Appendix 9 clarifies each statement. The use of each statement is also referred to against a specific product contain in the BNF.
- These "words" do not include the actual dosage amounts, however it is noted that there are standard recommended dosages also given in the BNF.
- It would be appropriate to print the statements and the standard recommended dosage where necessary but it would be inappropriate to print specific dosages given by a doctor for their particular patient as this may be construed as dispensing.
- Where a hospital might anticipate using medicines and do not want the standard recommended dosage adding, then it seems appropriate to leave the space blank.
- Note: The NHS QA group has published a document 'National requirements for the overlabelling of imported medicines' which provides useful guidance.

3.12.4 What license is required if a licensed pack of e.g. 50 tablets is opened and the tablets repacked as 2 tablets in a bottle. The bottles are then labelled and the details on the label filled out when they are given to the patient?

- a. If this activity is done in a hospital Pharmacy to supply patients in A& E departments and clinics **within that Trust**.

This activity can be covered by section 10 of the 1968 Medicines Act through

Regulation 4 of the Human Medicines Regulations 2012 [SI 2012/1916]. If large quantities of medicines are to be assembled then the operation should be carried out under a Manufacturer's Specials Licence and GMP.

b. As (a) but for supply **outside the Trust.**

These cannot be supplied under via the section 10 route unless the hospital pharmacy in question is dispensing the medicine against a prescription that they have been given. Some NHS Trust hospitals that hold a Manufacturer's Specials Licence for the assembly of large quantities of medicines for use within their own legal entity have over time extended the supply to other NHS Trusts. This is because of the way the NHS has evolved with the merging and demerging of Trust sites.

c. If this activity is done in by commercial companies for NHS hospitals.

Commercial companies do not normally conduct this type of activity. This would require a manufacturer's licence and the Marketing Authorisation of the product concerned will have to be varied accordingly to show the company as an authorised assembler and the new pack size and presentation of the product.

3.12.4 What license is required if a blister strip is removed from a licensed pack which contains multiple blisters and inserted into a new blank white carton which is then labelled?

a. If this activity is done in a hospital Pharmacy to supply patients in A& E departments and clinics **within that trust with a small amount of medicine until they can get to their GP.**

This activity can be covered by section 10 of the 1968 Medicines Act through Regulation 4 of the Human Medicines Regulations 2012 [SI 2012/1916]. If large quantities of medicines are to be assembled then the operation should be carried out under a Manufacturer's Specials Licence and GMP.

b. As (a) but for supply **outside the trust.** These cannot be supplied under via the section 10 route unless the hospital pharmacy in question is dispensing the medicine against a prescription that they have been given. Some NHS Trust hospitals that hold a Manufacturer's Specials Licence for the assembly of large quantities of medicines for use within their own legal entity have over time extended the supply to other NHS Trusts. This is because of the way the NHS has evolved with the merging and demerging of Trust sites.

c. If this activity is done by commercial companies for NHS hospitals.

Commercial companies do not normally conduct this type of activity. This would

require a manufacturer's licence and the Marketing Authorisation of the product concerned will have to be varied accordingly to show the company as an authorised assembler and the new pack size and presentation of the product.

3.12.5 Does commercial reconstitution of a licensed product result in a product that is licensed or unlicensed?

- If a licensed Product is reconstituted at the patient's bedside, immediately before administration, and the reconstitution process is performed in accordance with the SPC, the assumption is that the product has been prepared for administration and use by that patient. This activity is therefore classed as reconstitution.
- Whilst pure reconstitution itself is not a manufacturing or an assembly activity, labelling would be classified as assembly and therefore a manufacturing authorisation would be required if it was not labelled in a pharmacy or other under another professional exemption that removes the need for such a licence.

3.12.6 What is the requirement regarding the provision of a patient information leaflet (PIL) for MS products?

- There is an expectation that all pre-packs are supplied with a PIL.
 - There should be systems to ensure that any PIL included in a pre-pack must be the same version as the leaflet included in the original product being packed.
- ❖ Line clearance of packaging areas and printers should include any photocopiers used for leaflet copying.
- For other products supplied as "Specials" there is no mandatory requirement to provide a PIL although some products have well established usage and leaflets have been developed for the benefit of the patient-this should be seen as best practice. Such guidance should be approved by an appropriately qualified medical professional with knowledge of the use of the product for the patients in question.

3.12.7 Is there a requirement for Braille on pre-packs?

- The provisions in the 2001 Review that require a medicinal product to have braille on the packaging and for the MAH to ensure that the PIL is made available on request from patient's organisations in formats appropriate for the blind and partially sighted were contained in Article 42 of Directive 2004/27/EC.
- These requirements only apply to MIA and MAH and not MS holders. The only statutory labelling requirements for specials are those contained in Schedule 26

(Part 2) of the Human Medicines Regulations 2012.

- Care should be taken when over labelling that this does not prevent the reading of Braille on pack. Batch documentation should confirm the position of the over label to facilitate compliance with this requirement.

3.12.8 What should appear as a minimum on the label?

- Unlicensed medicines should be labeled as per the BP general monograph for unlicensed medicines (part II and V) and in accordance with the general monograph for the specific dosage form. The monograph lists critical information which must appear on the label which includes the common name of the product, a statement of the active ingredients stated quantitatively and qualitatively per dosage unit or for a given volume or weight, route of administration and instructions for use including any special warnings. It is also required that excipients of known effect or all excipients for injectable, topical (including inhalations), ophthalmic are included on the label. The general monograph for 'Substances for Pharmaceutical Use' also states that, where appropriate, the name and concentration of any excipient should be included on the label.
- The license number should only be on the label if the product is manufactured under an MS license. If the unlicensed medicine is manufactured in the UK but packed in another country in the EU, it should be imported as an unlicensed medicine and the MS number should not be on the label.

3.12.9 Should the label state POM?

- Advice received from the MHRA Regulatory Advice Group has stated that POM should not appear on the label of a manufactured special based on the following rationale:
- Unlicensed medicines do not appear on the GSL List so they are not GSL.
- They cannot be sold over the pharmacy counter in a pharmacy therefore they are not P medicines.
- Although they are supplied on prescription, it is the Marketing Authorisation that records the POM status and requires it on the label. An unlicensed medicine does not have an MA therefore the requirement is not the same.
- An unlicensed medicine does not record a status.
- The only labeling requirements for unlicensed medicines are listed in the BP. There are no other labeling requirements. E.g. Controlled Drug regulations do not apply.

3.12.10 What is preparing and dispensing under a Section 10 exemption (via Regulation 4 of HMR 2012)?

- Some manufacturing sites are also registered or non registered pharmacies, who carry out a portion of preparing and dispensing medicines under the auspices of Section 10 of the Medicines Act (via Regulation 4 of HMR 2012). Preparing and dispensing activities under the Section 10 exemption fall outside of MHRA's regulatory oversight, as the responsibility for the regulation of registered pharmacy operations lies with the General Pharmaceutical Council (GPhC) or the Care Quality Commission (CQC) for non registered pharmacies.
- Two exemptions amongst others exist within Section 10 of the Medicines Act (1968), 10(1) (a), which covers preparation or dispensing of medicinal products and Section 10(1) (b) which covers assembly. The proceeding section discusses Section 10(1) (a) in the main as this is the most common use of the Section 10 exemption. The MHRA legal interpretation of the circumstances in which the Section 10(1) (a) exemption can legitimately be used are described below.

In order to prepare or dispense a product under Section 10(1) (a) of the Act (via Regulation 4 of HMR 2012), the following must be satisfied:

- A medicinal product as defined in HMR 2012 must be:
- Prepared by or under the supervision of a pharmacist in a registered pharmacy, a hospital, a care home service or a health centre.
- In accordance with a medical prescription given by a practitioner.
- For a specific patient.

Information from MHRA Regulatory advice and legal departments is that the requirements of Section 10(1)(a) would not be met if there was no prescription in existence prior to preparation, because preparing or dispensing under this provision must be in accordance with a prescription provided by a practitioner.

Further, it is considered that there must be sight of the prescription form to satisfy the provision, this is for two reasons. Firstly, so that person preparing the medicinal product can ensure it is prepared in accordance with the prescription; something that is not possible without sight of the prescription. Secondly, so that the pharmacy can satisfy the MHRA of this by being in a position to produce a copy of the prescription for inspection. The company must be able to satisfy the MHRA by the provision of the necessary evidence that the exemption from the licensing requirements available under Section 10(1) is being appropriately and lawfully applied, and this is not possible without being in a position to make the prescription form available. In a registered Pharmacy, it is possible for a

Pharmacist to prepare a limited quantity of product in anticipation of a prescription which they will dispense themselves or another Pharmacy in the same retail Pharmacy business but not where they are supplying another legal entity.

- There is no restriction of supply to within the same legal entity for a medicinal product prepared under Section 10(1) (a); however such a restriction does exist for medicines supplied under Section 10(1) (b) that have been assembled in a registered pharmacy.
- For a facility that supplies products under both the Section 10 exemptions and an unlicensed medicines under a manufacturer's licence it is important that:
 - For shared areas the potential impact of Section 10 activities on licensed work should be considered.
 - The labels for Section 10 products must not include a reference to the manufacturer's specials licence number.
 - For NHS units there should be evidence of a periodic EL audit by Regional QA (of Section 10 activity). In the absence of such audits a comment will be made in the MHRA post inspection letter.

Any serious issues relating to Section 10 supply found by a GMP Inspector will be brought to the attention of the staff at the unit and a comment in the post inspection letter.

3.12.11 Can I manufacture veterinary products under a MS licence?

- These activities are covered by a ManSA licence and specific advice should be sought from the Veterinary Medicines Directorate (VMD) about the cascade process if required.

3.12.12 Can I advertise a product manufactured under a MS licence?

- On the 19th August 2010 a change was made to the way in which appropriately authorised wholesale dealers and manufacturers can make healthcare professionals aware of the unlicensed medicines they have available. Holders of a licence permitting the manufacture, importation and/or distribution of unlicensed medicines can issue a price list to healthcare professionals without first having received a bona fide unsolicited order. MHRA advice is that any price list supplied should only consist of a basic line listing providing the following information: "reference number", "drug name" (British Approved Name or equivalent), "dosage form", "strength", "pack size" and "price". No product claims may be included.

- The remaining restrictions on unlicensed medicines are unchanged in Regulation 167 and Schedule 4 of the Human Medicines Regulations. This means that catalogues and circular letters may only be sent to healthcare professionals on receipt of a bona fide unsolicited order, and that unlicensed medicines cannot be advertised to the public.

3.12.13 Are there any labelling requirements for imported unlicensed medicines?

- The BP 2013 section V on unlicensed medicines states under 'legal requirements' that: Imported unlicensed medicines are outside the scope of the general monograph on unlicensed medicines. However where an individual monograph exists for an imported unlicensed medicine then the product must comply. Note: requirements for imported unlicensed medicines are listed in NHS guidance section 5.

4 GLOSSARY

Closed systems

A closed system is defined as: Addition of sterile materials to a pre-sterilised container via a system closed to the surrounding environment. A hypodermic needle inserted through a rubber septum, or 'luer to luer' connection is an example.

Biological products

The biologicals manufacture box on the MS licence should be for sites manufacturing the biological API / final bulk i.e. carrying out upstream processing such as mammalian, bacterial and fungal cell culture, harvest, then downstream processing and purification.

For the purposes of this Q&A, 'biological products' excludes the reconstitution compounding of commercial biological products such as monoclonal antibodies, enzyme replacement therapies and peptide hormones etc. These products may be prepared in shared facilities using closed systems, where the risk of cross contamination is low, and there is no risk of adventitious pathogen transfer.

CIVAS - centralised intravenous additive service

5 REFERENCE DOCUMENTS

- 5.1** The Pharmaceutical Journal Volume 281 dated 18th October 2008.
- 5.2** Aseptic Dispensing for NHS Patients - August 1995 Dr John Farwell
- 5.3** The Unlicensed Medicinal Products for Human Use (Transmissible Spongiform Encephalopathies) (Safety) Regulations 2003 [S.I. 2003/1680]

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- 5.4** National Requirements for the Overlabelling of Foreign (Non-English Language) Imported Medicines Unlicensed in the UK 1st Edition December 2011 NHS Pharmaceutical Quality Assurance Committee.

6 REVISION HISTORY

Initial: August 2013.

Revision 1: Updated January 2015.
