VIAL SHARING IN ASEPTIC SERVICES

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Vial Sharing in Aseptic Services

1. Campaign Working

The sharing of vials of starting materials between patients is an acceptable process provided it is carried out on a campaign basis and is subject to robust risk assessment processes. A campaign basis means that two or more doses may be drawn up from the same vial or the same pool of vials as long as these doses are made sequentially, that no other products are present in the work zone throughout the process, and that the vials stay within the grade A workzone throughout the process. Note that ampoules can only ever be used for a single withdrawal under the description of a closed process. Vial sharing for single use vials outside of pharmacy aseptic services departments is totally unacceptable under all circumstances.

There should be measures in place to ensure that there is robust in-process checking carried out by accredited in-process checkers, including the drug, concentration and volume measured, unless all measurements can be checked retrospectively (i.e. the product is a liquid medicine solely drawn up into syringes which can then be volume checked) at the product approval stage.

Further to this there needs to be a thorough reconciliation process carried out at the product approval stage. Ideally then this reconciliation should be completed on a specific worksheet which covers the products made up in each vial sharing process.

Note that vial sharing on a campaign basis has similarities with a batch process as carried out in some MHRA licensed facilities, however, there are also differences including the potential for different doses and different labels for the final products. Any decision to move forward with vial sharing on a campaign basis needs to be subjected to formal change control and risk management processes.

Potential benefits of this process include:

- Potential cost savings and reduced wastage.
- Improved ability to manage medicines shortages,
- Potential flexibility to use a smaller range of vial sizes in routine processing.

Risks which need to be considered include:

- Reduced ability for final product reconciliation
- A more complex process which needs to be managed with specific SOPs and worksheets
- Potential delays to specific patients treatments whilst the campaign is completed
- Increased risk of wastage if doses are made ahead of confirmation.

Control measures adequate to control any risks identified would need to be introduced as part of the change control process, these may include:

- Additional in-process checks
- Additional documentation to control the process
- Management of expectations from prescribers and clinics

In order for this campaign working process to work efficiently then liaison with prescribers and ward staff will be paramount to ensure that those patient's treatments which could lead to significant vial sharing savings are scheduled for the same day / time or at least grouped so that they can be treated within the shelf life of the final product.

2. Vial Sharing as a More Generic Process

With the current financial pressures across the whole NHS the idea of vial sharing within pharmacy aseptic services is a frequent topic for discussion. There is also pressure being applied by suppliers of certain vial access devices to use their device to 'extend' the in-use shelf life of a vial hence saving money on drug costs.

In October 2013 the MHRA issued a "Q&A Document" giving up-to-date guidance on how it interprets current EU GMP as it relates to holders of a Manufacturer's "Specials" Licence. The guidance has been developed to ensure consistency during routine Good Manufacturing Practice (GMP) inspections and to ensure MS licence holders are aware of MHRA expectations in this complicated area. It is planned as a 'living' document which will be updated as required. A period of 6 months was given for MS Licence holders to become familiar with this document and any changes to their operations as a result of this should have been implemented before 1st April 2014. The Q and A document contains a specific text on the subject of vial sharing in paragraph 3.5.24

3.5.24 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.

The question has been asked as to whether this requirement will also be applied to section 10 units. The answer clearly has to be yes, as the risks are at best the same and are probably even greater in section 10 units. It would be absurd if a unit could carry out a process under section 10 exemption that had been deemed unacceptable in a licensed unit for quality assurance reasons.

Hence the current position is that vial sharing, apart from on a campaign basis, is unacceptable.

It is acknowledged in the MHRA statement above 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.'

In response to this, and knowing the general intentions of some suppliers of clean room sundries to encourage multiple-use of vials utilising storage or 'saving' devices, the following is what we consider would need to be in place both generically and specifically for individual products before we feel that a proposal can be taken back to the MHRA.

3. Issues which need to be Resolved

There are many issues which must be addressed before the matter of vial sharing on a non campaign basis can be taken forward within any NHS aseptic unit.

1) Within current normal working practice it should not be possible to leave a part-used vial within the work zone whilst other products were being worked on as this would not meet the requirements of sufficient line clearance.

   It may be possible to have some segregated storage area within the grade A zone which could give adequate segregation. **Segregation would need to be clearly demonstrable and secure**.

   However, even if this was possible, there is the added risk of product miss-selection when the remains of the vial are selected for use. A robust in-process checking procedure would need to be established, ideally with some kind of electronic (bar code) audit trail. Currently, most vials do not have bar codes incorporated into their labelling, and adding an in-house bar code is an additional risk step to be considered and controlled.

2) It may be assumed therefore that the vial will need to be removed from the grade A work zone, so the following considerations will apply:

   a. Bearing in mind vials are now often accessed with needle-free access devices, a vial with such a device attached could not be decontaminated for transfer using a spray and wipe technique. (It is impossible to adequately reach and decontaminate all crevices and uneven surfaces with this methodology, and puncture holes in the vial closure may allow penetration of the disinfectant solution or vapour).

   b. If the transfer was subject to Vapour-phase Hydrogen Peroxide gassing (VHP), this would require very robust validation. The risk of hydrogen peroxide penetrating the vial and /or the access device would have serious consequences for product stability as it is a very powerful oxidising agent.

   c. Hence if a vial is to be removed from the grade A zone for later reintroduction it would have to be sealed in a sterile plastic overwrap or alternative internally sterile packaging so that surface sterility assurance levels expected in grade A conditions are preserved around the vial at all times. On re-transferring the outside should be easily and effectively sanitised into the isolator or cabinet. This process would also need to be fully validated.

3) The integrity of the vial is of fundamental importance, and robust microbiological integrity testing to a standard expected with syringe and closure systems would need to be undertaken for each combination of vials and devices. Vials with different stopper sizes and / or different closure materials would need to be validated separately. This integrity testing would need to offer a margin of safety on

the maximum storage period of a part used vial. It would seem prudent that the storage period should never exceed seven days even if additional storage and integrity data is available.

Any integrity data submitted by companies supplying these devices should be subjected to a close and expert review by a suitable panel, e.g. the NHS Pharmaceutical Microbiology Protocols Group, (a subcommittee of the NHS Pharmaceutical Quality Assurance Committee).

4) The **stability** of the drug in the vial is a major issue which needs a lot of consideration. Decisions would need to be made on an individual product basis. The potential temperature cycling of the product (as it is removed and returned to the refrigerator) would need to be included in any stability assessment.

   For some drugs the stability in a punctured vial is likely to be a lot shorter than seven days, hence this becomes another stock control issue to ensure that expired items are removed and destroyed on a regular basis.

5) Another consideration is assurance of the **compatibility** of the drug solution with the device employed and would also need assessing on an individual basis. Vials will need to be stored upright and with the solution not in contact with the vial spike.

   Clearly both of these concerns (4 & 5) are heightened where the medicine in question is a monoclonal antibody (mAb) or other complex, biologically derived pharmaceutical. These agents are commonly identified as where most of the potential savings can be made.

   Factors such as froth potential or the shear pressure applied to molecules during preparation are important with mAbs, and therefore the gauge of the device and interactions with all of the materials that may be in contact with the drug product need to be understood.

   In most cases the information from suppliers of the commonly handled mAbs is limited to 24 hours or less shelf life in a punctured vial.

6) Any data submitted in support of drug stability for vials with access devices attached should be subjected to a close and expert review by a suitable panel, e.g. the NHS Pharmaceutical Research and Development Group (a subcommittee of the NHS Pharmaceutical Quality Assurance Committee).

7) Other major concerns include:
   a. How the logistics would work during the set-up process;
   b. How units would manage the additional risk of mix ups with a set of part-used vials in a fridge with identical access devices attached;
   c. How units would keep track of what is left in each vial to avoid set up errors (i.e. insufficient stock to make a dose);
   d. How the movement in and out of a refrigerator is managed, including monitoring of the time out of the refrigerator for any vial.
   e. How the shelf life assigned to the product is managed to take into account the remaining shelf life on a part used vial.
   f. From a practical viewpoint then the shelf life of the product should be kept within that assigned to the part-used vial. This may be an issue to licensed units using extended shelf lives for products.

These issues would all have to be resolved, perhaps by working with pilot sites to carry out full risk management assessments using tools such as FMEA (Failure Modes and Effects Analysis) and process mapping. Robust Change Control procedures will be of paramount importance if these types of process are to be considered.

8) In addition, there is a need to label the part-used vial so that it is fully and readily identifiable and traceable throughout its use. This traceability should be to the original product in which it was used and hence to the session in which it was prepared and the staff member who had prepared it. It may be expected that electronic systems would play a part in this traceability. Consideration needs to be given as to whether to label the vial itself (in which case a sterile label will be required) or the outside of the sterile packaging.

4. Conclusion

Vial sharing within the controlled environment of a pharmacy aseptic service, using a variety of vial access devices is allowed on a campaign basis. For this to be permissible *and* safe, doses for individual patients should be drawn up sequentially, without the vial leaving the grade A work zone and no other product should be handled in the same space in the meantime. This process must be fully risk assessed and controlled including in-process checking and full material reconciliation.
If any NHS aseptic units are to introduce vial sharing on a multi-sessional basis then all of the issues raised in this report need to be resolved, some of these issues may prove very challenging. Units wishing to move forward should submit their proposals, evidence and documentation for review by their Regional Quality Assurance Specialists.

Document History	Issue date and reason for change
Version 1	Issued August 2014
Version 2	
Version 3	
Version 4	