Extending the beyond-use date of sterile compounded preparations

Benjamin Tanguay, Pharm.D., MBA

Speaker Bio

- Pharm.D. – Université de Montréal (2016)
- MBA – HEC Montréal (2021)

- Pharmacist – Development & Hospital Affairs
  - Gentès & Bolduc Pharmacists – Galenova
- Part-Time Professor
  - University of Ottawa

- How did I get into compounding?
  - University compounding competitions
  - Ambulatory infusion therapy

Presenter/Speaker Personal Disclosure

- Presenter's Name: Benjamin Tanguay

- I have the following relationships with commercial interests:
  - Employee of Galenova – Gentès & Bolduc, pharmacists

- Speaking Fees for current program:
  - I have received no speaker's fee for this learning activity

Learning Objectives

- At the conclusion of this activity, participants will be able to explain the regulatory requirements for extending the beyond-use date of sterile preparation
- Participants will be able to describe the necessary steps to validate and perform a sterility test
- Participants will be able to identify when pyrogen testing is required in sterile compounding

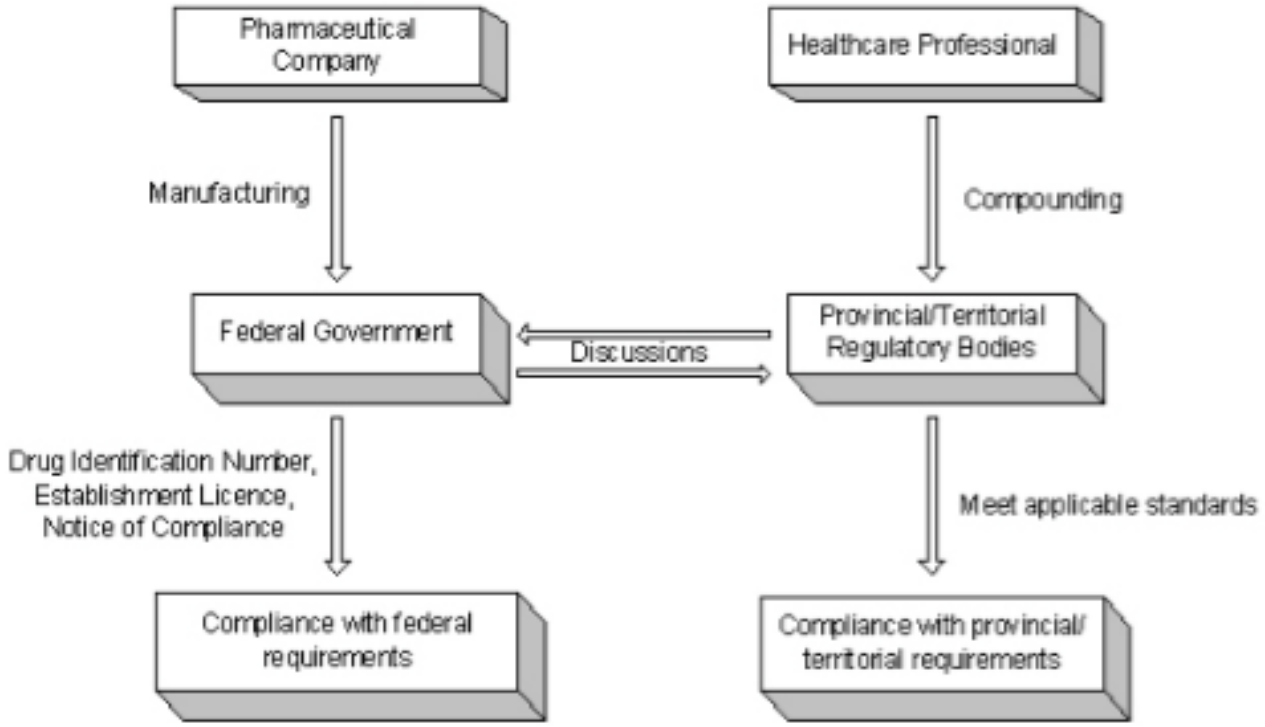
What is compounding ?

- Health Canada definition :
  - The combining or mixing together of two or more ingredients (of which at least one is a drug or pharmacologically active component) to create a final product in an appropriate form for dosing
  - It can involve raw materials or the alteration of the form and strength of commercially available product
  - Compounding should only be done if there is a **therapeutic need** or **lack of product** availability

Policy on manufacturing and compounding drug product in Canada POL-0051

Compounding versus Manufacturing

Figure 1.0 - Process in addressing Manufacturing and Compounding Issues



Policy on manufacturing and compounding drug product in Canada POL-0051

Canadian Compounding Legislation

- Federal level:
  - Policy on manufacturing and compounding drug product in Canada POL-0051

- Provincial level:
  - Each provincial college is responsible for establishing its own provincial guidelines
  - In Alberta = Alberta College of Pharmacy
  - Reference guidelines :
    - NAPRA Model Standards for Pharmacy Compounding of Non-Hazardous Sterile Preparations
    - NAPRA Model Standards for Pharmacy Compounding of Hazardous Sterile Preparations

Some Alberta Specificities

- ACP Council determined that in Alberta, **only a pharmacy technician or pharmacist may compound sterile preparations**. This must not be delegated to a pharmacy assistant or another unregulated individual.
- Different mask and gowning requirements for hazardous sterile compounding
- All pharmacies that perform **high-risk sterile compounding** will be inspected once **every 18 months**. **All pharmacies that perform sterile compounding** other than high risk will be inspected **once every three years** at minimum.

https://abpharmacy.ca/regulated-members/practice-resources/pharmacy-compounding/sterile-compounding/

What is sterile compounding ?

- Sterile compounding is the process of preparing custom medications in an aseptic environment to prevent contamination and ensure patient safety
- It can include :
  - Parenteral preparations/Injections (IV, IM, SC, etc…)
  - Nasal inhalation solutions
  - Irrigation solutions
  - Otic preparations if administered to the inner ear
  - Any other preparation where sterility is deemed to be required for patient safety

Aseptic vs Sterility

Important distinction to make

- Asepticity : free from contamination by harmful microorganism
- Sterility : the absolute absence of viable microorganism

What’s the difference ?

Asepticity vs Sterility

Asepticity = Aseptic Technique

- Relies on specific procedures, facilities and training to manipulate sterile products and maintain their sterility
- There is always a risk that the aseptic process contaminated the product

Sterility

- Implies that we are certain the product is exempt from any potential viable microorganisms
- Relies on validated processes

Aseptic vs Sterility

In summary:

Aseptic technique is a set of practices used to achieve and maintain sterility. Sterility is the goal, while aseptic technique is a means to achieve that goal.

Other ways to achieve the goal of sterility?

Aseptic vs Sterility

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Aseptic technique is a set of practices used to achieve and maintain sterility. Sterility is the goal, while aseptic technique is a means to achieve that goal.

Other ways to achieve the goal of sterility?

- Terminal sterilization (steam sterilization, dry heat, filtration, gas, radiation)

Risk-based approach

- Aseptic manipulations in sterile compounding = unavoidable risk
- You can never remove all risk

- What’s the biggest risk in sterile compounding?

Risk-based approach

- Aseptic manipulations in sterile compounding = an inherent risk
- You can never remove all risk

- What's the biggest risk in sterile compounding?
    - Human intervention = # of/complexity of manipulations

Types of sterile compounding ?

Sterile compounding is divided in different categories based on risk

- Hazardous vs Non-Hazardous
  - Risk of contamination and exposure

- Low, Medium and High-Risk
  - Number of manipulations in a batch
  - Complexity of manipulations

Types of sterile compounding ?

Contamination risk levels[82, 83]		
Low	**Medium**	**High**
• Final product compounded using up to 3 "sterile units" • No more than 2 septum punctures at the injection site for each sterile unit • Simple aseptic transfer technique • Drug prepared for one patient (patient-specific dose)	• Final product compounded using 4 or more "sterile units" • Complex manipulations • Prolonged preparation time • Batch preparations (preparing more than one unit of the same composition during one compounding session)	• Non-sterile ingredients or equipment used before terminal sterilization • Non-sterile preparations, containing water, stored for more than 6 hours before terminal sterilization • Improper garbing or gloving by compounding personnel

Determining a preparation's risk level is key to properly establish its beyond-use-date

Model Standards for Pharmacy Compounding of Non-Hazardous Sterile Preparations. 2016. NAPRA-ANORP

Types of sterile compounding ?

Contamination risk levels[82, 83]		
Low	Medium	High

Sterile unit

The concept of a "sterile unit" is used to specify certain criteria for establishing the BUD.

A sterile unit is a vial, ampoule or bag of drug or diluent. The following examples illustrate the concept:

- 1 bag of solute represents 1 "sterile unit."
- 2 vials of cefazolin represent 2 "sterile units."
- 1 vial of sterile water for injection represents 1 "sterile unit."

beyond-use-date

Model Standards for Pharmacy Compounding of Non-Hazardous Sterile Preparations. 2016. NAPRA-ANORP

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What is a Beyond-Use-Date

- A beyond-use date is the date after which a compounded preparation shall not be used

- BUD are NOT expiration dates
  - BUD are assigned from criteria different from those applied to expiration dates of manufactured drug product

- BUD ≠ stability

What is a Beyond-Use-Date

- The BUD is determined by the shortest of both concepts:
  - Physical and chemical stability
    - Determined by manufacturer or referenced stability data
    - Keep in mind the final concentration, dispensing container and storage temperature
  - Microbiological stability
    - Contamination risk based on the bacterial proliferation rate

Where no specific sterility testing is performed for a preparation or batch, the sterile compounding supervisor must assign a BUD on the basis of the following criteria.

The BUD must not exceed the earliest of the dates established by the following two criteria:

- expiration date based on chemical and physical stability[77, 78, 79] according to reference texts
- storage time related to risk of microbial contamination

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How to determine a Beyond-Use-Date

Table 7

Beyond-use dates (BUDs) for compounded sterile preparations, according to risk of microbial contamination[84]			
	BUD without sterility testing		
Risk of contamination	**At controlled room temperature**	**With storage in refrigerator**	**With storage in freezer**
Low	48 hours	14 days	45 days
Medium	30 hours	9 days	45 days
High	24 hours	3 days	45 days

Administration of the compounded sterile preparation must begin before the BUD has passed.

High-risk preparations must always be sterilized, and the BUDs in the high-risk row of Table 7 apply to high-risk *sterile* preparations.

Model Standards for Pharmacy Compounding of Non-Hazardous Sterile Preparations. 2016. NAPRA-ANORP

Determining a BUD - Sterile

Dr. John Smith
150 Hospital Road, Vancouver

Patient: Christine Draper _____
DOB: __1964-09-28_____

Dalteparin 25 000 units/mL

19 000 units SC once daily x 30d

Dr JSmith
April 3 2019

Assessment of the Stability of Dalteparin Sodium in Prepared Syringes for Up to Thirty Days: An In Vitro Study

Michael Laposata, MD, PhD, and Stephen M. Johnson, BS
Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts

Clin Ther. 2003 Apr;25(4):1219-25.

Table 6

Contamination risk levels[82, 83]		
Low	**Medium**	**High**
• Final product compounded using up to 3 "sterile units" • No more than 2 septum punctures at the injection site for each sterile unit • Simple aseptic transfer technique • Drug prepared for one patient (patient-specific dose)	• Final product compounded using 4 or more "sterile units" • Complex manipulations • Prolonged preparation time • Batch preparations (preparing more than one unit of the same composition during one compounding session)	• Non-sterile ingredients or equipment used before terminal sterilization • Non-sterile preparations, containing water, stored for more than 6 hours before terminal sterilization • Improper garbing or gloving by compounding personnel

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What is Sterility Testing?

- Sterility testing is a quality control test to assess the microbiological quality of a product or preparation

- In pharmacy compounding, the goal of sterility testing is to confirm that adequate aseptic techniques were used

- Why go through the trouble of sterility testing in compounding?

Why test for sterility in compounding?

- Why go through the trouble of sterility testing in compounding?

Where no specific sterility testing is performed for a preparation or batch, the sterile compounding supervisor must assign a BUD on the basis of the following criteria.

The BUD must not exceed the earliest of the dates established by the following two criteria:

- expiration date based on chemical and physical stability[77, 78, 79] according to reference texts
- storage time related to risk of microbial contamination

- As per NAPRA guidelines, sterility testing removes the need to assess microbiological risk
- The preparation's BUD can be assigned solely on its physico-chemical stability

Model Standards for Pharmacy Compounding of Non-Hazardous Sterile Preparations. 2016. NAPRA-ANORP

When do you test for sterility?

- To extend your sterile compounded preparation's BUD beyond the limits of Table 7 of the NAPRA guidelines

- Also required if :

Sterility test and bacterial endotoxin test[85]

A sterility test via membrane filtration and a bacterial endotoxin test must be performed for high-risk sterile preparations (*see* Table 6) in the following situations:

- when sterile preparations are compounded in batches of over 25 identical units;
- when there has been more than 12 hours of exposure time at a temperature between 2°C and 8°C before sterilization;
- when there has been more than 6 hours of exposure time at a temperature above 8°C before sterilization.

Model Standards for Pharmacy Compounding of Non-Hazardous Sterile Preparations. 2016. NAPRA-ANORP

Who can test for sterility in compounding?

- The NAPRA guidelines do not comment on who can conduct a sterility test

- In practice what do we see ?

Who can test for sterility in compounding?

- In practice what do we see ?

1) Using a contract microbiology lab
   - Advantages : Easy, no further training required, can provide some coaching
   - Disadvantages : delays, costly (especially if lots of tests to be done)

2) For hospital practice, using the hospital's microbiology lab
   - Advantages : Easy, usually at no cost or very little cost for pharmacy dept
   - Disadvantages : Will usually conduct direct inoculation vs membrane filtration

3) Internal testing in the pharmacy
   - Advantages : Quick, control the process, once implemented very cost effective
   - Disadvantages : Hard to implement, start-up costs, further training required

Sterility Testing Guidelines

USP <71> Sterility Tests

- Main reference text
- Lists the acceptable test methods
- How to conduct a sterility test
  - Minimum quantity to use
  - Minimum number of articles to test
- How to validate a test method

Sterility Testing Methods

Membrane Filtration

- Preferred method according to USP <71> Sterility Tests
- Samples are passed through a set of filters, the filters are rinsed, then each filter is placed in contact with growth media and incubated
- Samples must be filterable
- Requires a 14-day incubation period
- Analyst interprets results
- Easy to test large quantities
- Relatively low risk of contamination

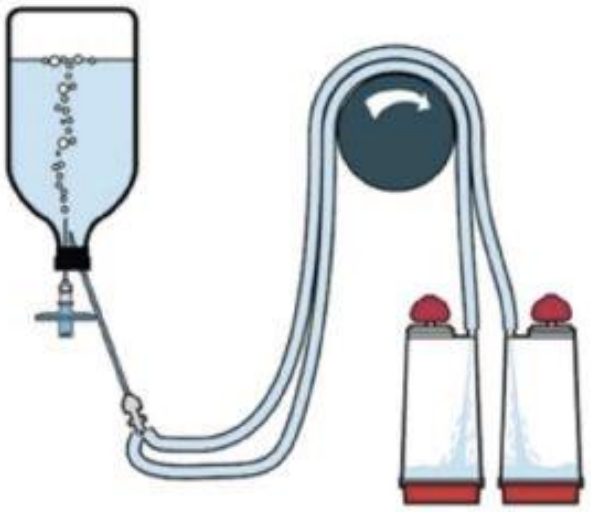

Figure 1: Setup of a Steritest™ EZ device for antibiotics

Membrane filtration

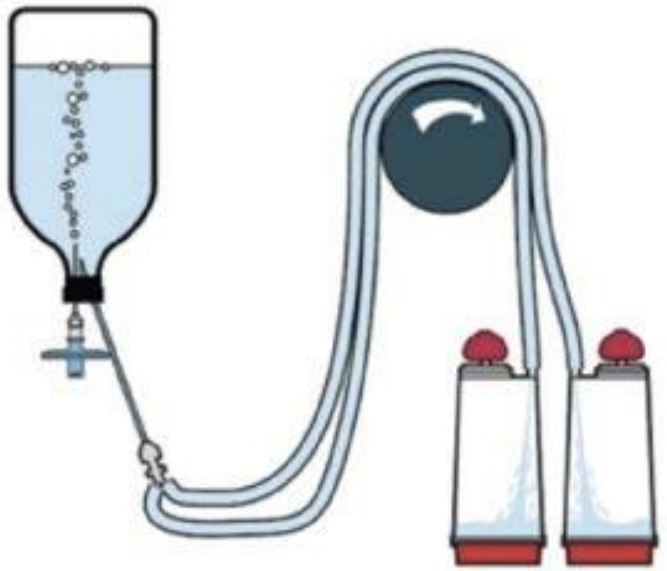

Figure 1: Setup of a Steritest™ EZ device for antibiotics

- Relies on bacterial growth
- Utilizes 2 growth media : Tryptic Soy Broth (TSB) and Fluid Thioglycollate Medium (FTM)

Sterility Testing Methods

Direct Innoculation

- The sample is directly added to the growth media and then incubated
- Easiest to perform
- Requires a 14 day incubation period
- Analyst interprets results
- Works well for products that cannot be filtered
- Fewer options to neutralize preservatives if they’re found in the formula

Sterility Testing Methods

Alternative sterility methods

- A growing field, lots of new products available
- Must demonstrate that the alternative test method is noninferior to membrane filtration
- These new methods utilize different technology and do not rely solely on bacterial growth
- Reduced incubation time if any incubation is required
- Faster turnaround time
- Objective testing technologies available

Sterility Testing Method Suitability

- Demonstrates the validity of the sterility test. Hence, if contamination is present in our sample, our test method will be capable of detecting it.
- As per USP <71> Sterility Tests, method suitability must be demonstrated for each formulation or in compounding for each product family
  - Test the worst-case approach
- Method suitability also applies to a specific test volume
  - If standard batch size increases, method suitability might need to be replicated

Sterility Testing Method Suitability

- Method suitability is performed by conducting the test 7 times
  - 1 negative control
  - 6 positive controls
- In the 6 positive controls, specific bacterial (4) and fungi (2) strains are added to the rinse fluid
- Test is performed and incubated as usual for 14 days
- After 14 days, we expect :
  - Negative control : show no bacterial growth
  - 6 positive controls : show growth of the corresponding microorganism strain

Performing a sterility test

1. Perform according to a USP <71> test method or equivalent
2. Method suitability has been demonstrated for the tested product
3. Sample the appropriate number of containers from your batch as specified in USP <71> Sterility Tests
4. Test the minimum quantity from each sampled container as specified in USP <71> Sterility Tests
5. Perform test, incubate and quarantine samples :

To establish a longer BUD, sterility tests must be performed for a given preparation or batch. Preparations must be quarantined while awaiting the results of the sterility test. Preparations may be released once the results of the sterility test are obtained.

Number of samples to test

Table 3. Minimum Number of Articles to be Tested in Relation to the Number of Articles in the Batch

Number of Items in the Batch*	Minimum Number of Items to be Tested for Each Medium (unless otherwise justified and authorized)**
Parenteral preparations	
Not more than 100 containers	10% or 4 containers, whichever is the greater
More than 100 but not more than 500 containers	10 containers
More than 500 containers	2% or 20 containers, whichever is less
• *For large-volume parenterals*	2% or 10 containers, whichever is less
Antibiotic solids	
Pharmacy bulk packages (<5 g)	20 containers
Pharmacy bulk packages (≥5 g)	6 containers
Bulks and blends	See *Bulk solid products*.
Ophthalmic and other noninjectable preparations	
Not more than 200 containers	5% or 2 containers, whichever is the greater
More than 200 containers	10 containers
If the product is presented in the form of single-dose containers, apply the scheme shown above for preparations for parenteral use.	

USP <71> Sterility Tests

Quantity per sample required

Table 2. Minimum Quantity to be Used for Each Medium

Quantity per Container	Minimum Quantity to be Used (unless otherwise justified and authorized)
Liquids	
Less than 1 mL	The whole contents of each container
1–40 mL	Half the contents of each container, but not less than 1 mL
Greater than 40 mL, and not greater than 100 mL	20 mL
Greater than 100 mL	10% of the contents of the container, but not less than 20 mL
Antibiotic liquids	1 mL

- Table 2 lists the quantity to be tested for each growth media
- For full testing = 2 growth media = double the quantities in Table 2

USP <71> Sterility Tests

What are pyrogens/endotoxins?

- Pyrogens are very small substances that can induce fever and other harmful reactions when they enter the body.

- Pyrogens are so small that they’re generally not filterable

- Endotoxins are the most common type of pyrogen. Endotoxins are found in the cell wall of gram-negative bacteria
  - Terms are often used interchangeably

What’s a safe limit?

- Particularly harmful in vulnerable patients
- Part of release testing for parenteral administered (injectables) drugs only
- The pyrogen limit for a drug will vary on the total administered dose and its route of administration
  - IV/IM/SC vs Intrathecal
- Endotoxin limit information can be calculated or often listed in the drugs’ pharmacopeai monograph

How to avoid pyrogens ?

- Keep in mind they’re not filterable! Hence cannot be removed
- The only solution = avoid introducing them
- Pyrogen prevention strategies :
  - Raw materials = use pyrogen-free raw materials (hard to find)
  - Use dry heat sterilization for glassware and equipment used
  - Conduct the non-sterile manipulations of a high-risk sterile compound in a controlled environment
  - Plan your compounding process to reduce the risk of contamination
    - Use sterile water for injection
    - Use disposable or commercially-available supplies (ex: tubing, vials, etc…)

When do you need to test for pyrogens?

- Low & Medium risk sterile compounding = not required as only sterile ingredients and supplies are used in the compounding process
- High risk sterile compounding :
  - My recommendation : for every high-risk parenteral preparation
  - NAPRA recommendation :

Sterility test and bacterial endotoxin test[85]

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- when sterile preparations are compounded in batches of over 25 identical units;
- when there has been more than 12 hours of exposure time at a temperature between 2°C and 8°C before sterilization;
- when there has been more than 6 hours of exposure time at a temperature above 8°C before sterilization.

How to test ?

- Requires specific testing equipment & additional microbiology training
- Most compounders use a contract microbiology lab
- Several test methods exist and like sterility testing, method validation is key
- Most common test method = Limulus Amebocyte Lysate (LAL) Test

Limulus Amebocyte Lysate (LAL) Test

- Uses an extract from the blood cells of the horseshoe crab
- Amebocytes (type of blood cell) are isolated into a concentrated solution
- The drug product is added to the amebocyte solution which will coagulate in the presence of endotoxins
- Very sensitive test method
- But, only specific to endotoxins and not other types of pyrogens

Limulus Amebocyte Lysate (LAL) Test

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The Washington Post
Democracy Dies in Darkness

A horseshoe crab's blood is vital in testing drugs. Critics say using it endangers the ancient creature.

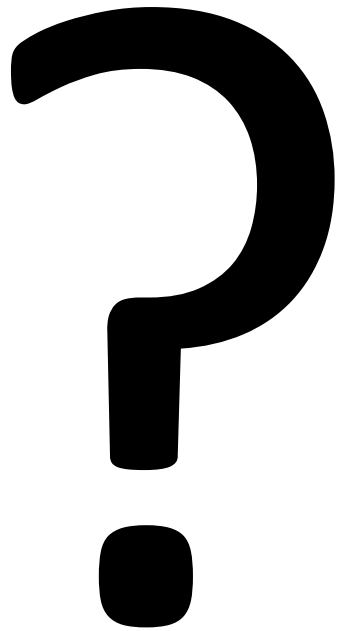
By Caren Chesler
August 1, 2021 at 8:30 a.m. EDT

https://www.washingtonpost.com/health/horseshoe-crab-lal-endotoxins-coronavirus/2021/07/30/cbc0a158-d525-11eb-9f29-e9e6c9e843c6_story.html

Summary

- Sterility testing removes the microbiological risk thus allowing a extended BUDs if the preparation is also chemically stable
- Sterility testing implies :
  - Using a recognized test method,
  - Conducting method suitability,
  - Adequate sampling and
  - Testing correct quantities
- Pyrogen/Endotoxin testing is required for high-risk parenteral preparations

Questions



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- NAPRA. Model Standards for Pharmacy Compounding of Hazardous Sterile Preparations. National Association of Pharmacy Regulatory Authorities. 2016.
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