Fertility nurses first

Sterile compounding of fertility medications

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The practice of compounding medication by a pharmacy has been around for centuries. Most commonly pharmacies compound creams, ointments, and oral solutions in concentrations not available from a manufacturer. These types of compounds are administered topically or orally and require accurate procedures to ensure the correct potency of the active ingredients. This type of compounding is referred to as non-sterile compounding.

If the compounded medication is to be administered parenterally, such as via subcutaneous or intravenous injection, strict procedures must be followed to ensure the correct potency of the ingredients and the absence of microbial contamination. This type of compounding is referred to as sterile compounding.

Pharmacies are allowed to compound medication that is not commercially available from a manufacturer if they follow United States Pharmacopeia standards and state board of pharmacy regulations. If strict procedures and standards are not followed, the results can be dangerous to the patient due to microorganism infection.

This was the case in 2012 when a New England Compounding Pharmacy was the center of a major meningitis outbreak. The outbreak sickened over 800 individuals and resulted in the death of 76 from patients who had received contaminated steroid injections from the pharmacy.[1] In August 2011, the FDA reported that repackaged injections of Avastin (bevacizumab) caused serious eye infections in the Miami, Florida, area. A pharmacy had repackaged the Avastin from single-use vials into multiple single-use syringes, distributing them to multiple eye clinics, and infecting at least 12 patients. Some patients lost the remaining vision in the eye being treated.[1]

These are just a couple devastating cases, but additional cases of contaminated medications occur which do not reach national attention.

So what is being done to prevent this from reoccurring?

State boards of pharmacy have increased their focus on pharmacy compounding practices by enforcing United States Pharmacopia (USP) 797 standards. These standards require pharmacies to have ISO 7 cleanrooms, strict aseptic handling procedures, quality assurance testing, and limit the Beyond Use Dating assigned to products. These and other requirements are in place to ensure accurate potency and microbial free products are produced by the pharmacy.[2]

In addition, new USP 800 Hazardous Drug Handing standards have been implemented to protect healthcare workers and patients from hazardous medications.[3] Common medications used in fertility treatments that are on the National Institute for Occupational Safety and Health (NIOSH) list of hazardous drugs include: Leuprolide, human chorionic gonadotropin, progresterone, estrogen, and ganirelix.[4]

What are the implications for pharmacies?

Pharmacies must comply with USP 797 which governs Sterile Compounding and the newly enacted USP 800 which governs compounding of hazardous drugs. USP 800 compliance is not required nationally until July 2018 but some states, such as California have enacted the rules already. Due to the scope of the requirements pharmacies are preparing well in advance. We will review the implication of USP 800 in a later section.

USP 797 Sterile Compounding standards[2]

In 2004, the first version of USP 797 was introduced and there was a revision in 2007. Each version is slightly more detailed and provides better defined practices for pharmacies to follow. The current

proposed standard was released in 2016 with plans to be implemented in 2018. We will use proposed version as our basis for discussion since these are the standards we are striving to be compliant with.

Table 1 - USP 797 Key components

- Proper cleanroom environment
- Beyond use dates assigned based risk levels
- Trained pharmacy personnel
- Verification of accuracy and sterility
- Cleanroom environmental quality control and monitoring
- Storage and handling procedure
- Patient and caregiver training
- Adverse event reporting
- Cleaning and sanitization with robust quality assurance

A key requirement in the standard is the Beyond Use Date (BUD), otherwise known as the expiration date. This is the date before which a pharmacy compounded sterile products must be administered to the patient. When determining the BUD, the chemical stability of the drug and the ability to maintain sterility must be considered. The shorter BUD of these two factors is assigned to the finished product.

Determining chemical stability

This data is generally available in reference material such as Extended Stability for Parenteral Drugs, Trissel's Handbook of Injectable Drugs, published literature, or from the manufacturer. In the absence of published chemical stability of a compounded product the pharmacy may choose to conduct extensive potency testing to justify their BUD dating.

Determining the ability to maintain sterility

This data is based on the engineering controls used during the compounding process since pharmacy compounded products are not terminally sterilized as is done during the manufacturing process. Thus the dates a pharmacy can use are much shorter than a manufacturer.

USP 797 provides the following maximum Beyond Use Dates that must be used by a pharmacy in the absence of sterility testing of each batch by the Pharmacy or antimicrobial effectiveness testing.

Based on the proposed revisions to USP 797 the Beyond Use Dates are assigned as below for aseptically prepared pharmacy compounded products:

Table 2 - Beyond use dates

Method of achieving sterility	Sterility testing performed prior to release	Preservative added	Prepared from one or more non-sterile ingredients	Refrigerated BUD
Aseptically prepared	No	No	Yes	7 days
			No	9 days
		Yes	N/A	42 days
	Yes	No	N/A	42 days
		Yes	N/A	42 days

The particular CSP formulation must pass antimicrobial effectiveness testing in accordance with USP 51 standards.

Since 9 days of BUD interferes with the pharmacies ability to dispense all the medication that is needed by the patient to complete therapy, the pharmacy may conduct independent testing to extend the Beyond Use Dating in certain situations. This may include preparing the medication in a batch, submitting sterility testing on the batch, and then releasing the batch once results are obtained. This allows the product to be given 42 days of dating with chemical stability is available for this length of time.

Extending the BUD outside of the guidance above involves very extensive and expensive testing protocols utilizing an FDA Registered analytical laboratory. Based on the type and chemical stability of the product, the pharmacy may need to conduct the following tests:

USP 71 Sterility test	USP 51 Antimicrobial Effectiveness test
Potency	Endotoxin
Particulate Matter and pH	Container Closure test

Conducting these studies is very expensive given the laboratory charges and cost of drug that is needed for the testing. For example, to conduct a study to test leuprolide 20mcg/0.1ml 10ml vial for a BUD of 42 days can cost between $20,000 - $30,000. Ongoing testing is also needed to verify pharmacy processes.

How does this apply to the beyond use date for fertility medication?

The Leuprolide Acetate 2 week kit is a common medication used in fertility treatment protocols. The manufacturer provides Leuprolide Acetate in strength of 1mg/0.2mL for parenteral use with preservatives, whiles fertility protocols utilize micro-dose leuprolide in concentrations between 20-100mcg/0.1 -0.2/ml. As a result, pharmacies need to compound the medication to obtain the exact concentration ordered by the prescriber.

To determine the Beyond Use Date, we need to determine where it fits into table 2.

Question #1 – Will the pharmacy prepare a batch in advance and conduct sterility testing prior to dispensing? Let's assume No.

Questions #2 – Does the product contain preservatives?

- Yes - Leuprolide standard solutions contain preservatives. But the caveat is the product must pass antimicrobial effectiveness testing in accordance with USP 51 standards.

  If the pharmacy has conducted Antimicrobial Effectiveness Testing, they can assign a BUD up to 42 days if the product is chemically stable. Otherwise the BUD needs to be 9 days if chemically stable.

- Progesterone in Oil for injection is another example and does not contain preservatives. In order to make the concentration required the pharmacy must start with non-sterile powder ingredients. Since we are using non-sterile ingredients the requirements are more stringent. In this case, if no sterility testing is conducted, the maximum BUD would be 7 days if chemically stable. If each batch is tested prior to release, the product can be given up to 42 days if chemically stable.

As mentioned earlier, we must consider and have proof of the chemical stability of the product along with the USP requirements when assigning BUD. For some hormonal products such as HCG, it is difficult for the laboratory to test chemical stability via potency tests. Thus we need to default to the manufacturer data in these cases.

Other fertility medication considerations

USP 800 Hazardous Drug Handling Standards are designed to protect healthcare workers and patients from hazardous products.[3] While these practices are not new in pharmacy, placing them in USP 800 makes them enforceable by State Boards of Pharmacy. Many of the common medications used in fertility treatments are on the NIOSH list of hazardous drugs including: Leuprolide, human chorionic gonadotropin, progresterone, estrogen, and ganirelix.[4]

The most significant requirement is that hazardous products must be compounded in a biological safety cabinet which is located in a negative pressure compounding room vented to the outside.[3]

Implementing these procedures and building the proper compounding room is very expensive and space prohibitive in many pharmacies. Thus many pharmacies are centralizing their compounding operations into specially built pharmacies with robust cleanrooms and ventilation systems.

How does this impact the ability to access fertility medications?

Some pharmacies may decide to stop compounding hazardous drugs completely. Other pharmacies will implement the standards in their location or create centralized compounding model. It is important for healthcare personnel to begin asking questions about how their current pharmacy plans to meet the USP 800 standard. With proper coordination of care we can improve patient safety and continue to meet the needs of the patient and provider.

What can be done at the time of parenteral medication administration to prevent

patient harm?

a. Check the label to ensure the patient name, drug, dose, frequency, and route are correct.

b. Check the label for the Beyond Use Date. If the date is beyond 42 days ask the pharmacy if they have conducted independent testing.

c. Ensure the medication was properly stored in the refrigerator or room temperature as indicated on the label.

d. Inspect the solution for particles or cloudiness. Call the Pharmacy if you suspect any issues.

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