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Review of GBUK NRFit syringe testing protocols and results against NHS protocols

Products: DASH 6 NRFit Lock Syringes and Caps from GBUK

The NHS Pharmaceutical Aseptic Services Group published its requirements for the introduction of NRFit neuraxial syringes and caps for the purposes of drug storage on 13th October 2016. This is necessary as, in line with other standard plastic syringes, these are CE marked for the administration of drug products but not for storage. Hence in order to allow aseptic facilities to draw up medication in advance and store ahead of administration the additional data was requested.

This additional testing involved:

1) Syringe integrity testing (microbiological and dye intrusion testing) in accordance with Protocols for the Integrity Testing of Syringes 2nd edition April 2013' – NHS Pharmaceutical Quality Assurance Committee.
2) Extractives and leachables testing in accordance with British Pharmacopoeia Sterile Single-use Plastic Syringes monograph and testing as per Appendix XIX G, and the additional requirements for extended testing for a minimum of 7 days at 4°C & 20°C to reflect normal hospital pharmacy practice and up to a maximum of 14 days.
3) Chemical stability and drug adsorption assessment in accordance with Chemical stability testing has been carried out as per 'A Standard Protocol for Deriving and Assessment of Stability Part 1 Aseptic Preparations (Small Molecules) 3rd edition December 2015' – NHS Pharmaceutical Quality Assurance Committee. Using Fentanyl 2micrograms/ml (with Bupivacaine 0.1%) in Sodium Chloride 0.9% stored at Room Temperature 15-25°C to represent adsorption risks and Hydrocortisone sodium succinate 1mg/ml in Water For Injections stored Refrigerated at 2-8°C to assess stability risks. These compounds were selected as markers to allow extrapolation to other drugs normally stored in neuraxial syringes that are more stable and less susceptible to adsorption.

   Following agreement with GBUK and under a confidentiality agreement I was permitted to review the various testing protocols carried out with or relevant to DASH 6 NRFit neuraxial syringes in accordance with the above.

1) <u>Stability studies – Fentanyl (with Bupivacaine)</u>

   There were some issues with the testing which are most likely due to extractives from the syringe interfering with the assay for fentanyl. The fentanyl assay results were very inconsistent and also the reported levels of degradation products are extremely high. It does look unlikely from the data that there is an adsorption issue nevertheless the conclusion is that no shelf life data can be taken from this study because of interference from other compounds in the HPLC

analysis; this study cannot be used for extrapolation to other products and offers little in the way of assurance that the syringes would be suitable for long term storage.

2) Stability studies – Hydrocortisone sodium succinate

There were significant degradation peaks seen for hydrocortisone which could again be as a result of extractives from the syringes rather than indicating instability. The hydrocortisone degradation itself was more or less in line with expectations; however, the levels of degradation product seen (including an unknown impurity which exceeds BP limits for the Hydrocortisone Sodium Succinate Injection related substances test on day 3) would limit the shelf life assigned. Although it is very likely that this unknown impurity was an extractive from the syringe it is recommended that this product should not be stored for more than 72 hours in these syringes.

3) Extractables testing / BP plastic syringe testing

The results seen are inconsistent across the range of syringes. The results for 20ml and 60ml syringes are non-compliant with the BP test after 24 hours at 37^{o}C (the standard test requirement of the BP) and also exceed the BP limits after 2 days at 22^{o}C and after 7 days at 4^{o}C. GBUK stated that there should be no difference in materials used in these syringes and that they were following up the inconsistency of results across the range with the manufacturers. For this reason it is recommended that the GBUK 20ml and 60ml syringes are not used for drug storage purposes.

The results for 1ml syringes shows an out of specification result after 7 days at 4^{o}C, however, this is clearly an outlier and would appear to be as a result of a laboratory error (the profile is not in line with any other result in the study).

All syringes comply with the pH test and the silicone oil tests in the BP.

Hence in conclusion the 1ml, 3ml, 5ml and 10ml GBUK syringes are compliant with the BP test and with the BP specification following 14 days storage at 4^{o}C and 22^{o}C.

4) Integrity testing

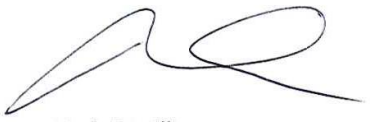
The dye intrusion test was carried out in accordance with protocol and results were satisfactory. The microbiological integrity test using *Brevundimonas diminuta* and *Escherichia coli* was carried out in accordance with the protocol and passed. During the study it was noted that some of the syringe caps were not fitted correctly and these syringes required retesting, and passed. Users should ensure that syringe caps are applied correctly to the syringes when required. It would be prudent for some in-house broth validation testing to form part of the change control before introducing the GBUK NRFit syringe range.

Conclusion

Overall results suggest that the following approach should be taken with GBUK DASH 6 NRFit lock syringes within aseptic services in the NHS, and by commercial suppliers supplying the NHS using these prefilled syringes for drugs for neuraxial routes of administration:-

1) Currently it is recommended that the 20ml and 60ml syringes are not used for drug storage purposes even in the short term.
2) Other sizes should be subject to assessment in order to assure that staff apply caps appropriately and it is suggested to include in-house broth validations ahead of implementation as part of the change control process.

3) Ideally a shelf life not exceeding 24 hours should be applied to drug products stored within these syringes, however, where drug adsorption is not likely to be a risk then this should be safe to extend to 72 hours if necessary. This is the case for cytarabine, methotrexate and hydrocortisone sodium succinate.
4) If shelf life beyond this is required then in-house studies should be undertaken or commissioned to support this practice.



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