
Photo by insung yoon on Unsplash

## Disclosure

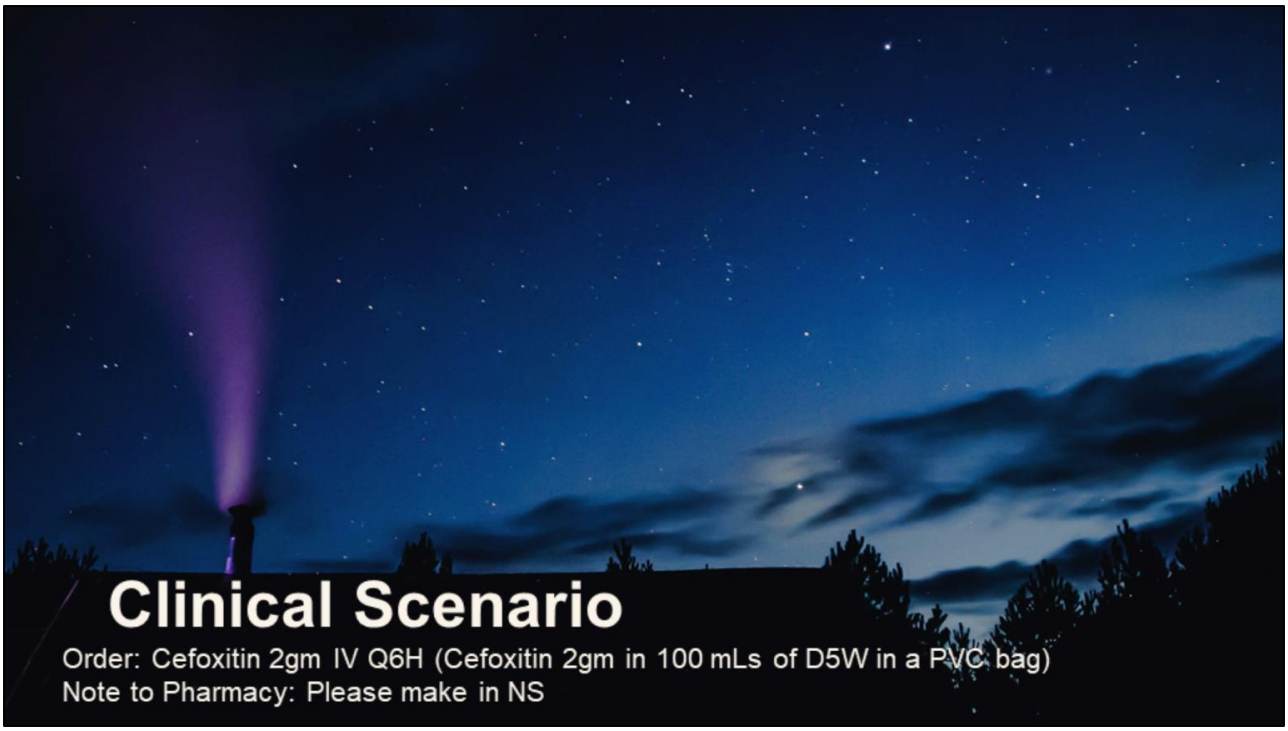
- I have no current or previous personal or financial relationships with commercial entities
- No conflict of interests to declare
- I have not received any financial or commercial funding or support for today's session
- I do not promote any specific brand or generic product though some generic names are used for examples
- All opinions stated are my own

## Objectives

1. Be able to describe the core components that contribute to a compounded sterile product (CSP) beyond use date (BUD)
2. Be able to assess and apply available stability data and NAPRA sterility guidelines to a CSP recipe to assign a BUD

# Outline

- Overview of BUD within the NAPRA Model Standards for Pharmacy Compounding of Non-Hazardous Sterile Preparations
- Review of physical and chemical stability core components
- Review of BUD application
- Clinical scenario walk through
- Key Takeaways
- Questions




- It’s a Saturday evening in the dispensary and you receive an order for: Cefoxitin 2gm IV q6H Note to Pharmacy, please make in NS
- There is no matching recipe built as you usually prepare this recipe in normal saline. It appears this has never been made on site before by pharmacy…..
- Photo by Evdokiya Lebedeva on Unsplash


There are many scenarios where we may need to create a new recipe, a new special access medication is brought in for a specific patient, a brand new formulation of a medication is brought in urgently for a patient, or the patient has a strong medical need for something unique ex. for a different diluent.

It is extremely important to ensure that the recipe you are being asked to review to assign a BUD to is clinically necessary and not a nice to have option. The amount of work that comes after this point is substantial, both for that person on the Saturday night and for all the teams that will be involved in potentially adding this recipe to the system.

- Photo by Jacob Thomas on Unsplash
- Photo by mrjn Photography on Unsplash

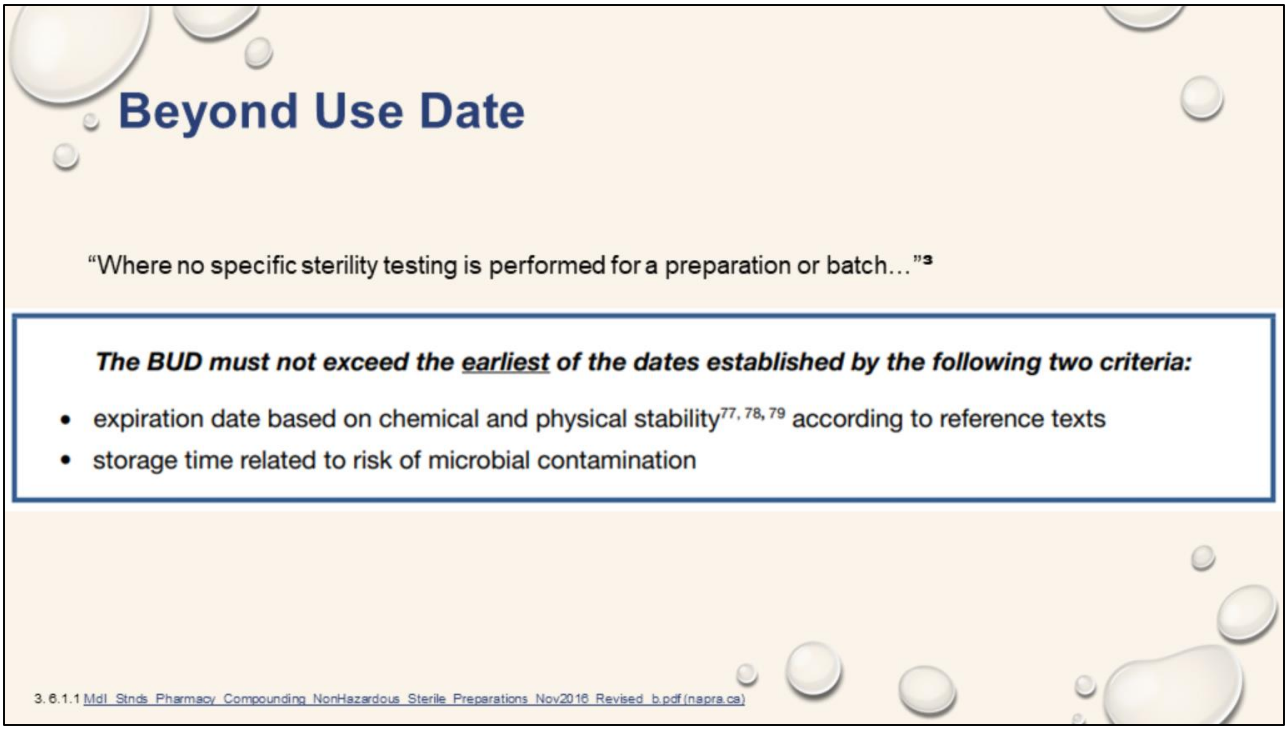

- There are many important safety considerations when deciding to compound a medication, and while many naturally come to mind ex. is this a high alert medication, does this require complex manipulations to prepare, one that may be less front of mind is – will this medication be safe and effective when it reaches the patient from a chemical and physical stability and sterility perspective?
- So consider, anytime you are “building a unicorn” or a unique one off recipe, that introduces risk!

Compounding really should be considered an option of last resort over using a commercial product, however when a product needs to be made, pharmacy has access to a clean sterile environment with a series of independent double checks at multiple stages where we can produce the safest possible compounded product

- When compounding or deciding between compounding and potentially nursing mixing on the unit, take time to consider safety
    - Is this a high alert product?
    - Does this product require complex manipulations to prepare correctly?
    - Is this medication for a high risk patient population?
    - Is this a Look Alike Sound Alike Drug?

However is it also important to consider safety from a BUD perspective, will the medication be safe when it reaches the patient? From a sterility and

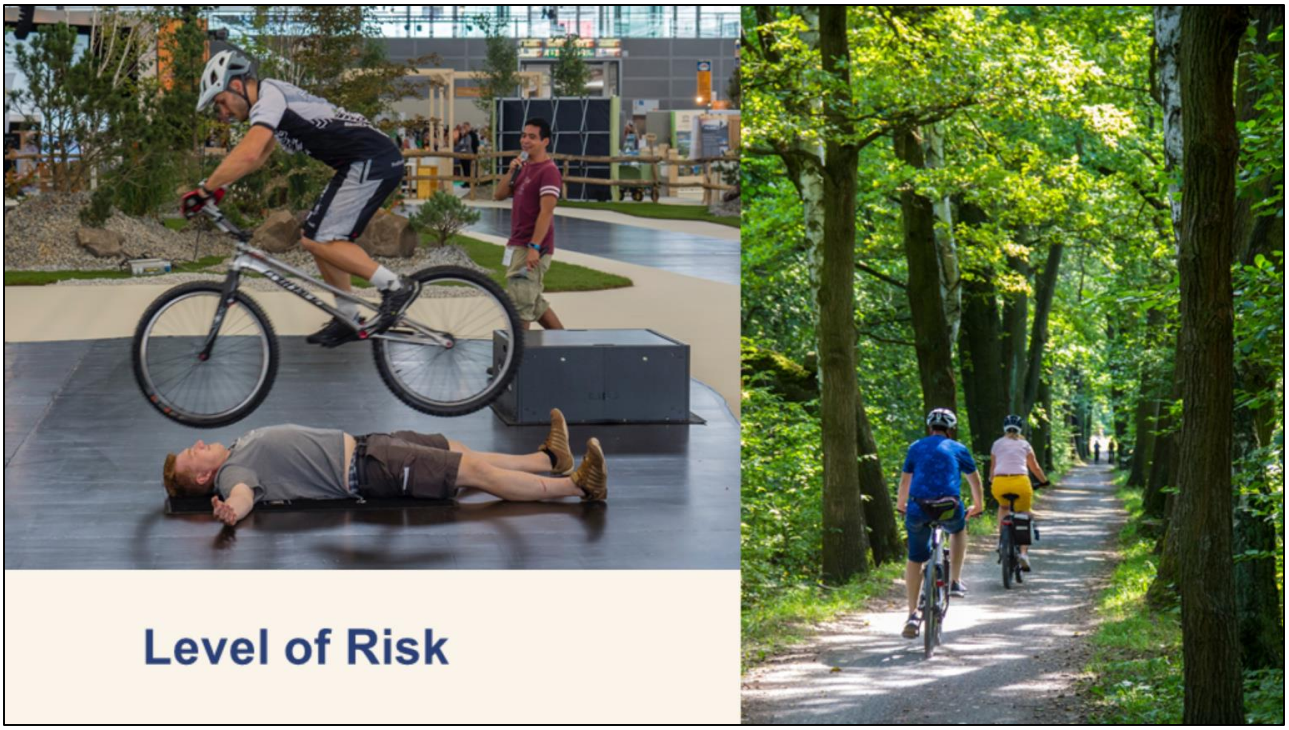
chemical/physical stability perspective
Photo by Mier Chen on Unsplash




- Microbial contamination risks (sterility) and their associated storage conditions are defined by NAPRA guidelines
- "Date and time after which a compounded sterile preparation cannot be used and must be discarded because of a risk of loss of sterility.

- For the purposes of these Model Standards, administration of the compounded sterile preparation must begin before the BUD has passed" NAPRA's Definition 3. 9 Glossary Mdl_Stnds_Pharmacy_Compounding_NonHazardous_Sterile_Preparations_Nov2016_Revised_b.pdf (napra.ca)


- I will focus on non-hazardous sterile compounding for the purpose of todays discussion, but NAPRA does have extensive guidelines with important nuances discussed in the NAPRA Model Standards for Hazardous Sterile Compounding Guidelines.
- I will also focus on a common practice situation where we are unable to perform sterility testing for each batch/product we make. NAPRA guidelines are designed to support practice based compounding where sterility testing is not available.
- Image from: Free Images : liquid, black and white, rain, petal, glass, raindrop, wet, barren, pattern, line, spray, autumn, monochrome, drip, circle, transparent, grey, background, drop of water, disc, depression, moisture, freezing, trist, beaded, run off, bad weather, window panes 3426x2284 - - 687227 - Free stock photos - PxHere




- NAPRA Guidelines first and foremost outline sterility (contamination risk) of a final product based on where and how it is made. The lower the contamination risk, the longer the product would be considered sterile and safe to use.
- Photo by Alexander Schimmeck on Unsplash
- Photo by Philippe Oursel on Unsplash

# NAPRA Model Standards For Non- Hazardous Sterile Compounding

**Table 6**

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

6.1.1 definitions, 6.1.3 Table 6 and 7
Mdl_Stnds_Pharmacy_Compounding_NonHazardous_Sterile_Preparations_Nov2016_Revised_b.pdf (napra.ca)

- For contamination risk levels - NAPRA takes into account how a product is made by weighing the number of steps in a process (Sterile units, manipulation complexity, time) and based on number of units/final preparation volume, also takes into account the end product destination (patient specific doses versus a batch that could reach many patients)

# NAPRA Model Standards For Non- Hazardous Sterile Compounding

**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.

6.1.1 definitions, 6.1.3 Table 6 and 7
Mdl_Stnds_Pharmacy_Compounding_NonHazardous_Sterile_Preparations_Nov2016_Revised_b.pdf (napra.ca)

- These Sterility BUDs have three key points:
  - They are specific to the level of risk of contamination for that recipe
  - They are not additive, and once the product is placed in a storage condition with a shorter BUD, it must be used by the end of that BUD
  - These cannot be used in the place of no stability data, these compliment stability data but they are only one part of two that results in the final BUD
- Table 7 refers to products prepared in an ISO Class 5 air quality of better hood within an ISO Class 7 or better clean room
- 6.1.1 "…administration of the compounded sterile preparation must begin before the BUD has passed."

- "The BUD also specifies the storage time and temperature conditions that must be in effect before administration."


- Photo by Bekir Dönmez on Unsplash

## Criteria for Stability[4]

- Chemical stability
- Physical stability
- Therapeutic Effect
- Toxicological
- Microbiological integrity (NAPRA)

All 5 pieces are essential to ensure the stability of a compounded sterile product, so while NAPRA gets a bad rap, keep in mind NAPRA might not always be the reason for a shorter BUD..

- Chemical stability
- Physical stability
- Therapeutic Effect remains unchanged
- Toxicological – no significant increase in toxicity occurs
- Microbiological integrity (NAPRA)

Image from: The Simpsons Family Values: How the Cartoon Took Over TV | Vanity Fair

Reference: Buchanan EC, Schneider PJ. Compounding sterile preparations. 3rd ed. Bethesda, MD: American Society of Health System Pharmacists: 2009. 496 pages [Cited March 21, 2022]

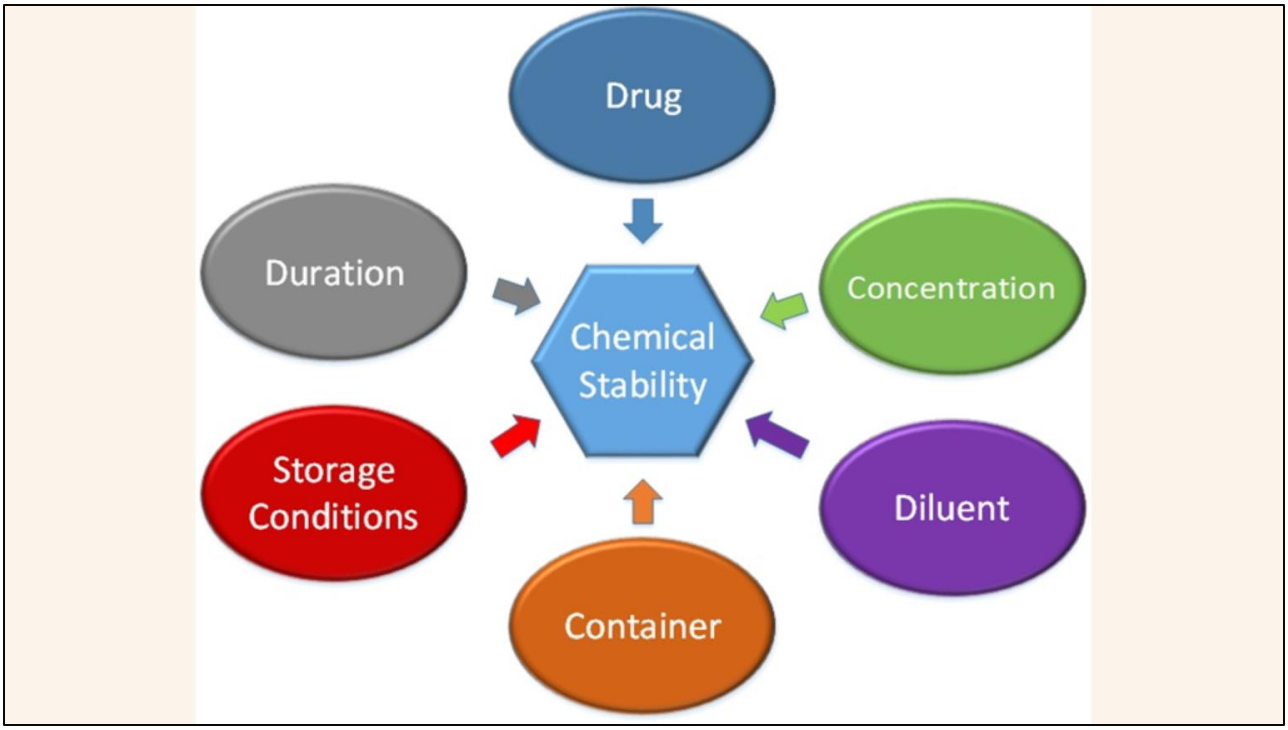
## Core Components of Physical Stability

- Solubility
- pH
- Sorption
- Temperature
- Light Exposure
- Humidity

- For compounded sterile products, these are some of the core factors affecting stability
- Sorption includes absorption and adsorption, the classic example of the later is some drugs adsorb to PVC bags and tubing and require non-PVC materials for storage ex. Insulin for many types of plastic including PVC, Calcitriol, sufentanil
    - Good resource (albeit from a manufacturer of non-PVC bags so not entirely free of bias) PVC (bbraunusa.com)
    - Image from: Free Images : cloud, sky, sun, sunlight, cloudy, daytime, cumulus, clouds, rays, meteorological phenomenon, atmosphere of earth 3872x2592 - - 1009618 - Free stock photos - PxHere

# Core Components of Chemical Stability

For Compounded Sterile Products




- For each recipe, we will need to find information to support all 6 components. This information has to match our product so when we are looking for data, for each component there are important factors to consider.

# Drug

- Must be an exact drug match between the data and the recipe
- Cannot use data from two drugs individually to make a combo product
  - The reverse is also true – cannot use data from a combination study for an individual drug

- Cannot extrapolate between “similar drugs” or drugs within a class ex. between opioids
- Each drug, and each salt form of a drug, has its own physicochemical properties
- Ideally, this includes excipients and the full formulation of the product

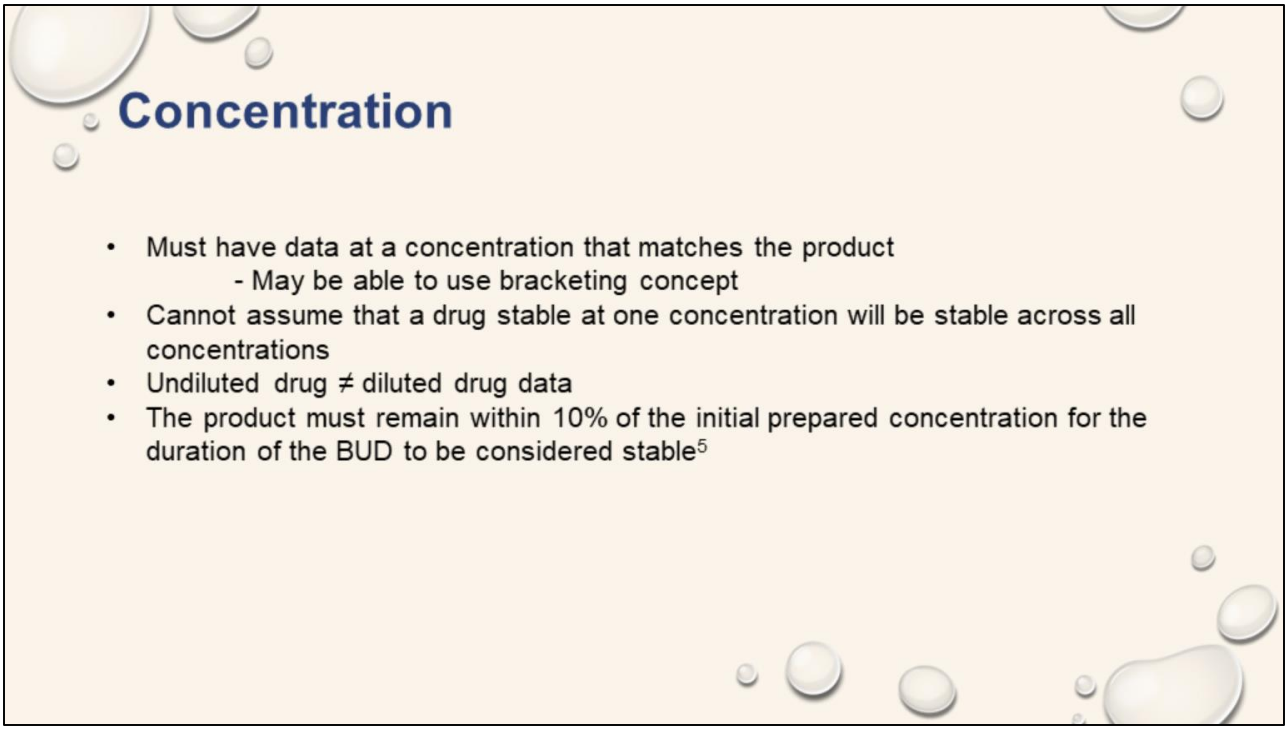
- Wine picture: Photo by Terry Vlisidis on Unsplash
- Hot Sauce picture: Photo by shri on Unsplash

## Diluent

- Diluents have their own physicochemical properties
- Cannot assume stability in a diluent, even if it is described as visually compatible

- Combined with the physicochemical properties of a drug, this can result in a very different outcome between diluents!
- Includes both the reconstitution diluent (if applicable) and infusion solution diluent
- Micro precipitate or drug degradation could still be occurring!

- Picture from: https://pxhere.com/en/photo/1122436?utm_content=shareClip&utm_medium=referral&utm_source=pxhere

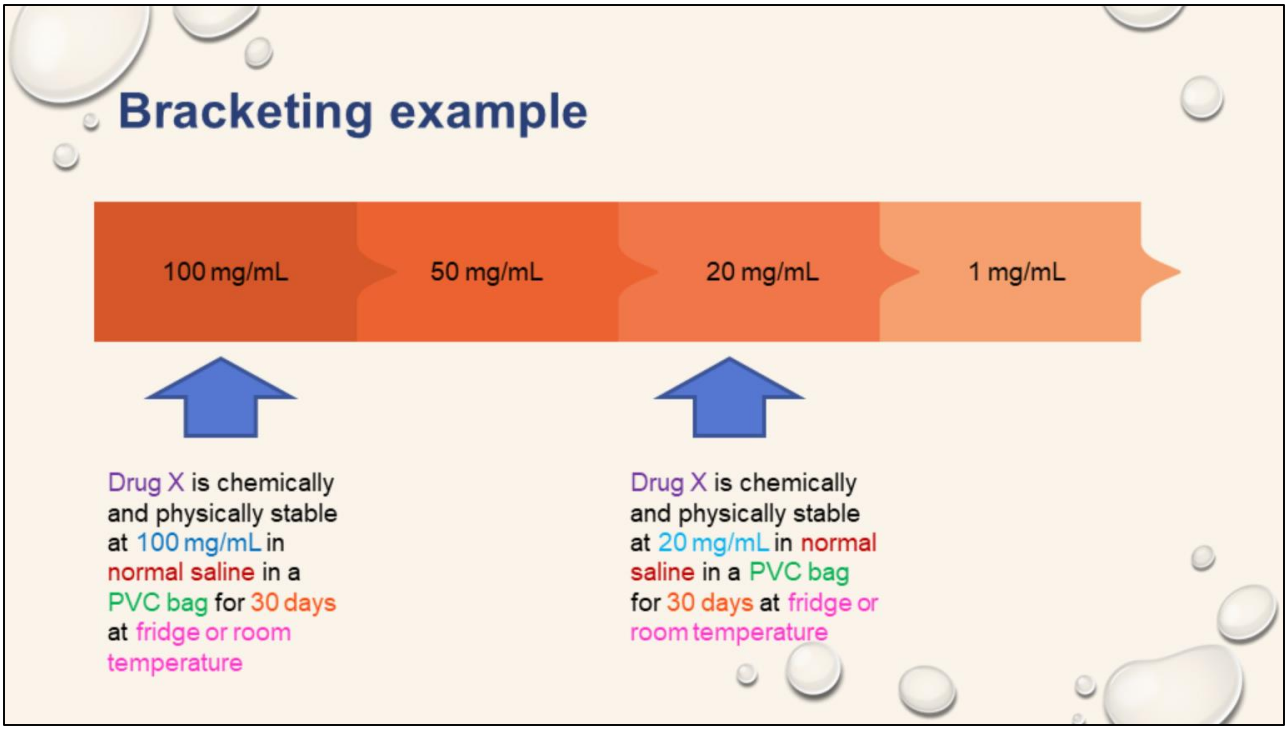



Data must be at a concentration that matches our product, either by being an exact match, or by having data on either side of that concentration ie bracketing
Cannot assume that a drug that has stability data at one concentration will be stable across all concentrations, and that includes higher or lower concentrations

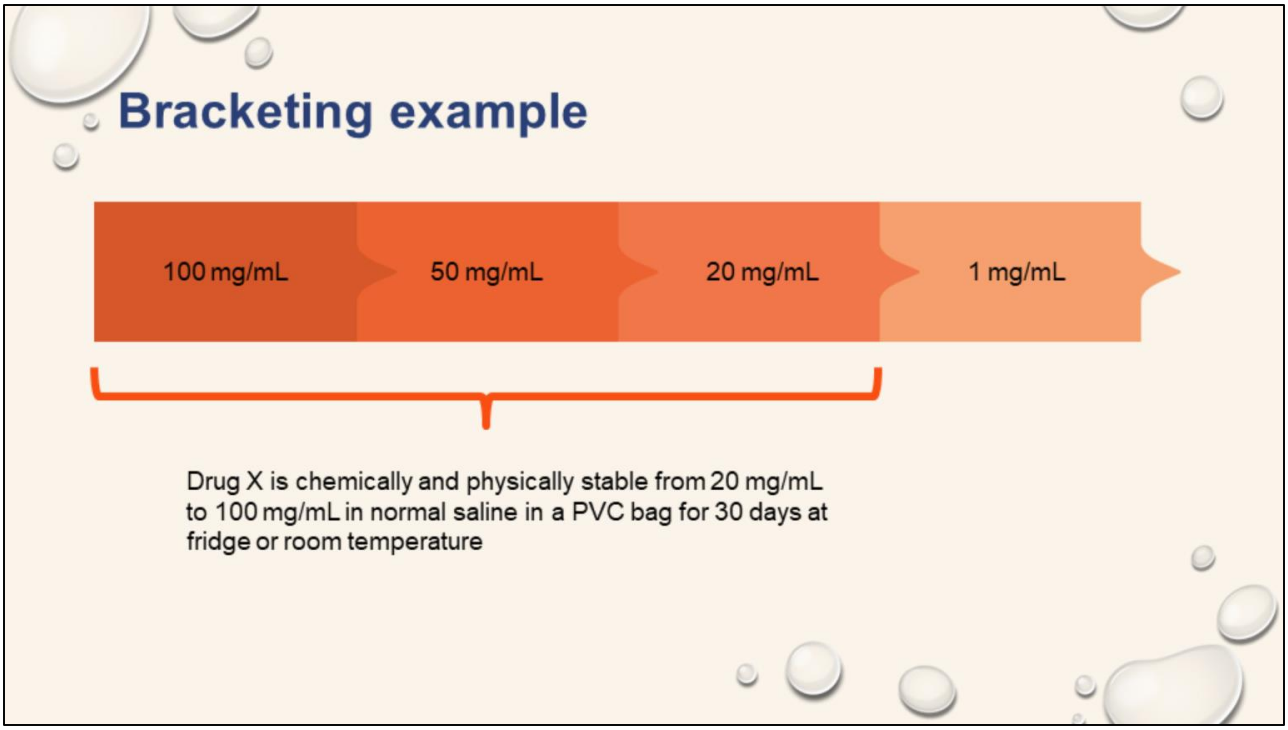
- Some studies will set the % loss at <5% to be even more conservative
- There must be no change/loss >10% at any point during the study to be considered stable
- Some studies will calculate their rate of loss to estimate a T90 for their product as well

Undiluted drug is unique and you cannot apply data from undiluted drug to diluted drug or vice versa

Photo by Shifaaz shamoon on Unsplash
Photo by Jacek Dylag on Unsplash

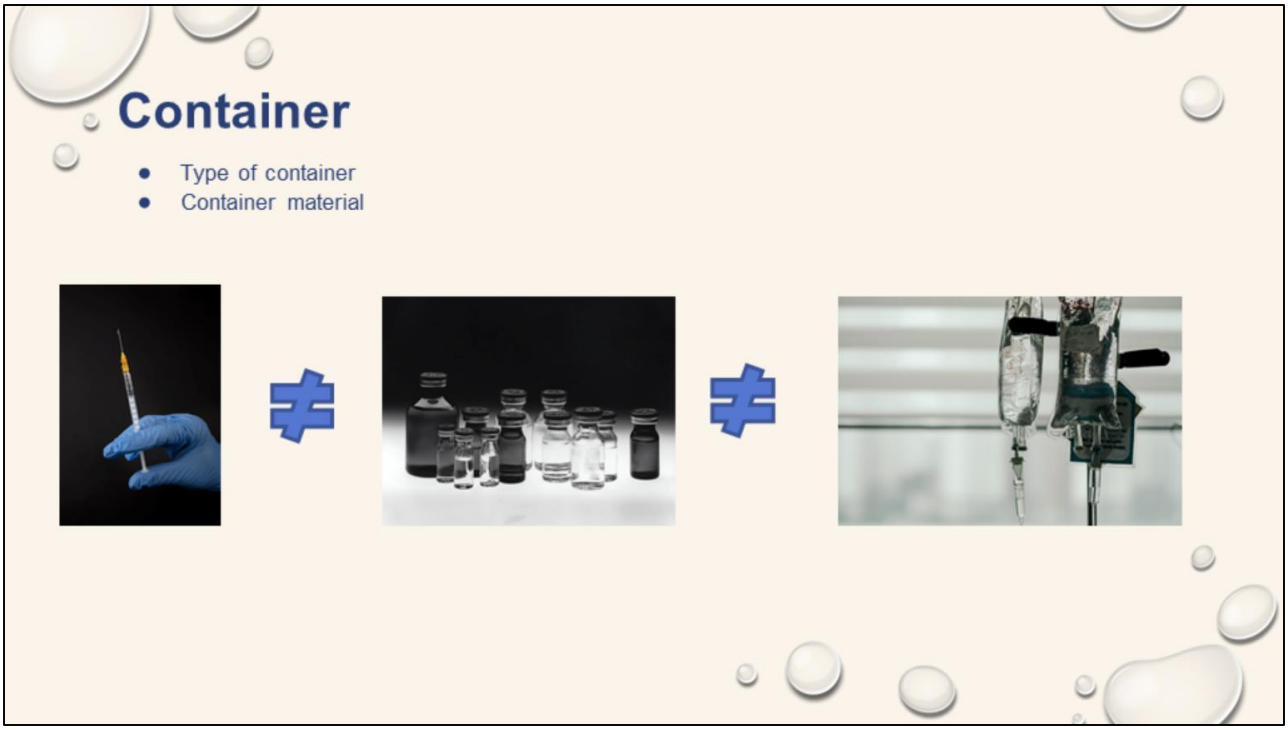



Bracketing – if we have data at two concentrations, in the same diluent, same container, with the same drug we can extrapolate data between these two concentrations to also be stable under the same conditions




Bracketing – if we have data at two concentrations, in the same diluent, same container, with the same drug we can extrapolate data between these two concentrations to also be stable if the conditions used in each study are the same or components are the same.

- If for instance the 20 mg/mL concentration was only stable for 7 days Fridge or Room Temperature, from 20 mg/mL to < 100 mg/mL it would only be stable for 7 days Fridge or Room Temperature (since 7 days is the common denominator between those two studies for both conditions)
- If the 20 mg/mL study was only studied for 30 days Room Temp, then we could use bracketing and apply Room Temp data to the bracket (20 mg/mL to < 100 mg/ml) but could not use the fridge data from the 100 mg/mL for the bracket since there was no corresponding fridge data at the lower concentration




- Keeping in mind Sorption, leaching, light exposure, impact of humidity etc is different for each type of container and each container material
- So to find data for a polypropylene syringe recipe, you need to find a chemical stability study done in a polypropylene syringe

- NAPRA Guidelines Section 6.7 Packaging – “6.7.1 – During packaging, compounding personnel must … put all final compounded sterile preparations in packaging that maintains each preparations stability, integrity …”
- Syringe Image: Photo by Mika Baumeister on Unsplash
- Vial Image: Photo by National Cancer Institute on Unsplash
- Bag image: Photo by insung yoon on Unsplash
- Elastomeric Pump image: File:Elastomeric pumps.jpg - Wikimedia Commons

# Storage Conditions

- Temperature
- Light Exposure
- Humidity

**APPENDIX 10 TEMPERATURES FOR DIFFERENT TYPES OF STORAGE**

| Storage type | Temperature range |
|---|---|
| Freezing | –25°C to –10°C* |
| Refrigeration (cold) | 2°C to 8°C* |
| Refrigeration (cool) | 8°C to 15°C* |
| Controlled room temperature | 15°C to 20°C† |
| Drug conservation temperature | 15°C to 30°C |

*United States Pharmacopeial Convention (USP). General notices and requirements. In: *USP pharmacists' pharmacopeia*. Rockville, MD: USP; 2008. p. 29.

†United States Pharmacopeial Convention (USP). General chapter <797>: pharmaceutical compounding — sterile preparations. USP 36. Rockville, MD: USP; 2013.

Appendix 10 Mdl Stnds Pharmacy Compounding NonHazardous Sterile Preparations Nov2016 Revised b.pdf (napra.ca)

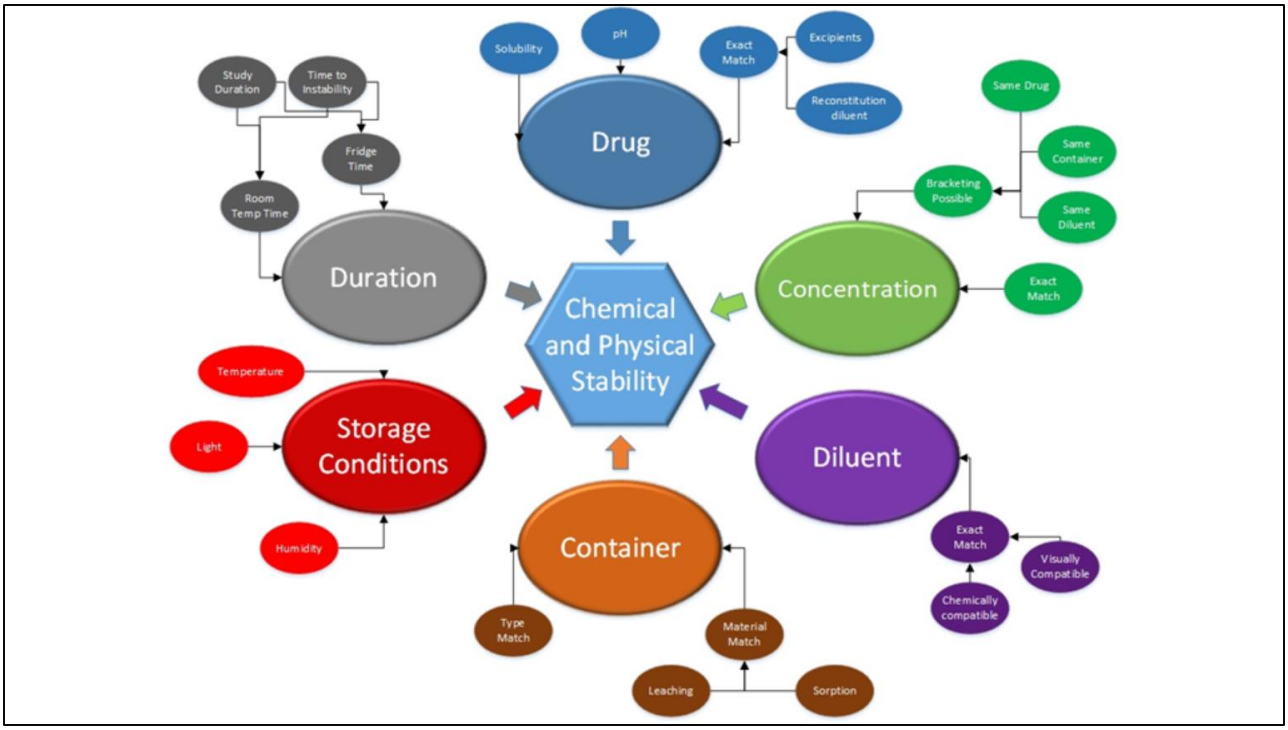
Humidity impacts are more challenging to find, but when information is reported about impacts on humidity it is important to take note, particularly as it can significantly impact medications provided in an overwrap when the overwrap is removed

- Watch as some studies use body temp 37°c or higher temperatures ex. Ambulance studies
- Drugs supplied in overwrap packaging may have reduced dating outside of the overwrap due to gas exchange or water loses

# Duration

How long at specified storage conditions is the product considered stable?

- Hourglass picture: Photo by Nathan Dumlao on Unsplash




- Not only do we need all of the 6 core components, we need all 6 core components all together from at least one source or complimentary sources

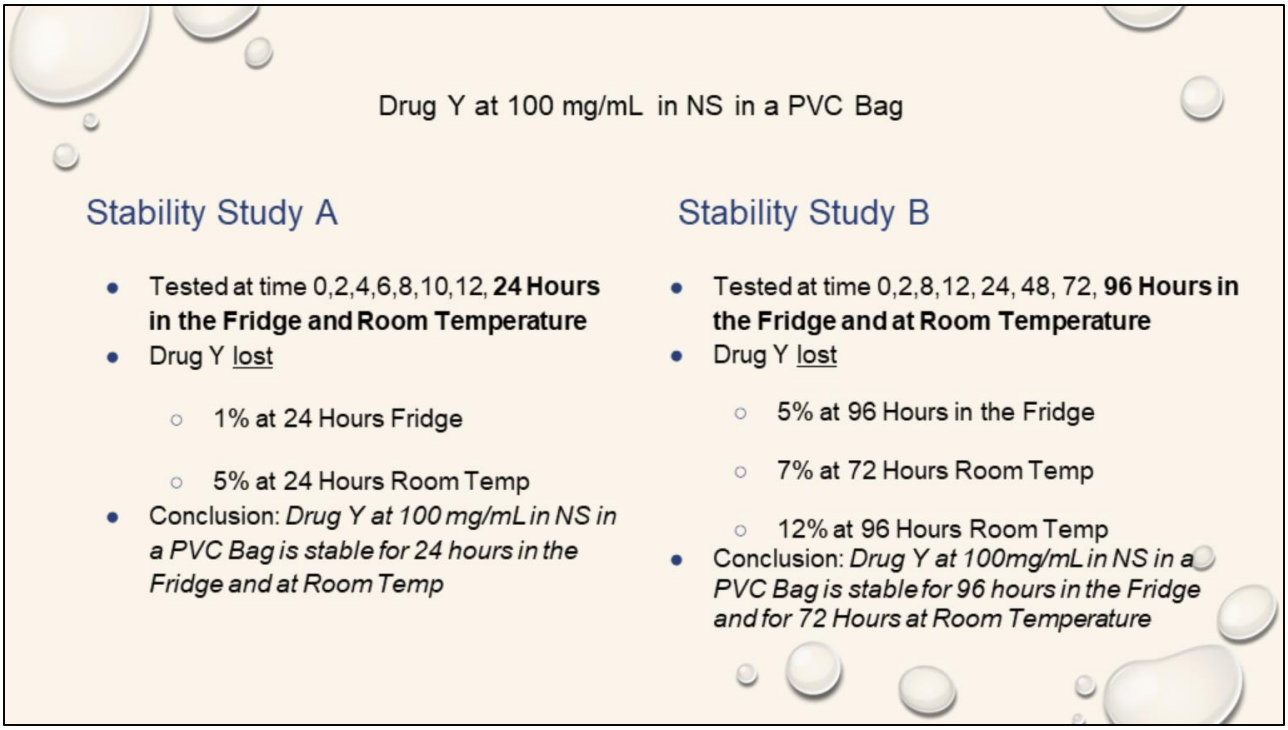
Examples

- A stability study that includes the drug, concentration, diluents, containers, temperatures and durations (everything in one place!)
- Manufacturers monograph has drug, concentration, diluent, temperature and duration + letter from manufacturer specifying container type
- One stability study at a low concentration and one stability study at a high concentration with the same drug, diluent, container, and temperatures
    - Duration can be different, BUT then we are limited to the LOWER of the 2 durations
    - Ex. Low concentration = 3 days fridge and high concentration = 9 days fridge
        - Final duration is 3 days fridge for that concentration range UP TO the high concentration

# Stability Data Outcomes

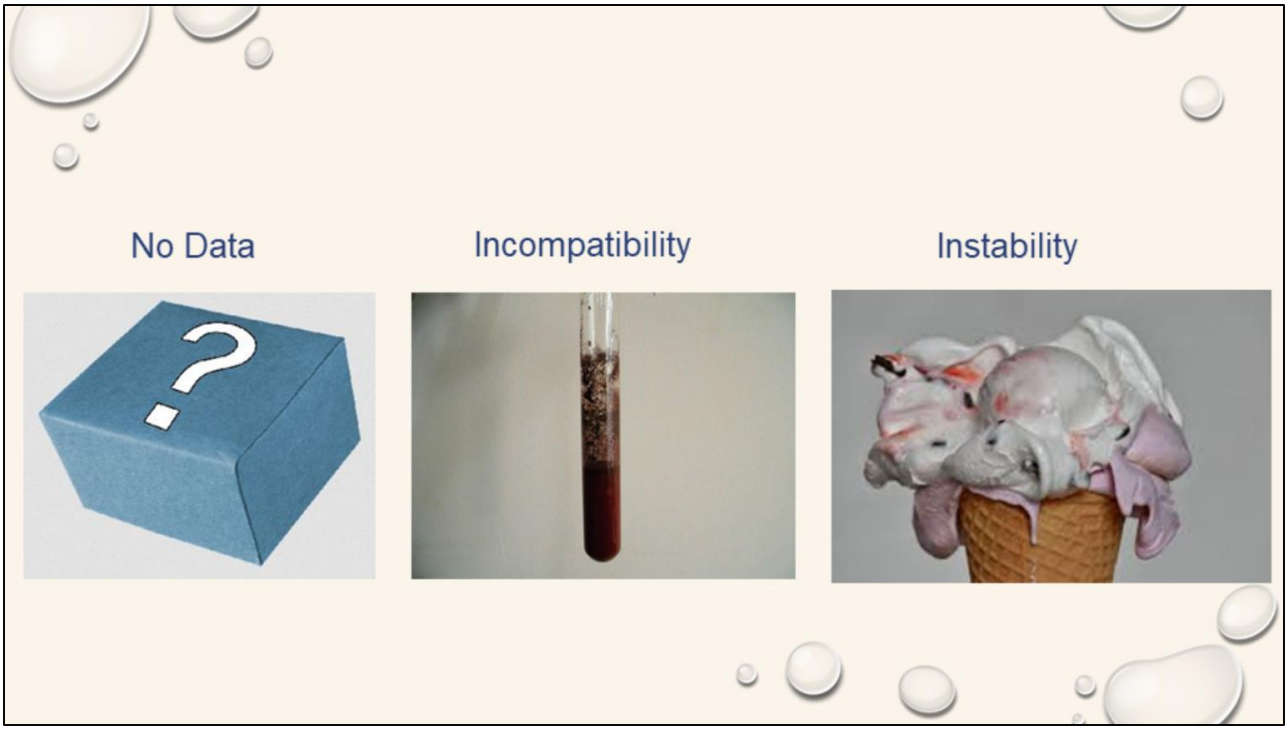
Cannot assume data outside of what is available will be “fine”

We must respect concerning data and avoid preparing products that may have a concerning outcome occur




- We may want to assume that at hour 25 in Study A and Hour 97 in Study B that this drug would still be stable in the fridge, but we have nothing that supports that conclusion. We are in a situation where we have no data beyond these study times and as such cannot guess or hope that the drug would be stable. As such we are limited by these times as our chemical and physical stability duration.

- Study A only went for 24 hours
- Study B studied Fridge and Room Temperature and each for 96 hours
    - Because of the longer duration, the study was able to better pinpoint when the drug crossed the 10% concentration change threshold in room temperature storage, and was able to confirm that at 96 Hours in the fridge the drug was still stable




- For some products, when it comes to stability we may have very limited to no data, we may only know that they appear physically or visually compatible but have no data to confirm that there is no incompatibility or instability occurring
- Incompatibility is a physical incompatibility such as precipitation, cloudiness, haziness, color change, viscosity change, gas production etc or chemical incompatibility that reduces the concentration of active ingredients ex. precipitation, acid base reactions. Incompatibilities can also be due to the container itself.
- Instability is the chemical reactions that result in degradation or change in the active ingredients (considered irreversible and occur at a set rate)

- Blow Torch Image: File:Blow Torch (3257353199).jpg - Wikimedia Commons
- Ice Cream image: Free picture: cornet, delicious, desert, icecream, cold, sweet, cream, food, cone, vanilla (pixnio.com)
- CU2C2 Precipitate image: File:Cu2C2 precipitate.JPG - Wikimedia Commons
- Mystery Box image: File:Three mystery boxes.jpg - Wikimedia Commons

## What we cannot do…

Study #1 – Drug A is stable at 100 mg/mL in NS in a Syringe for 24H Fridge and Room Temp

Study #2 – Drug A is stable at 1mg/mL in D5W in a Syringe for 7 days Room Temp

Study #3 – Drug A is stable at 10 mg/mL in LR in a PVC Bag for 24H Fridge

(False) Conclusion: Drug A is stable at 100 mg/mL in NS in a PVC Bag for 7 Days RT and 24H Fridge

- All three of these studies on their own may be valid and applicable to a similar product, but we cannot pick portions of that data and apply it to a product that does not match that study
- The only common denominator between these three studies is the drug

# Drug A Example – Visual Depiction


Each of these three studies are valid and can be accepted, but we cannot combine the data in any way

## What we can do..

Study #1 – Drug A is stable at 100 mg/mL in NS in a PVC Bag for 7 days Fridge and 24H Room Temp

Study #2 – Drug A is stable at 1mg/mL in NS in a PVC Bag for 7 days Room Temp

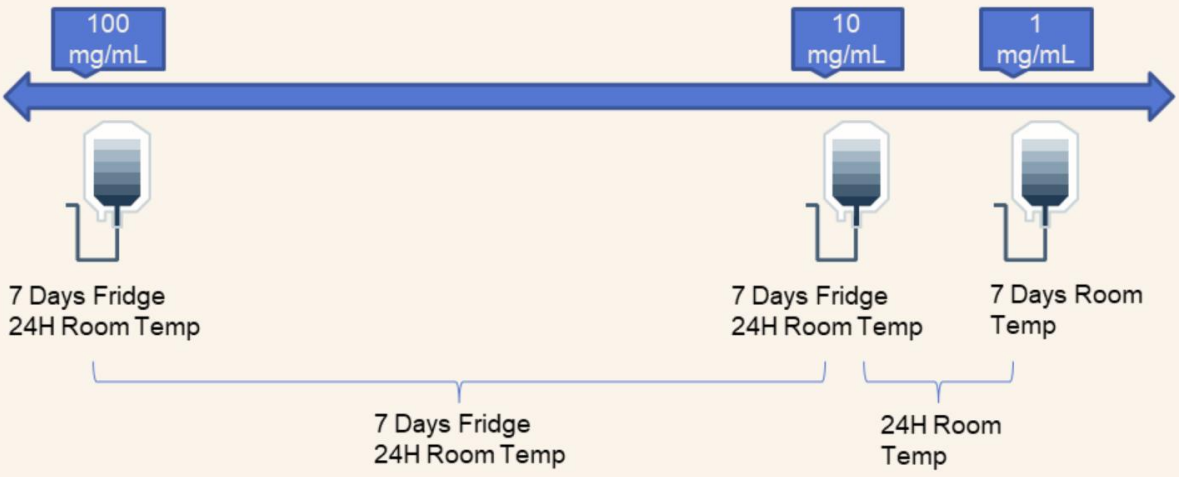
Study #3 – Drug A is stable at 10 mg/mL in NS in a PVC Bag for 7 days Fridge and 24H Room Temp

Conclusions:

- Drug A is stable from 10mg/mL to 100 mg/mL in NS in a PVC bag for 7 days Fridge and 24H Room Temp (Studies #1 and #3)
- Drug A is stable from >1 mg/mL to <10 mg/mL in NS in a PVC bag for 24 H Room Temp (Studies #2 and #3)
- Drug A is stable at 1 mg/mL in NS in a PVC bag for 7 days Room Temp (Study #2)

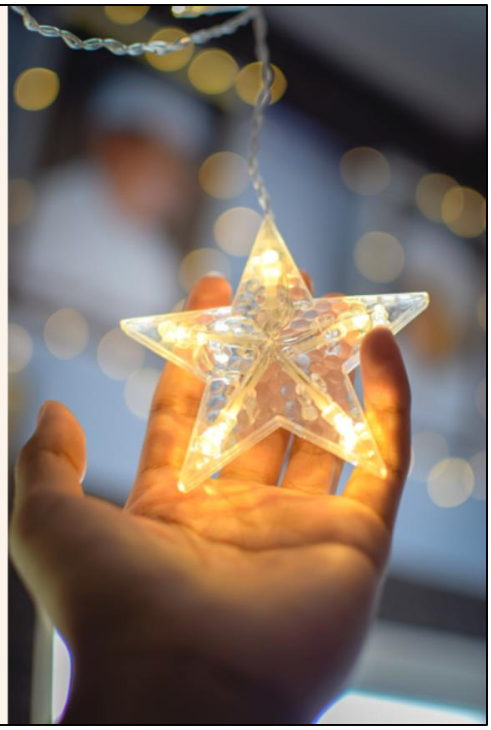
- Here there are three essential common denominators between these studies, the drug itself, the container type, and the diluent. We can use the variables of concentration to bracket the acceptable concentration, and the temperatures/duration used in each study can be used to find the lowest common denominator to apply to our final products that fall between the.

# Drug A Example – Visual Depiction

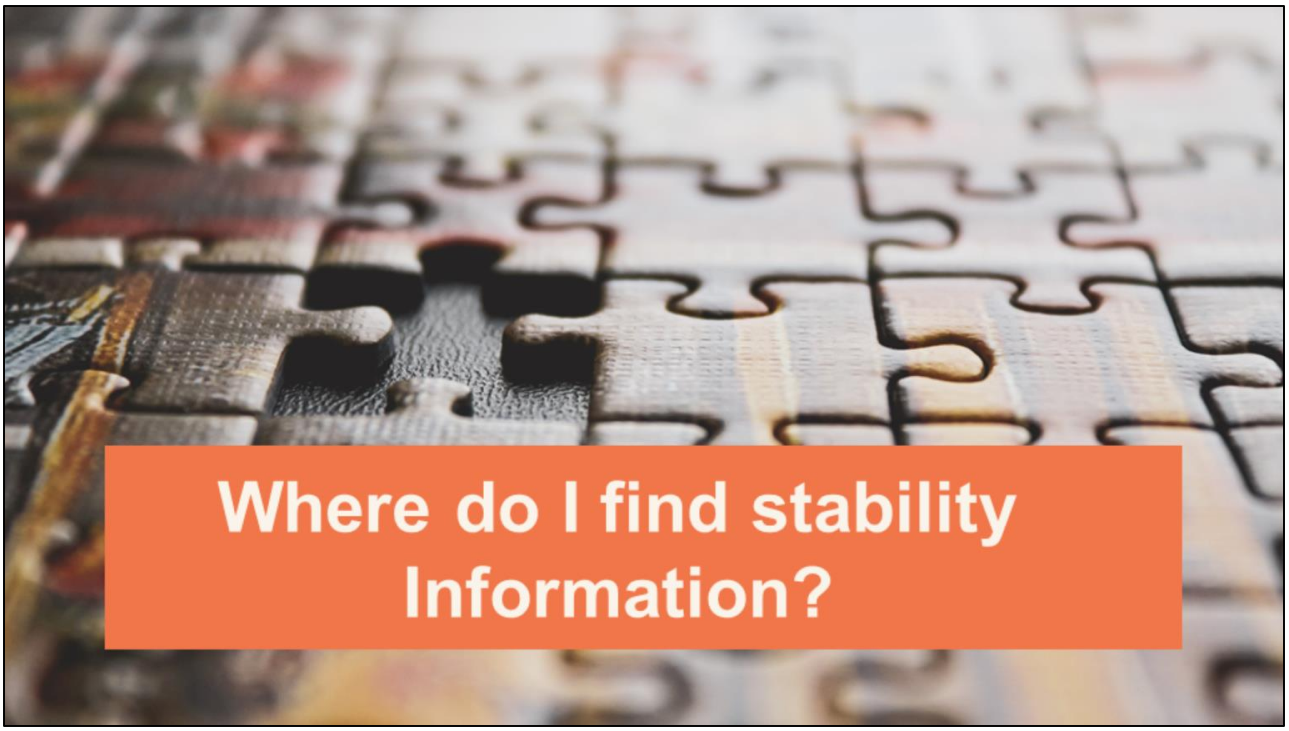


## Quality Stability Studies[2]

- Provide detailed methodology and describe materials used
- Use a stability indicating assay ex. HPLC
- Test their product immediately after mixing and throughout the study
- Preform the test in multiples/batches
- Provide all the data
- Their conclusion is supported by the data



- Can you walk through what they did step for step, and seeing the data do you agree with their conclusions?
- Trissel, Lawrence A. Avoiding Common Flaws in Stability and Compatibility Studies of Injectable Drugs. American Journal of Hospital Pharmacy. July 1983 Vol 40 1159-1160
- Photo by Hikarinoshita Hikari on Unsplash




- Chemical and Physical stability data
- Photo by Sigmund on Unsplash


- Canadian Manufacturers monographs should always be the first place you start your search
- Manufacturers may not provide extensive information or complete information (ex. container often missing) but they do provide extensive information in their product monographs.
- Manufacturers medical information teams may also be able to find additional data they can share that was not included in their monograph so if you have the time (and it is during the week day) they are always worth a phone call or email!
- Image: Photo by Hans Reniers on Unsplash

## Manufacturer Monographs

- In Canada available from the Health Canada Drug Product Database online query (canada.ca)or the manufacturer's website
- USA prescribing information and labelling available from drugs@fda: fda-approved drugs or dailymed (nih.Gov)
  - Ensure the formulation matches your product!

- If you review a product from another country, ensure you review the formulation thoroughly to be certain it matches your product!

## Potential References

- Trissels IV-Chek within Lexicomp
- Micromedex IV Compatibility
- King Guide to Parenteral Admixtures
- ASHP Injectable Drug Information
- Extended Stability for Parenteral Drugs (Bing's) – by ASHP

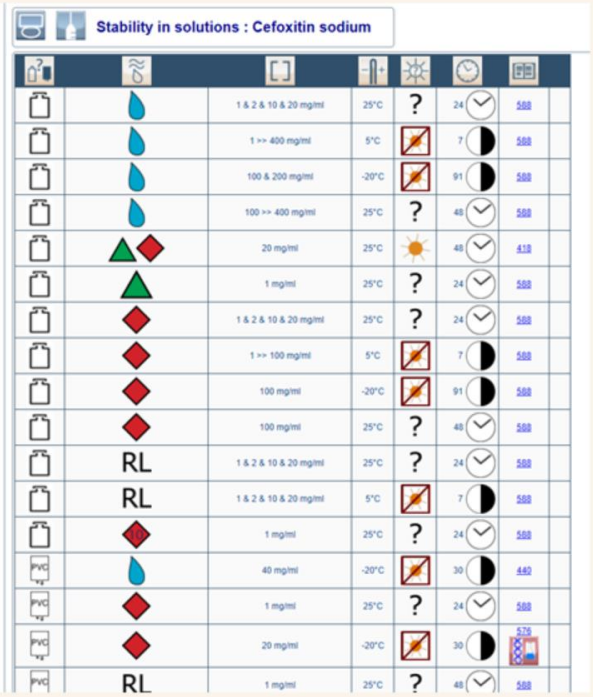
Many quality tertiary references exist that have already pulled together vast amounts of primary literature stability data including but not limited to:

- Trissels IV-Chek within Lexicomp
- Micromedex IV Compatibility
- King Guide to Parenteral Admixtures
- ASHP Injectable Drug Information
- Extended Stability for Parenteral Drugs (Bing's) – by ASHP

- Image from: Photo by ASTERISK KWON on Unsplash

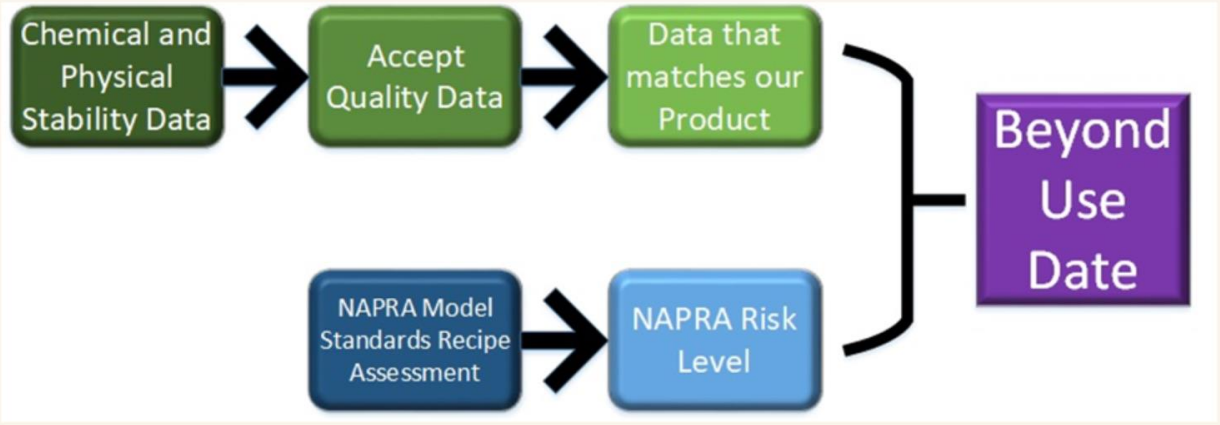
# Other Potential References

- Canadian Journal of Hospital Pharmacy (cjhp-online.ca)
- International Journal of Pharmaceutical Compounding (ijpc.com)
- American Journal of Health-System Pharmacy (academic.oup.com)
- Stabilis.org
- MEDLINE or PUBMED search for primary literature



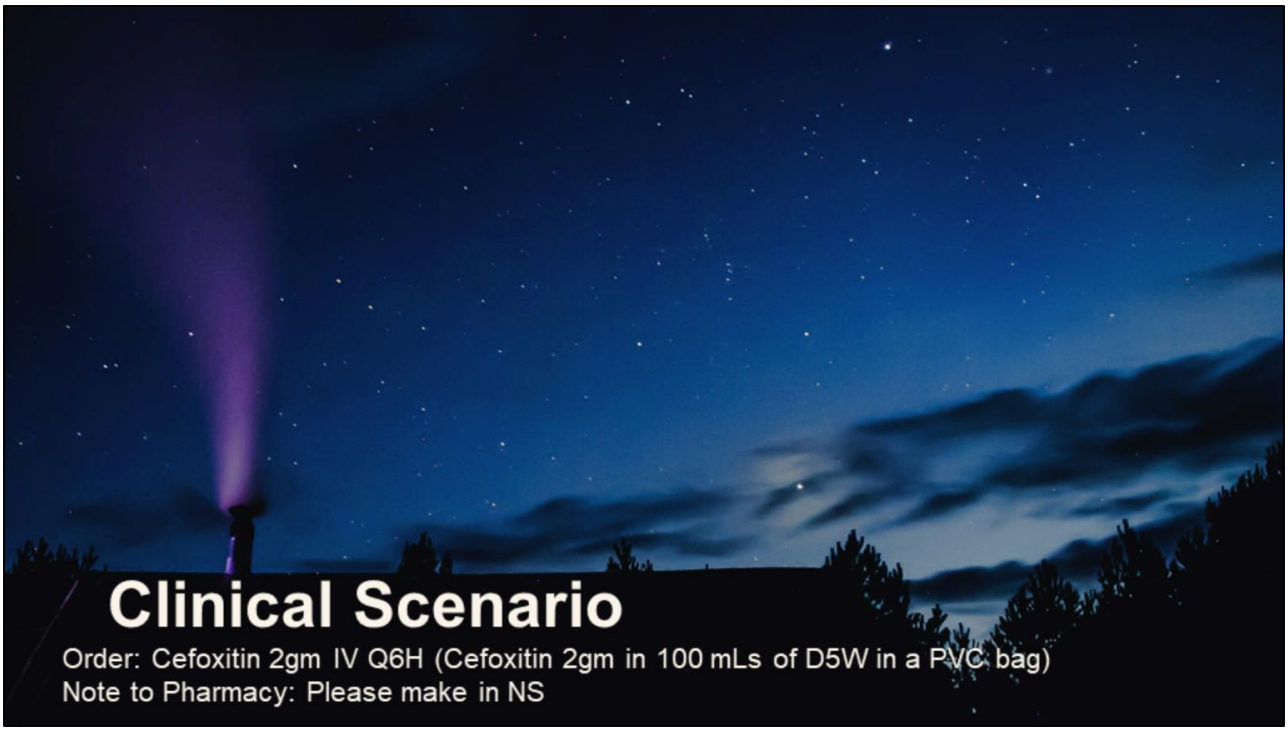

Stabilis - A very useful free database that includes references to available stability studies, but important to note it may not contain all available data and does contain information from North Americana an European product studies

- Information is broken down by container type, diluent type, concentration, temperature, light exposure (if known), duration and then includes the reference study listing, so you can easily pull the study if time permits for further review, they also sometimes include in the last column their evaluation of the study quality based on their internal rating scale
- Can hover over icons to figure out what each means




# Putting it all Together!

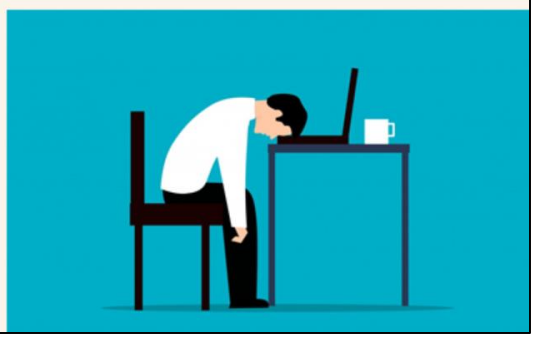
| Stability | NAPRA Sterility Medium Risk | Final BUD | Rationale |
|---|---|---|---|
| 30 Days Fridge<br>72 Hours Room Temp | **9 Days Fridge**<br>**30 Hours Room Temp** | 9 Days Fridge<br>30 Hours Room Temp | Sterility is the shorter dating for both temperatures |
| **8 Days Fridge**<br>**24 Hours Room Temp** | 9 Days Fridge<br>30 Hours Room Temp | 8 Days Fridge<br>24 Hours Room Temp | Stability is the shorter dating for both temperatures |
| 30 Days Fridge<br>**8 Hours Room Temp** | **9 Days Fridge**<br>30 Hours Room Temp | 9 Days Fridge<br>8 Hours Room Temp | Sterility is shorter for Fridge, stability is shorter for Room Temp |
| **48 Hours Fridge**<br>48 Hours Room Temp | 9 Days Fridge<br>**30 Hours Room Temp** | 48 Hours Fridge<br>30 Hours Room Temp | Stability is shorter for Fridge, sterility is shorter for Room Temp |
| 48 Hours Room Temp | 9 Days Fridge<br>**30 Hours Room Temp** | 30 Hours Room Temp | Sterility is shorter, cannot apply any Fridge dating as there was no Fridge Stability data found |




- It’s a Saturday evening in the dispensary and you receive an order for: Cefoxitin 2gm IV q6H Note to Pharmacy, please make in a different diluent
- There is no matching recipe built as you usually prepare this recipe in normal saline. It appears this has never been made on site before by pharmacy…..
- Photo by Evdokiya Lebedeva on Unsplash

# My Advice (Learned the Hard Way)

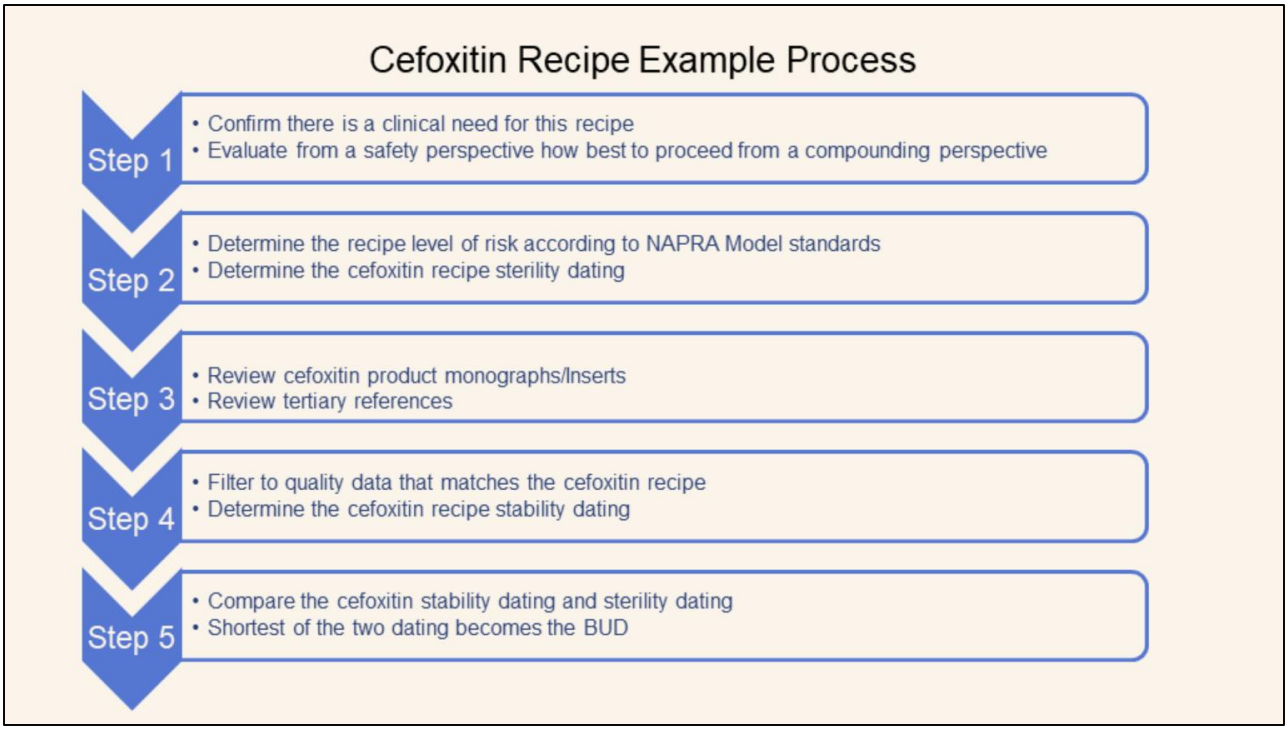
1. Record all the data in some fashion + include your rationale
2. Look at as many sources as you can with the time you have
3. Determine a consistent process you and your team will follow
4. If possible, seek out a second opinion on gray zone data (or better yet seek out team decisions on how to proceed)
5. Call or email manufacturers
6. Don't give up



- my advice is to write this information down/take screenshots and then write down your rationale and thought process. If you get asked 6 months later why you assigned this BUD trust me when I say you will want this to look back on.
- If your time is limited, it is okay and perfectly reasonable to use information at face value, but one caveat, I have found multiple issues in tertiary references with how studies are reported ex. combo study reported as individual drug, wrong concentrations/containers reported, so if you have more time, it is always worth it to pull the original study
- Consistent process is key! As you will see, with this data decisions need to be made, so it is important we strive to interpret data the same way
- Image from: Free Images : stress, exhausted, bored, feeling, business, tired, depressed, depression, employee, work, head, lazy, people, sad, problem, office, sleep, man, overworked, desk, laptop, job, cartoon, headache, frustrated, table, product, azure, font, parallel, elbow, rectangle, electric blue, chair, illustration, drawing, sitting, graphics, balance, sleeve, machine, peripheral, podium, waste container, employment, clip art 5696x3520 - mohamed hassan - 1638940 - Free stock photos - PxHere

**DISCLAIMER**

Information presented for this example is for education purposes only, not or pharmacy application or use


Cefoxitin Recipe Example Process
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Step 3
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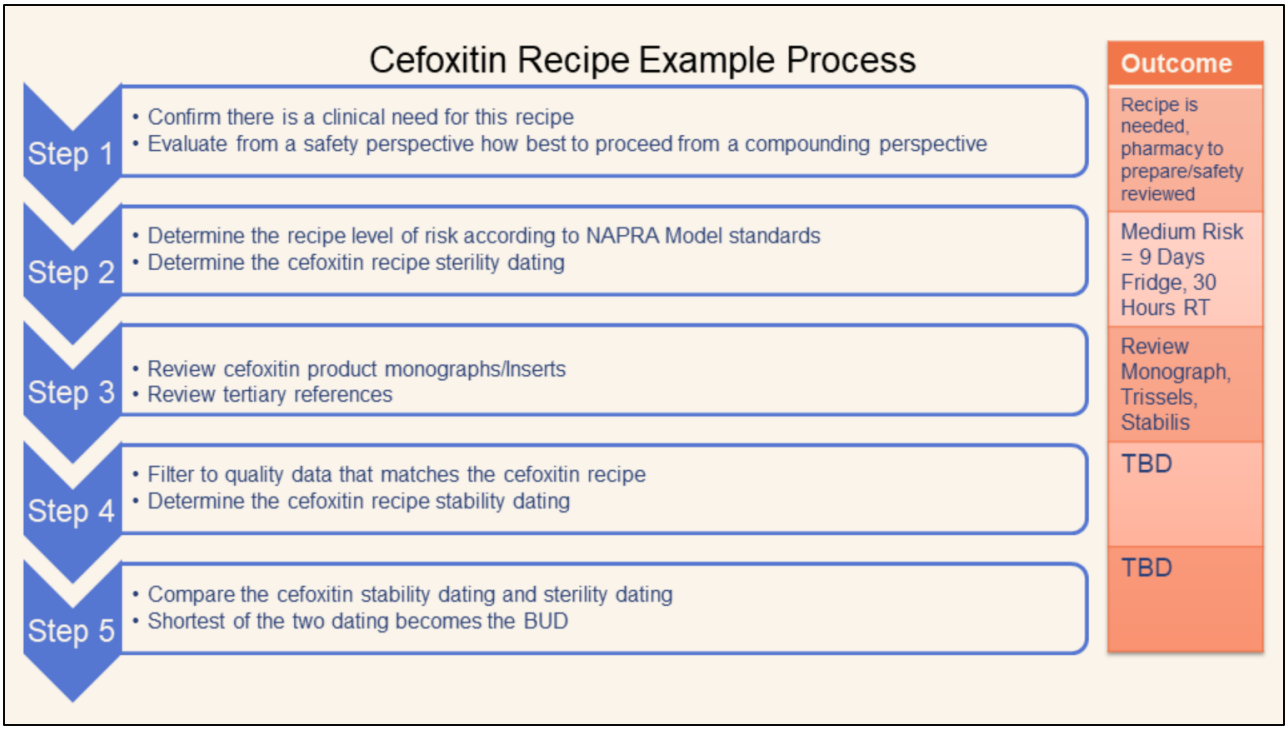
• Review tertiary references
Step 4
• Filter to quality data that matches the cefoxitin recipe
• Determine the cefoxitin recipe stability dating
Step 5
• Compare the cefoxitin stability dating and sterility dating
• Shortest of the two dating becomes the BUD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Step 5
• Compare the cefoxitin stability dating and sterility dating
• Shortest of the two dating becomes the BUD
Outcome
Recipe is needed, pharmacy to prepare/safety reviewed
Medium Risk = 9 Days Fridge, 30 Hours RT
Review Monograph, Trissels, Stabilis
TBD
TBD

# Example of Cefoxitin Monograph Data

- "**Composition:** Vials of Cefoxitin for Injection, USP contain Cefoxitin sodium. The pH values of freshly constituted solutions range from 4.2 to 7.0. Each gram of Cefoxitin sodium contains approximately 2.3 mEq of sodium."

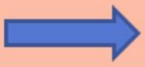
- "For intravenous use, the following solutions can be used for **reconstitution:** Sterile Water for Injection or, if required, Sterile Sodium Chloride 0.9% or, Sterile Dextrose Injection 5% or 10% I.V."

**I.V. RECONSTITUTION TABLE**

| Strength | Amount of Diluent to be Added* (mL) | Approximate Withdrawable Volume (mL) | Nominal Concentration (mg/mL) |
|---|---|---|---|
| 1 g vial | 10 | 10.5 | 95 |
| 2 g vial | 10 or 20 | 11.1 or 21.0 | 180 or 95 |

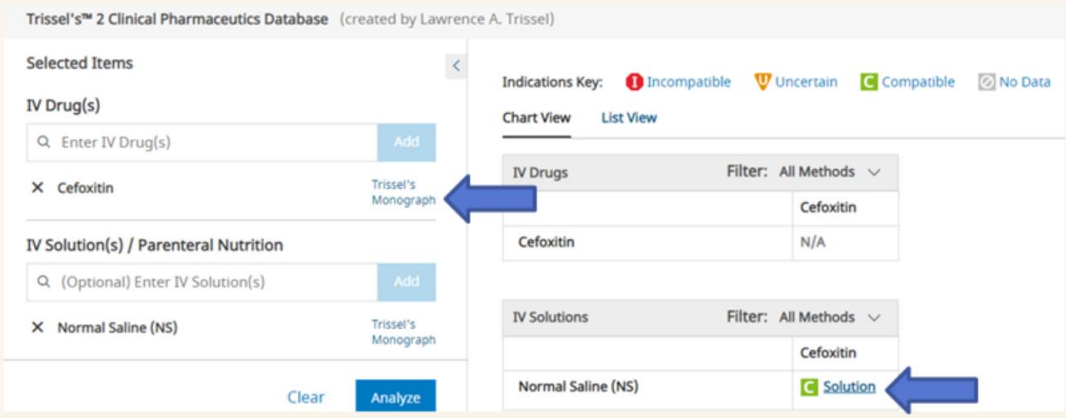
* Shake to dissolve and let stand until clear. The prepared solution may be further diluted to the desired volume with any of the solutions for I.V. infusion listed below.

- Amongst a lot of other important data, the manufacturer has provided the composition which includes the pH of freshly constituted solutions, as well as acceptable reconstitution solutions.
- They also tell us that the prepared reconstituted solution may be further diluted (which is what we need!) "to the desired volume" with any of the solutions for I.V. infusion listed below
    - Here they let us down a bit, what are the limits on desired volume? Can I put 1 gm in 2 Litres or 2 mLs?

| | |
|---|---|
| "The reconstituted solution may be **added to an appropriate intravenous bottle or bag containing any of the solutions for I.V. infusion listed below…**:<br><br>**Sodium Chloride Injection 0.9%**<br>Dextrose Injection 5% or 10% …."<br><br>"Stability of Reconstituted or Diluted Solutions:<br>…<br>**The further diluted solutions for intravenous infusions should be used within 12 hours if kept at room temperature or 24 hours if stored under refrigeration (2-8ºC)."** | **Key Takeaways for our recipe:**<br>Drug: Cefoxitin (composition/physical stability data)<br>Diluent: NS<br>Container: IV bag or bottle<br>Storage Conditions: Room Temp or Fridge<br>Duration: 12 Hours Room Temp and 24 Hours Fridge in a diluted solution<br><br>**Missing:**<br>1. Exact Concentration limits ("Can be diluted to the desired volume" is too vague)<br>2. Material type of the IV bag or bottle<br><br>Other references  |

- They go on to tell us that putting a diluted solution into an appropriate intravenous bottle or bag, yet do not tell us what type or material these could be made of.
- They go on to list our diluent NS as being acceptable
- They also give us storage conditions! The product after further dilution is stable for 12 H Room Temp or 24 Hours Fridge, not great duration, but better than nothing!

# Trissel's IV-Chek Data




- Click on the underlined solution link to see a full list of studies and on the Trissels Monograph to find additional information

## Normal Saline (NS) + Cefoxitin - Details

Print

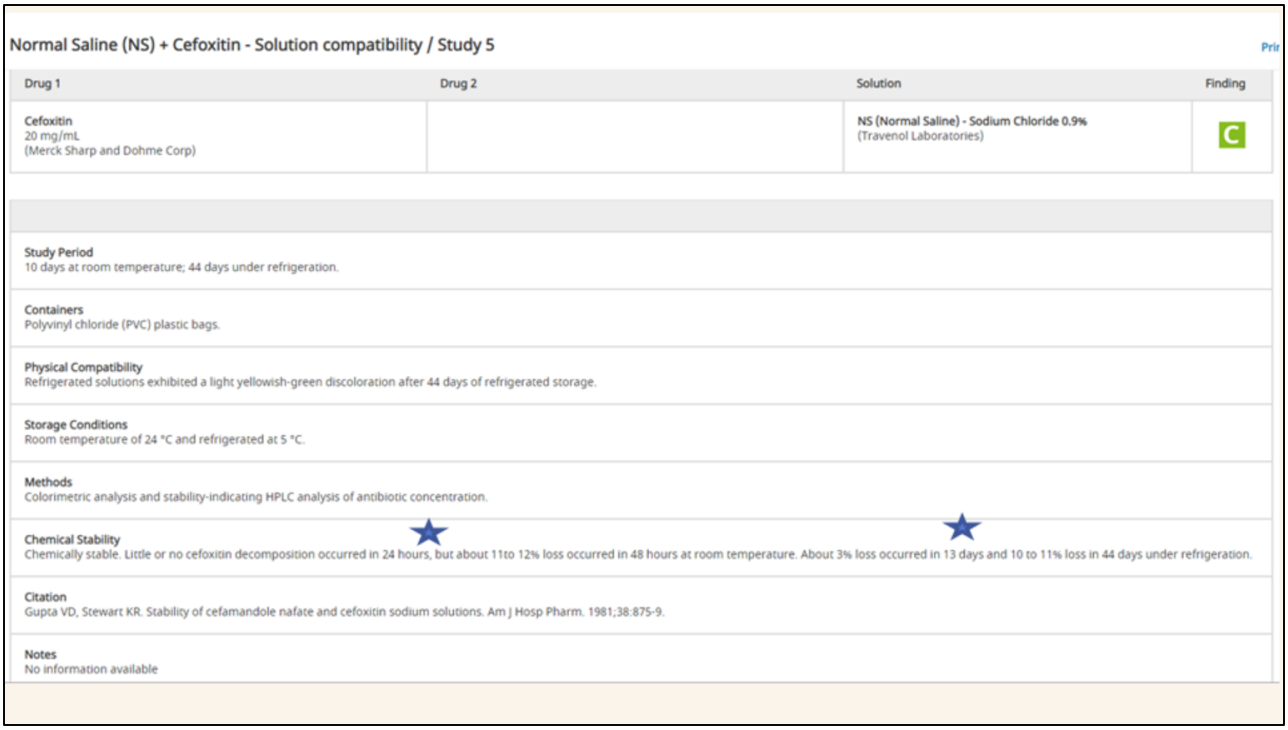
**You searched on the following parameters:**

**Administration Method:** Solution
**Drugs:** Cefoxitin
**Vehicles:** None
**Solutions:** NS (Normal Saline) - Sodium Chloride 0.9%

**Results:** 8 compatible study result(s). *Click on a study to view details*

| Study | Drug 1 | Vehicle 1 | Drug 2 | Vehicle 2 | Solution | Finding | Notes |
|---|---|---|---|---|---|---|---|
| Study 1 | Cefoxitin 1 mg/mL | Glass Container Study | | | NS (Normal Saline) - Sodium Chloride 0.9% | C | |
| Study 2 | Cefoxitin 1 mg/mL | Glass Container Study | | | NS (Normal Saline) - Sodium Chloride 0.9% | C | |
| Study 3 | Cefoxitin 10 mg/mL | Glass Container Study | | | NS (Normal Saline) - Sodium Chloride 0.9% | C | |
| Study 4 | Cefoxitin 20 mg/mL | Glass Container Study | | | NS (Normal Saline) - Sodium Chloride 0.9% | C | |
| Study 5 | Cefoxitin 20 mg/mL | PVC Bag Study | | | NS (Normal Saline) - Sodium Chloride 0.9% | C | |
| Study 6 | Cefoxitin 20 mg/mL | Glass Container Study | | | NS (Normal Saline) - Sodium Chloride 0.9% | C | |
| Study 7 | Cefoxitin 5 mg/mL | Elastomeric Pump Study | | | NS (Normal Saline) - Sodium Chloride 0.9% | C | |
| Study 8 | Cefoxitin 60 mg/mL | Elastomeric Pump Study | | | NS (Normal Saline) - Sodium Chloride 0.9% | C | |

# Trissel's Studies in NS



Normal Saline (NS) + Cefoxitin - Solution compatibility / Study 5

| Drug 1 | Drug 2 | Solution | Finding |
|---|---|---|---|
| **Cefoxitin**<br>20 mg/mL<br>(Merck Sharp and Dohme Corp) | | **NS (Normal Saline) - Sodium Chloride 0.9%**<br>(Travenol Laboratories) | C |

**Study Period**
10 days at room temperature; 44 days under refrigeration.

**Containers**
Polyvinyl chloride (PVC) plastic bags.

**Physical Compatibility**
Refrigerated solutions exhibited a light yellowish-green discoloration after 44 days of refrigerated storage.

**Storage Conditions**
Room temperature of 24 °C and refrigerated at 5 °C.

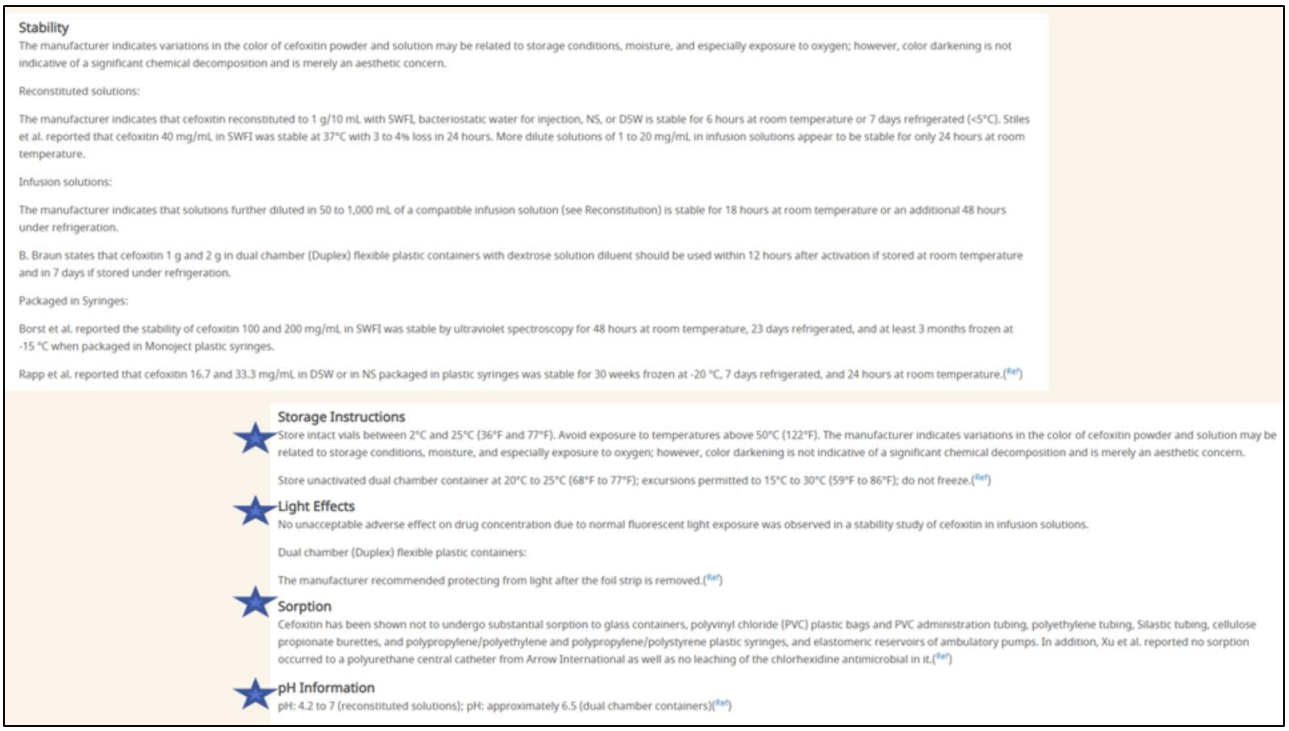
**Methods**
Colorimetric analysis and stability-indicating HPLC analysis of antibiotic concentration.

**Chemical Stability**
Chemically stable. Little or no cefoxitin decomposition occurred in 24 hours, but about 11to 12% loss occurred in 48 hours at room temperature. About 3% loss occurred in 13 days and 10 to 11% loss in 44 days under refrigeration.

**Citation**
Gupta VD, Stewart KR. Stability of cefamandole nafate and cefoxitin sodium solutions. Am J Hosp Pharm. 1981;38:875-9.

**Notes**
No information available

- This study has everything we need – Physical Compatibility and Chemical Stability
- Drug: Cefoxitin – Merck Sharp and Dohme Corp product
- Diluent: in NS
- Concentration: 20 mg/mL
- Container: PVC Bags
- Storage Conditions: Room Temperature and Fridge Temp
- Duration: Stable for 24 Hours RT and 13 Days Fridge (the time before unacceptable (>10%) losses occurred)



**Stability**

The manufacturer indicates variations in the color of cefoxitin powder and solution may be related to storage conditions, moisture, and especially exposure to oxygen; however, color darkening is not indicative of a significant chemical decomposition and is merely an aesthetic concern.

Reconstituted solutions:

The manufacturer indicates that cefoxitin reconstituted to 1 g/10 mL with SWFI, bacteriostatic water for injection, NS, or D5W is stable for 6 hours at room temperature or 7 days refrigerated (<5°C). Stiles et al. reported that cefoxitin 40 mg/mL in SWFI was stable at 37°C with 3 to 4% loss in 24 hours. More dilute solutions of 1 to 20 mg/mL in infusion solutions appear to be stable for only 24 hours at room temperature.

Infusion solutions:

The manufacturer indicates that solutions further diluted in 50 to 1,000 mL of a compatible infusion solution (see Reconstitution) is stable for 18 hours at room temperature or an additional 48 hours under refrigeration.

B. Braun states that cefoxitin 1 g and 2 g in dual chamber (Duplex) flexible plastic containers with dextrose solution diluent should be used within 12 hours after activation if stored at room temperature and in 7 days if stored under refrigeration.

Packaged in Syringes:

Borst et al. reported the stability of cefoxitin 100 and 200 mg/mL in SWFI was stable by ultraviolet spectroscopy for 48 hours at room temperature, 23 days refrigerated, and at least 3 months frozen at -15 °C when packaged in Monoject plastic syringes.

Rapp et al. reported that cefoxitin 16.7 and 33.3 mg/mL in D5W or in NS packaged in plastic syringes was stable for 30 weeks frozen at -20 °C, 7 days refrigerated, and 24 hours at room temperature.(Ref)

**Storage Instructions**

Store intact vials between 2°C and 25°C (36°F and 77°F). Avoid exposure to temperatures above 50°C (122°F). The manufacturer indicates variations in the color of cefoxitin powder and solution may be related to storage conditions, moisture, and especially exposure to oxygen; however, color darkening is not indicative of a significant chemical decomposition and is merely an aesthetic concern.

Store unactivated dual chamber container at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F); do not freeze.(Ref)

**Light Effects**

No unacceptable adverse effect on drug concentration due to normal fluorescent light exposure was observed in a stability study of cefoxitin in infusion solutions.

Dual chamber (Duplex) flexible plastic containers:

The manufacturer recommended protecting from light after the foil strip is removed.(Ref)

**Sorption**

Cefoxitin has been shown not to undergo substantial sorption to glass containers, polyvinyl chloride (PVC) plastic bags and PVC administration tubing, polyethylene tubing, Silastic tubing, cellulose propionate burettes, and polypropylene/polyethylene and polypropylene/polystyrene plastic syringes, and elastomeric reservoirs of ambulatory pumps. In addition, Xu et al. reported no sorption occurred to a polyurethane central catheter from Arrow International as well as no leaching of the chlorhexidine antimicrobial in it.(Ref)

**pH Information**

pH: 4.2 to 7 (reconstituted solutions); pH: approximately 6.5 (dual chamber containers)(Ref)

- Note in Trissels and many tertiary references they list primarily American product information – “infusion solutions – the manufacturer indicates that solutions further diluted in 50 to 1000 mL of a compatible infusion solution is stable for 18 hours at room temperature or an additional 48 Hours under refrigeration”
    - If we were doing an in depth review, or if we really needed more data, we could see if this American product matches our product, but since we have a study that may match our product that has a longer BUD we will look at it first

# Stabilis Data

- Does not include the Gupta Study
- No other studies in a PVC bag in NS found

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| PVC |  | 40 mg/ml | -20°C |  | 30  | 440 | |
| PVC |  | 1 mg/ml | 25°C | ? | 24  | 588 | |
| PVC |  | 20 mg/ml | -20°C |  | 30  | 576  | |
| PVC | RL | 1 mg/ml | 25°C | ? | 48  | 588 | |

# Stability Data Outcome

**Manufacturer Data:** (incomplete) Cefoxitin in NS in a IV Bag or Bottle is stable for 12 H Room Temp and 24H Fridge

*Caveats to this data - concentration not specified only "diluted to desired volume", and bag material type unknown

**Gupta Study Data**: Cefoxitin 20 mg/mL in NS in PVC bags was stable for 24H Room Temperature and 13 days Fridge

*Caveat to this data – this product was made by a different company, cannot confirm excipients match our product without further digging

**Trissels Monograph Data:** No concerns with sorption (PVC bag likely okay from this perspective), No light effects anticipated, some color darkening may occur particularly if exposed to moisture or oxygen during storage

**Our Recipe: Cefoxitin 2gm in 100 mLs of NS in a PVC Bag (20 mg/mL)**

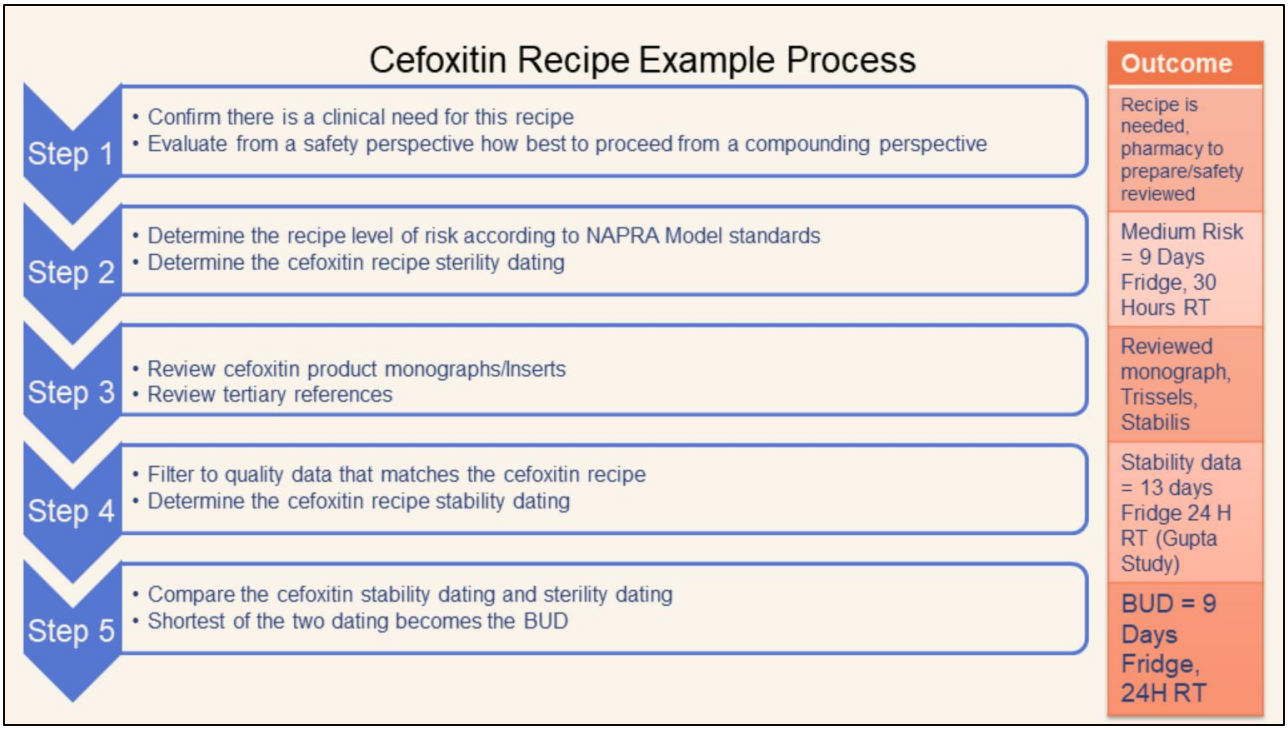
Decision – which data do we accept?

- The Manufacturers (missing concentration and container material) and it is shorter
- Gupta Study – complete data, but the product was made by a different manufacturer and we have not had time to confirm excipients

## BUD Outcome

- NAPRA Assessment = Recipe is Medium Risk
- Medium Risk = 9 days Fridge 30 Hours Room Temp
- Gupta Study Stability = 13 days Fridge 24 H Room Temp

- Final BUD for Cefoxitin 2gm in 100 mL of NS in a PVC Bag (20 mg/mL)
  - 9 Days Fridge (NAPRA was shorter than Gupta Study)
  - 24H Room Temp (Gupta Study was shorter than NAPRA)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• Shortest of the two dating becomes the BUD
Outcome
Recipe is needed, pharmacy to prepare/safety reviewed
Medium Risk = 9 Days Fridge, 30 Hours RT
Reviewed monograph, Trissels, Stabilis
Stability data = 13 days Fridge 24 H RT (Gupta Study)
BUD = 9 Days Fridge, 24H RT


- Photo by Kelly Sikkema on Unsplash

## Potential paths forward

- Consider full review if you only did a short review (look at absolutely every source you can)
- Can the recipe be adjusted to match available data? (and remain safe)

Ultimately:
back to the drawing board/tough decisions need to be made

- Keep in mind when adjusting a recipe it must still meet the patient need, safety parameters (ex. not too concentrated to infuse peripherally) etc and you may not want to deviate from a concentration if that is a standard concentration from an organization perspective .
    - Another aspect is sometimes we need a specific container for a specific route of admin/population
- Photo by Alexander Milo on Unsplash

# Key Takeaways:

- Be able to describe the core components that contribute to a compounded sterile product (CSP) beyond use date (BUD)
    - Chemical and Physical Stability + Sterility are the two core components that are both required for a BUD

- Be able to assess and apply available stability data and NAPRA sterility guidelines to a CSP recipe to assign a BUD
    - Chemical and physical stability data is available from manufacturers and in tertiary references but may not match or provide all 6 key stability components of your recipe
    - It is important to find robust stability data that matches your recipes' drug, diluent, concentration, container, storage conditions, and duration because these factors all significantly impact product stability.
    - Whichever component is shorter, Stability or Sterility, determines the BUD

# References


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# Thank You! & Happy PAM 2022!

Questions?
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