Kap 27.9 Lagringstid - Användningstid

Prior to Use Storage and Patient Administration Periods for CSPs

The subject of “beyond use dating” for compounded sterile preparations published in USP-NF 27 <797> has been a continuing source of questions and concern for pharmacies. Questions regarding storage times, sterility test requirements and administration times are commonplace in the industry. <797> has specific requirements that must be met:

- Appropriateness of containers to preserve sterility and strength
- Before-administration storage periods
- Patient administration times

This technical bulletin seeks to clarify the USP issues and provide the pharmacist with a clear understanding of and a rationale for I-Flow’s position on the subject as well as a list of available I-Flow references for chemical and microbiological studies performed in support of this position.

USP-NF 27 <797> is concerned with two issues, risk of microbiological contamination and chemical stability. In the section titled RESPONSIBILITY OF COMPOUNDING PERSONNEL, item number 8, the USP states “Packaging selected for CSPs is appropriate to preserve the sterility and strength until the beyond-use date”. To satisfy this requirement I-Flow has performed Protocol Number PSI-04073 entitled *Microbial Ingress Testing of the I-Flow ON-Q Device*. In this study, ON-Q pumps were filled with a microbial growth supporting medium and then immersed for 24 hours in a circulating bath containing *Brevundimonas diminuta*. *Brevundimonas* is the bacteria of choice for filter bacteria retention studies and packaging ingress studies due to its extremely small size and motility. Following the exposure to the bacterial challenge solution, the filled devices were incubated at 20-25°C for 7 days. At the end of the seven days the pumps were emptied and the growth medium inspected for bacterial contamination. No bacterial contamination was present. This study clearly demonstrates that the ON-Q pump meets the USP requirements for an appropriate container to maintain product integrity and content sterility. Item number 11 of the same USP section states, “Beyond-use dates are assigned based on direct testing or extrapolation from reliable literature sources and other documentation”. The referenced testing performed by
I-Flow, at an independent contract laboratory, meets the requirement of “other documentation” as stated
in <797>.

The ON-Q Soaker Post-Op Pain Relief System is intended to provide continuous infusion of a local anesthetic directly into the intra-operative site for postoperative pain relief. In USP-NF 27 <797> under Examples of Medium-Risk Compounding, item number 3 provides for a description of a medium risk device such as the ON-Q pump, and states “Filling of reservoirs of injection and infusion devices with volumes of sterile drug solutions that will be administered over several days at ambient temperatures between 25° and 40°. The same statement
can be applied to devices filled in high-risk situations in the surgical suite. The only reason the I-Flow pump is
re-classified as high-risk is because the air quality in the surgical suite does not meet the standard of ISO Class 5. USP <797> specifically states that if a device is filled in an area with an environmental classification of greater than ISO Class 5, that the device must be classified as a high risk device. Surgical suites are typically operated with a controlled environment greater than ISO Class 5. The USP has provided for classification of CSPs that will be administered over several days. I-Flow recommends a maximum patient administration period of 5 days.

Since USP has chosen to include devices such as the ON-Q pump as medium-risk the storage conditions before administration must meet the USP guidelines: “For a medium-risk preparation, in absence of passing a sterility test, the storage periods cannot exceed the following time periods: Before administration, the CSPs are properly stored and are exposed for not more than 30 hours at controlled room temperature (see General Notices and Requirements) for not more than 9 days at cold temperatures (see General Notices and Requirements), and for 45 days in solid frozen state at -20° or colder.” The General Notices Section of USP lists requirements for temperature monitoring, etc. Cold temperatures are defined by the USP as 2-8°C. For a high-risk CSP the room temperature storage period drops to < 24 hours and the cold temperature time to < 3 days.

These sections of the USP are clearly discussing the risk of microbial contamination and the ability of the CSP to remain sterile for both the storage period and the administration period. To this end, I-Flow has performed protocol number PSI-04063 entitled *Microbial Storage Stability of the I-Flow ON-Q Device*. In this study, 10 ON-Q pumps were filled with a microbial growth supporting medium and then stored at 2-8 °C for seven days. At the completion of the seven days the pumps were transferred to room temperature storage (20-25 °C) for an additional 14 days. Another group of 10 pumps was stored at room temperature only for 14 days. Appropriate media growth promotion studies and bacteriostasis/fungistasis studies were performed with this stability study. At the completion of the prescribed storage periods the pumps were examined for microbial growth. In all cases all pumps were sterile. This study demonstrates that the ON-Q pump, when filled under aseptic conditions, by appropriately trained personnel, maintains its contents sterile for time periods that exceed the USP pre-administration storage periods and also exceeds the manufacturers recommendations of a maximum 5 day administration period. The USP states in the section on DETERMINING BEYOND-USE DATES that “compounding personnel may consult the manufacturer of particular products for advice on assigning beyond-use dates based on chemical and physical stability y parameters.”

I-Flow has also performed protocols PSI-04062 entitled Medium Risk Media Fill Protocol of the I-Flow ON-Q Device using the BAXA Repeater Pump, protocol PSI-04059 entitled Medium Risk Media Fill Protocol of the I-Flow On-Q Device and PSI-04061 entitled High Risk Media Fill Protocol of the I-Flow On-Q Device. In these three studies the media fill qualifications recommendations of USP-NF 27 <797> were followed. The final container filled and incubated for 14 days was the ON-Q pump. These three studies provide even more
documentation as to the suitability of the ON-Q pump as a final container for CSPs in both medium-risk and high-risk conditions.

I-Flow has also performed appropriate chemical stability studies for the most commonly used local anesthetics. These studies demonstrate that the anesthetics are stable for periods that exceed the USP prior to administration storage periods and the I-Flow’s recommended patient administration period. Chemical stability of the pump has been verified with the following drugs:

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Drug Description	Concentration	Storage Time at RT
Bupivacaine	0.25 – 0.5%	30 days
Lidocaine	1%	30 days
Ropivacaine	0.2%	30 days
Ropivacaine	0.2 – 0.75%	14 days

Kommentar av Solann:
0,25 - 0,5% = 2,5 - 5 mg/ml
1% = 10 mg/ml
0,2% = 2 mg/ml
0,2 - 0,75% = 2 - 7,5 mg/ml

Summary

- Microbial ingress studies and media fill challenges performed by I-Flow have demonstrated the ON-Q pump is an appropriate container for CSP storage.
- The USP makes a clear difference between “before-administration” storage periods and patient administration periods.
- Studies performed by I-Flow have demonstrated both microbiological and chemical stability of the filled ON-Q pump for time periods that exceed the USP requirements for before-administration storage and I-Flows recommended patient administration times.

For copies of the referenced protocols and final reports, please contact I-Flow Technical Service.