Risk Level Determination and Assignment of Beyond-Use Dates

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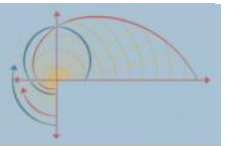
October 9, 2013

Determination of Risk Level



- Responsibility of the person completing the compounding
- No single ‘iron-clad’ determination
- Requires professional judgment
- General descriptive statements to aid people performing compounding (not prescriptive)

Exception:
Non-sterile raw materials or equipment always high risk level

USP <797> Risk Levels

Ingredient: CSP Relationship	Risk Level	Example
One to One (1:1)	Low-Risk Compounding	• Reconstitution and transfer of a 1 gram vial of cefazolin into one syringe or minibag
One to Many or Many to One (1:?) or (? to 1) # components > 3	Medium-Risk Compounding	• A bulk 10 gram vial of vancomycin distributed among several final doses • The combination of several ingredients (>3) into one final dose (TPN)
Any ingredient-CSP relationship using nonsterile ingredients and/or devices or a CSP that requires terminal sterilization (filtration, steam, heat, gas or ionizing radiation)	High-Risk Compounding	• Alum bladder irrigation • PCA or epidural from powdered ingredients

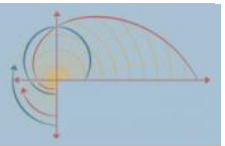
Kastango ES. A Blueprint for Implementing USP Chapter <797>, Pharmaceutical Compounding: Sterile Preparations; Am J Health-Syst Pharm. 2005. 62:1271-88.

Polling Question

It is possible for a particular type of CSP to represent all risk levels depending on how it is prepared.

1. True
2. False

Risk Levels: It depends…



- If a vial/bag system is used or a premixed IV is dispensed
  - Not applicable
- If prepared as stat dose outside ISO Class 5 PEC
  - Immediate-use
- One dose for one patient made in a cleanroom
  - Low-risk level
- Prepared in a segregated compounding area
  - Low risk level with 12 hour BUD
- Batch of identical dosage forms made in a cleanroom
  - Medium risk level
- Prepared from non-sterile ingredients
  - High risk level

Single/Multiple Dose Vials

- Definitions of SDV and MDV are in the USP General Notices and Requirements
- Single dose vials:
  - Punctured in ISO 5 environment may be used for up to 6 hours
  - Punctured in worse than ISO 5 must be used within 1 hour or discarded
- Single dose ampules must be discarded after opening and not stored for any time period

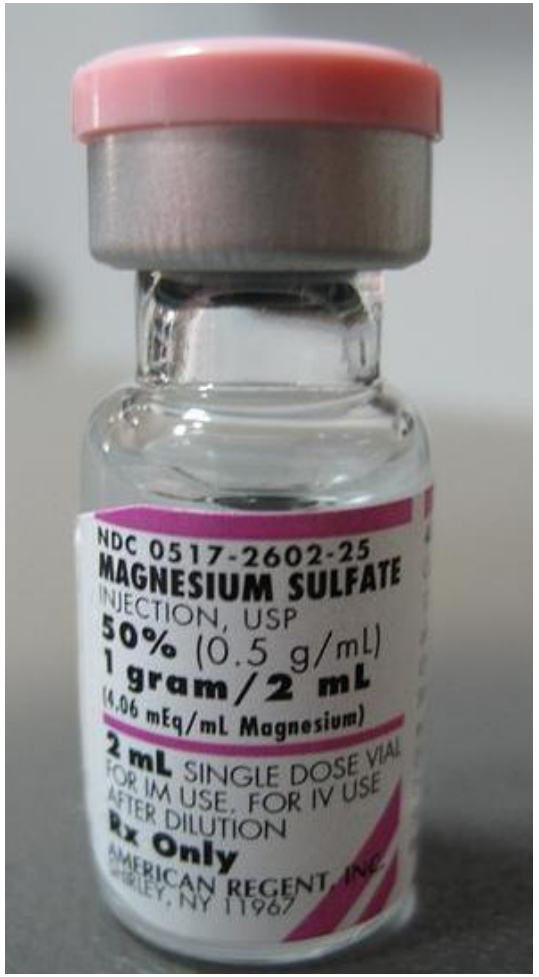


Image courtesy www.flickr.com

Multiple Dose Vials

- Multiple dose vials – contain antimicrobial preservative(s)
- Designed for entry on multiple occasions
  - BUD: 28 days after initial entry unless specified otherwise by the manufacturer.
- Based on USP <51> Antimicrobial Preservative Testing
- Expiration date on vial is based on an unopened, properly stored vial

Image courtesy of www.pfizerinjectables.ca

Pharmacy Bulk Package (PBP)

- USP <1> Injections
- Sterile preparation for parenteral use that contains many single doses
- Restricted to the preparation of admixtures for infusion or filling empty sterile syringes
- Closure penetrated only once
- Used in a suitable work area such as a laminar flow hood
- Includes a statement limiting the time frame in which the container may be used once it has been entered

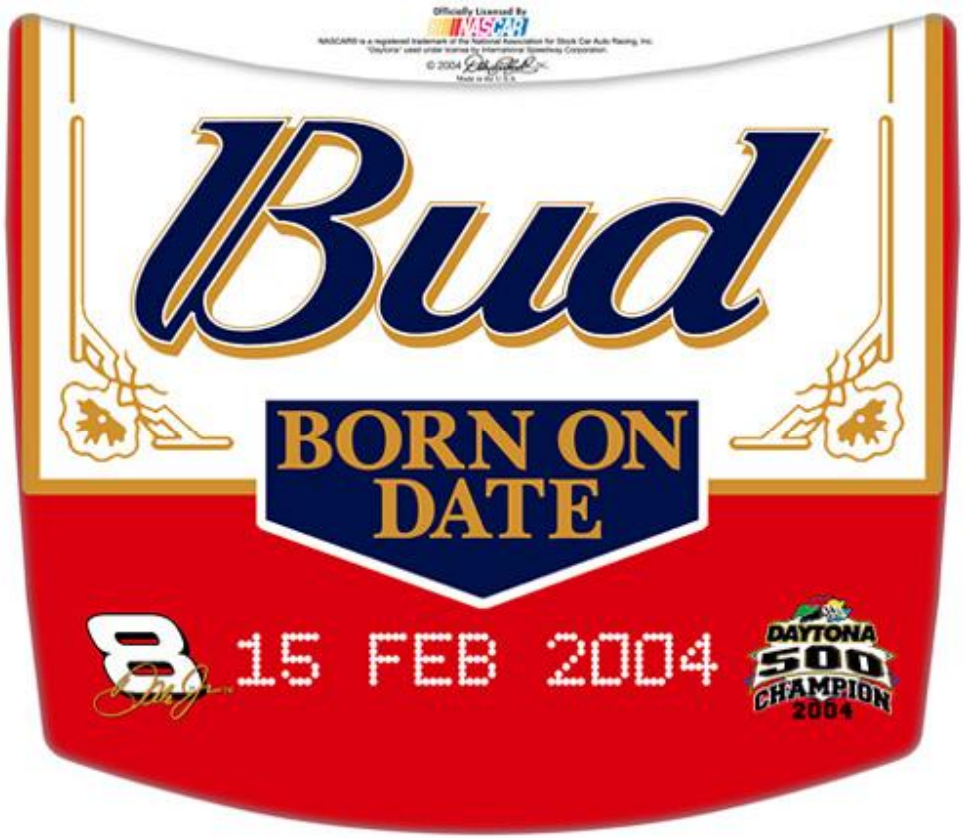
Image courtesy of http://www.hospira.com

Cefazolin 20 gram PBP

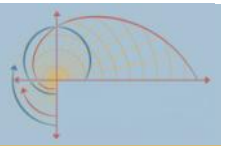
- Typical package insert
  - After entry, use entire contents of the vial promptly
  - Dispense and discard PBP within 4 hours of initial entry

Image courtesy of http://www.wgcriticalcare.com

Beyond-Use Dating (BUD)



Parameters for Establishing BUD

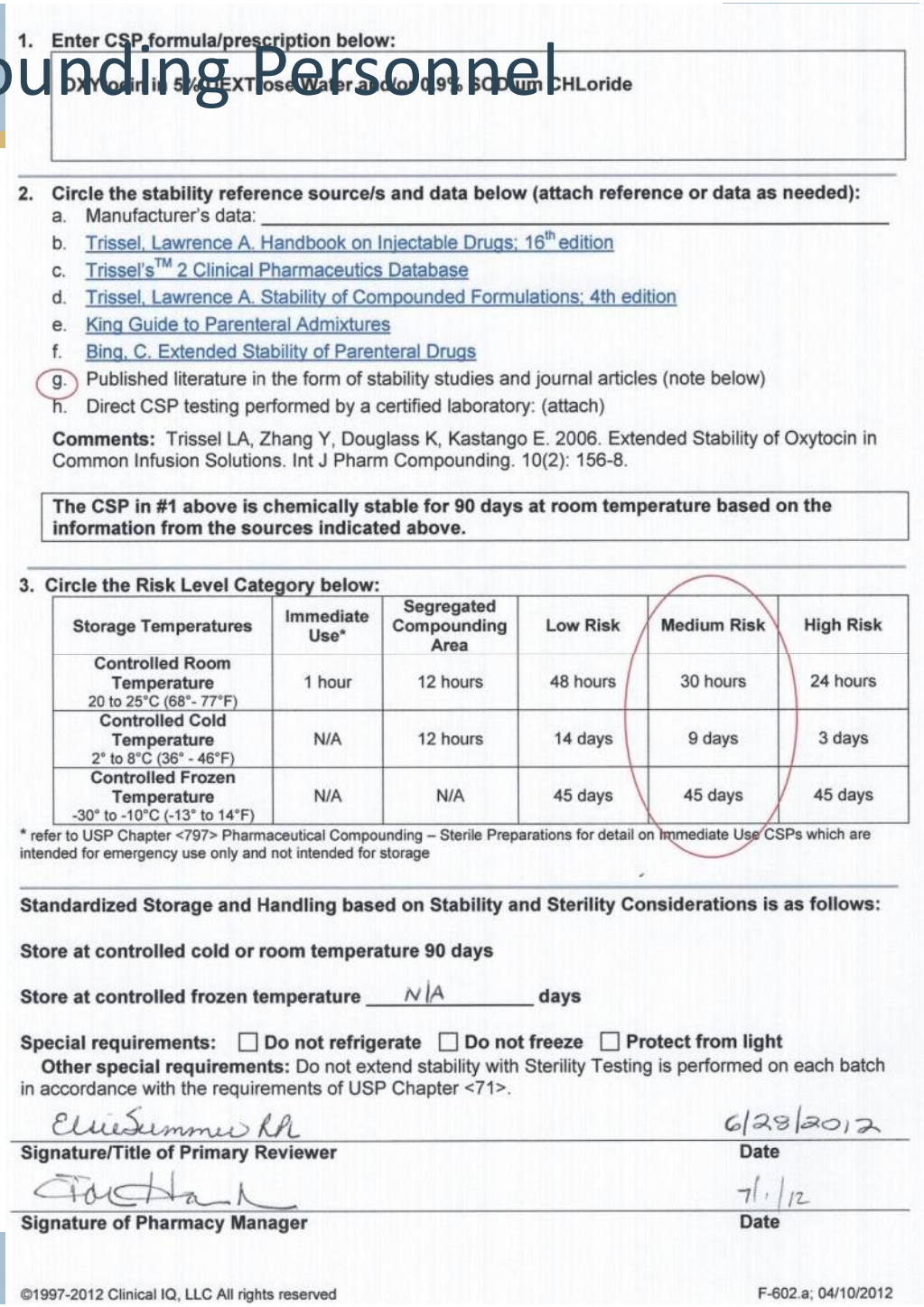


- Recognizes the probability of contamination even under best conditions:
  - Optimal employee performance
    - 0.1% (1 contaminated dose out of 1,000)
  - Contamination rates published in the literature
    - 0.3% – 16%
- Patient Safety: Protect patients from dangerous or even fatal overgrowths of microorganisms that may have been accidentally introduced
- Storage time: needs to be greater than zero but less than positive infinity*
  - (> 0 and < +∞)

* Personal conversation with Dr. David W. Newton, September 30, 2009

Responsibilities of Compounding Personnel

"Beyond-use dates are appropriate and based on valid scientific criteria"



1. **Enter CSP formula/prescription below:**

OXYtocin in 5%DEXTrose Water and/or 0.9% SODium CHLoride

2. **Circle the stability reference source/s and data below (attach reference or data as needed):**
   a. Manufacturer's data: _____
   b. Trissel, Lawrence A. Handbook on Injectable Drugs; 16th edition
   c. Trissel's™ 2 Clinical Pharmaceutics Database
   d. Trissel, Lawrence A. Stability of Compounded Formulations; 4th edition
   e. King Guide to Parenteral Admixtures
   f. Bing, C. Extended Stability of Parenteral Drugs
   g. Published literature in the form of stability studies and journal articles (note below)
   h. Direct CSP testing performed by a certified laboratory: (attach)

Comments: Trissel LA, Zhang Y, Douglass K, Kastango E. 2006. Extended Stability of Oxytocin in Common Infusion Solutions. Int J Pharm Compounding. 10(2): 156-8.

The CSP in #1 above is chemically stable for 90 days at room temperature based on the information from the sources indicated above.

3. **Circle the Risk Level Category below:**

Storage Temperatures	Immediate Use*	Segregated Compounding Area	Low Risk	Medium Risk	High Risk
Controlled Room Temperature 20 to 25°C (68°- 77°F)	1 hour	12 hours	48 hours	30 hours	24 hours
Controlled Cold Temperature 2° to 8°C (36° - 46°F)	N/A	12 hours	14 days	9 days	3 days
Controlled Frozen Temperature -30° to -10°C (-13° to 14°F)	N/A	N/A	45 days	45 days	45 days

* refer to USP Chapter <797> Pharmaceutical Compounding – Sterile Preparations for detail on Immediate Use CSPs which are intended for emergency use only and not intended for storage

Standardized Storage and Handling based on Stability and Sterility Considerations is as follows:

Store at controlled cold or room temperature 90 days

Store at controlled frozen temperature N/A **days**

Special requirements: ☐ **Do not refrigerate** ☐ **Do not freeze** ☐ **Protect from light**

Other special requirements: Do not extend stability with Sterility Testing is performed on each batch in accordance with the requirements of USP Chapter <71>.

Ellie Summers RPh — 6/28/2012
Signature/Title of Primary Reviewer — **Date**

[signature] — 7/1/12
Signature of Pharmacy Manager — **Date**

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Products vs. Preparations

- Manufactured Products
  - have Expiration Dates
- Compounded Preparations
  - have Beyond-Use Dates (or times)
  - Commonly used terms for Beyond-Use date include:
    - Discard after
    - Use before
    - Use by
    - Administer by

Expiration Dates

- Applies to manufactured drug products
- Determined by multiple, scientifically valid, product/package-specific research studies
- Based on the Arrhenius Equation ($k = Ae - E_a/RT$) in statistical analysis
- Strict, specific, and proven to be valid
- Approved by the FDA

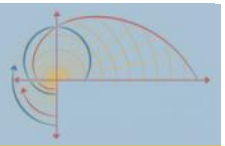
$$k = Ae^{-\frac{E_a}{RT}} \quad or \quad ln\ k = -\frac{E_a}{RT} + ln\ A$$

Where:

k =	Chemical Reaction Rate
A =	Pre-exponential Factor
E_a =	Activation Energy
R =	Gas Constant
T =	Temperature in Kelvin

Image courtesy www.chemwiki.ucdavis.edu

Beyond-Use Dates



- The date (or time) beyond which the drug should not be stored
- Assigned by the facilities doing compounding
  - Needs to be consistent
- Deviates from the official labeling (package insert)
  - Considered compounding
- Should be based on drug-specific, scientifically valid research studies
  - Original articles and print and electronic compilations
- May use more general guidelines when specific information is unavailable
  - USP <795>

Traditional BUD Paradigm

- Assume the compounded preparation is sterile
- Base the BUD solely on the drug's chemical stability

<797> BUD Paradigm

- Recognize the possibility that the preparation was inadvertently contaminated during compounding
- Based the BUD on
  1. the drug's chemical stability in conjunction with
  2. microbiological limits for patient safety

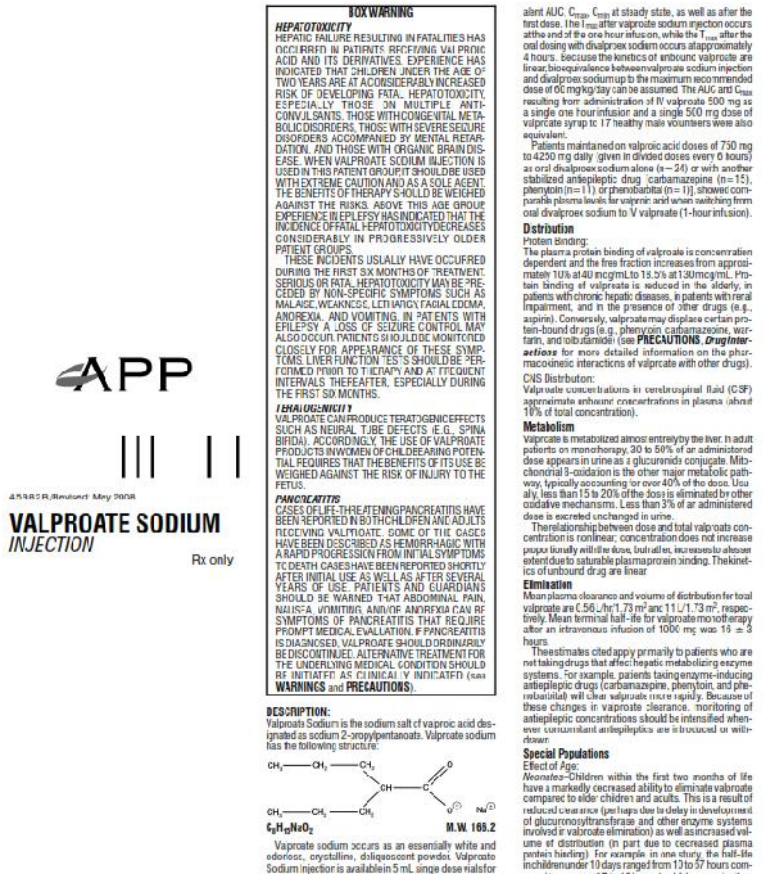
BUD: Microbiological Limits

- Most shelf life labels or listed expiration dates are used as guidelines based on normal handling of products.
- Use prior to the BUD does not necessarily guarantee the safety of the drug.
- Immediately after the date, a CSP is not always dangerous nor ineffective*
- BUD storage limits are applied whenever an actual sterility test in accordance with USP Chapter <71> has not been performed

* Report 1 of the Council on Scientific Affairs (A-01) Full text: Pharmaceutical Expiration Dates. American Medical Association, June 2001. AMA Policy H-115.983

Sources of Stability Information for BUD

- Drug manufacturers, including the package insert
- Valid testing of the specific preparation and container
- Relevant published stability information in original articles or reliable print compilations and electronic databases



APP

VALPROATE SODIUM
INJECTION

Rx only

BOXED WARNING

HEPATOTOXICITY

HEPATIC FAILURE RESULTING IN FATALITIES HAS OCCURRED IN PATIENTS RECEIVING VALPROIC ACID AND ITS DERIVATIVES. EXPERIENCE HAS INDICATED THAT CHILDREN UNDER THE AGE OF TWO YEARS ARE AT A CONSIDERABLY INCREASED RISK OF DEVELOPING FATAL HEPATOTOXICITY, ESPECIALLY THOSE ON MULTIPLE ANTICONVULSANTS, THOSE WITH CONGENITAL METABOLIC DISORDERS, THOSE WITH SEVERE SEIZURE DISORDERS ACCOMPANIED BY MENTAL RETARDATION, AND THOSE WITH ORGANIC BRAIN DISEASE. WHEN VALPROATE SODIUM INJECTION IS USED IN THIS PATIENT GROUP, IT SHOULD BE USED WITH EXTREME CAUTION AND AS A SOLE AGENT. THE BENEFITS OF THERAPY SHOULD BE WEIGHED AGAINST THE RISKS. ABOVE THIS AGE GROUP, EXPERIENCE IN EPILEPSY HAS INDICATED THAT THE INCIDENCE OF FATAL HEPATOTOXICITY DECREASES CONSIDERABLY IN PROGRESSIVELY OLDER PATIENT GROUPS.

THESE INCIDENTS USUALLY HAVE OCCURRED DURING THE FIRST SIX MONTHS OF TREATMENT. SERIOUS OR FATAL HEPATOTOXICITY MAY BE PRECEDED BY NON-SPECIFIC SYMPTOMS SUCH AS MALAISE, WEAKNESS, LETHARGY, FACIAL EDEMA, ANOREXIA, AND VOMITING. IN PATIENTS WITH EPILEPSY, A LOSS OF SEIZURE CONTROL MAY ALSO OCCUR. PATIENTS SHOULD BE MONITORED CLOSELY FOR APPEARANCE OF THESE SYMPTOMS. LIVER FUNCTION TESTS SHOULD BE PERFORMED PRIOR TO THERAPY AND AT FREQUENT INTERVALS THEREAFTER, ESPECIALLY DURING THE FIRST SIX MONTHS.

TERATOGENICITY

VALPROATE CAN PRODUCE TERATOGENIC EFFECTS SUCH AS NEURAL TUBE DEFECTS (E.G., SPINA BIFIDA). ACCORDINGLY, THE USE OF VALPROATE PRODUCTS IN WOMEN OF CHILDBEARING POTENTIAL REQUIRES THAT THE BENEFITS OF ITS USE BE WEIGHED AGAINST THE RISK OF INJURY TO THE FETUS.

PANCREATITIS

CASES OF LIFE-THREATENING PANCREATITIS HAVE BEEN REPORTED IN BOTH CHILDREN AND ADULTS RECEIVING VALPROATE. SOME OF THE CASES HAVE BEEN DESCRIBED AS HEMORRHAGIC WITH A RAPID PROGRESSION FROM INITIAL SYMPTOMS TO DEATH. CASES HAVE BEEN REPORTED SHORTLY AFTER INITIAL USE AS WELL AS AFTER SEVERAL YEARS OF USE. PATIENTS AND GUARDIANS SHOULD BE WARNED THAT ABDOMINAL PAIN, NAUSEA, VOMITING, AND/OR ANOREXIA CAN BE SYMPTOMS OF PANCREATITIS THAT REQUIRE PROMPT MEDICAL EVALUATION. IF PANCREATITIS IS DIAGNOSED, VALPROATE SHOULD ORDINARILY BE DISCONTINUED. ALTERNATIVE TREATMENT FOR THE UNDERLYING MEDICAL CONDITION SHOULD BE INITIATED AS CLINICALLY INDICATED (see **WARNINGS** and **PRECAUTIONS**).

DESCRIPTION:

Valproate Sodium is the sodium salt of valproic acid designated as sodium 2-propylpentanoate. Valproate sodium has the following structure:

$C_8H_{15}NaO_2$ M.W. 166.2

Valproate sodium occurs as an essentially white and odorless, crystalline, deliquescent powder. Valproate Sodium injection is available in 5 mL single dose vials for

alent AUC. C_{max}, C_{min} at steady state, as well as after the first dose. The t_{max} after valproate sodium injection occurs at the end of the one hour infusion, while the T_{max} after the oral dosing with divalproex sodium occurs at approximately 4 hours. Because the kinetics of unbound valproate are linear, bioequivalence between valproate sodium injection and divalproex sodium up to the maximum recommended dose of 60 mg/kg/day can be assumed. The AUC and C_{max} resulting from administration of IV valproate 500 mg as a single one hour infusion and a single 500 mg dose of valproate syrup to 17 healthy male volunteers were also equivalent.

Patients maintained on valproic acid doses of 750 mg to 4250 mg daily (given in divided doses every 6 hours) as oral divalproex sodium alone (n = 24) or with another stabilized antiepileptic drug (carbamazepine (n = 15), phenytoin (n = 11), or phenobarbital (n = 11), showed comparable plasma levels for valproic acid when switching from oral divalproex sodium to IV valproate (1-hour infusion).

Distribution

Protein Binding:

The plasma protein binding of valproate is concentration dependent and the free fraction increases from approximately 10% at 40 mcg/mL to 18.5% at 130 mcg/mL. Protein binding of valproate is reduced in the elderly, in patients with chronic hepatic diseases, in patients with renal impairment, and in the presence of other drugs (e.g., aspirin). Conversely, valproate may displace certain protein-bound drugs (e.g., phenytoin, carbamazepine, warfarin, and rolitamide) (see **PRECAUTIONS**, ***Drug Interactions*** for more detailed information on the pharmacokinetic interactions of valproate with other drugs).

CNS Distribution:

Valproate concentrations in cerebrospinal fluid (CSF) approximate unbound concentrations in plasma (about 10% of total concentration).

Metabolism

Valproate is metabolized almost entirely by the liver in adult patients on monotherapy, 30 to 50% of an administered dose appears in urine as a glucuronide conjugate. Mitochondrial β-oxidation is the other major metabolic pathway, typically accounting for over 40% of the dose. Usually, less than 15 to 20% of the dose is eliminated by other oxidative mechanisms. Less than 3% of an administered dose is excreted unchanged in urine.

The relationship between dose and total valproate concentration is nonlinear; concentration does not increase proportionally with dose, but rather, increases to a lesser extent due to saturable plasma protein binding. The kinetics of unbound drug are linear.

Elimination

Mean plasma clearance and volume of distribution for total valproate are 0.56 L/hr/1.73 m^2 and 11 L/1.73 m^2, respectively. Mean terminal half-life for valproate monotherapy after an intravenous infusion of 1000 mg was 16 ± 3 hours.

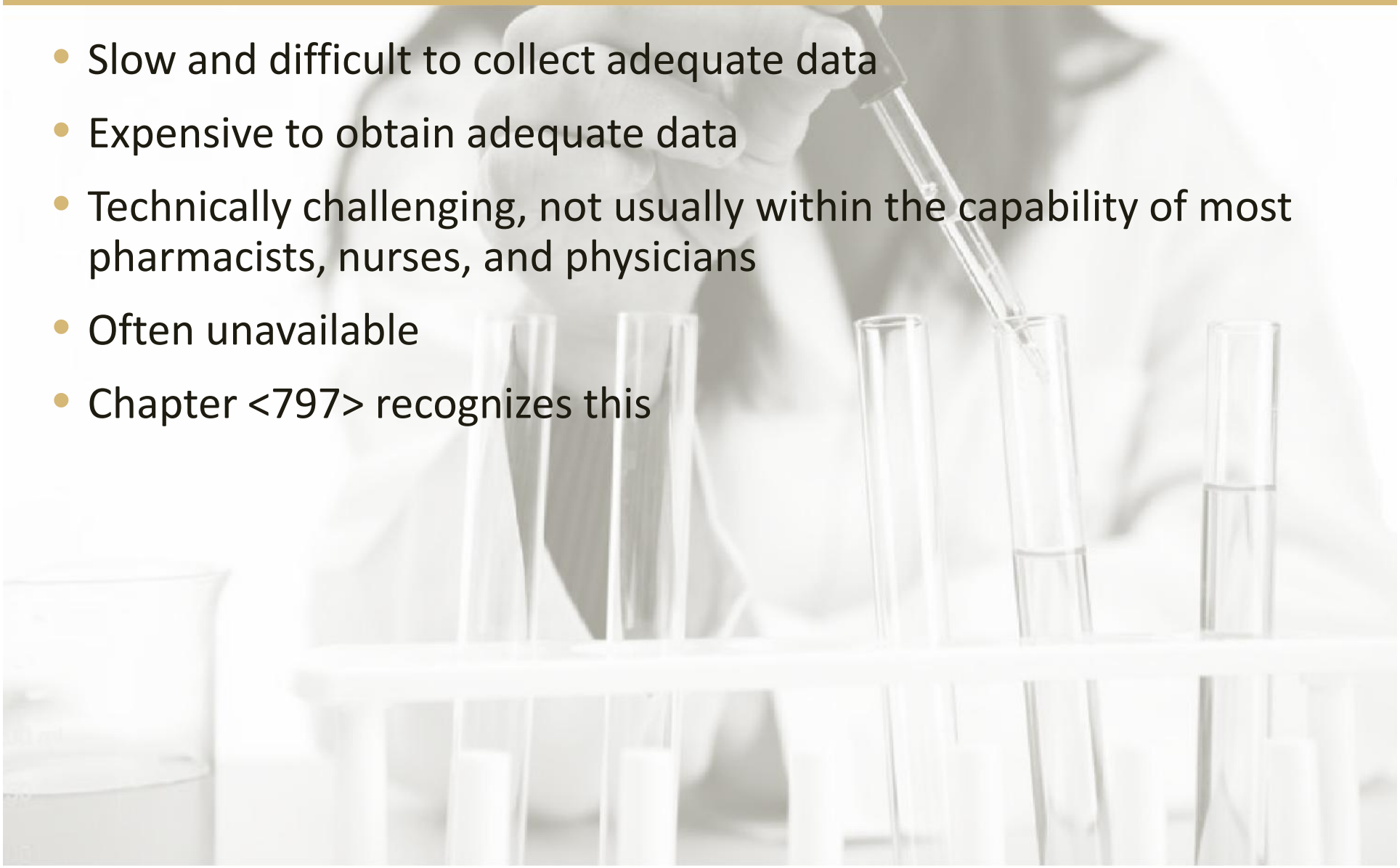
These estimates cited apply primarily to patients who are not taking drugs that affect hepatic metabolizing enzyme systems. For example, patients taking enzyme-inducing antiepileptic drugs (carbamazepine, phenytoin, and phenobarbital) will clear valproate more rapidly. Because of these changes in valproate clearance, monitoring of antiepileptic concentrations should be intensified whenever concomitant antiepileptics are introduced or withdrawn.

Special Populations

Effect of Age:

Neonates—Children within the first two months of life have a markedly decreased ability to eliminate valproate compared to older children and adults. This is a result of reduced clearance (perhaps due to delay in development of glucuronosyltransferase and other enzyme systems involved in valproate elimination) as well as increased volume of distribution (in part due to decreased plasma protein binding). For example, in one study, the half-life in children under 10 days ranged from 13 to 67 hours com-

Chemical Stability Information



- Slow and difficult to collect adequate data
- Expensive to obtain adequate data
- Technically challenging, not usually within the capability of most pharmacists, nurses, and physicians
- Often unavailable
- Chapter <797> recognizes this

<795> Beyond-Use Guidance

- In the absence of specific chemical stability information, follow the guidelines of USP Chapter <795>
  - Nonaqueous Fo[illegible]ations
    - BUD not later than t[illegible] remaining [illegible]e earliest expiration of any API or 6 months, which[illegible]earlier
  - Water-Containing Oral Fo[illegible]ns
    - BUD not later than 14 days [illegible]a controlled cold temperatures
  - Water-Containing To[illegible]Derma[illegible]Mucosal Liquid and Semisolid Formula[illegible]
    - BUD not > 30 da[illegible]

Polling Question

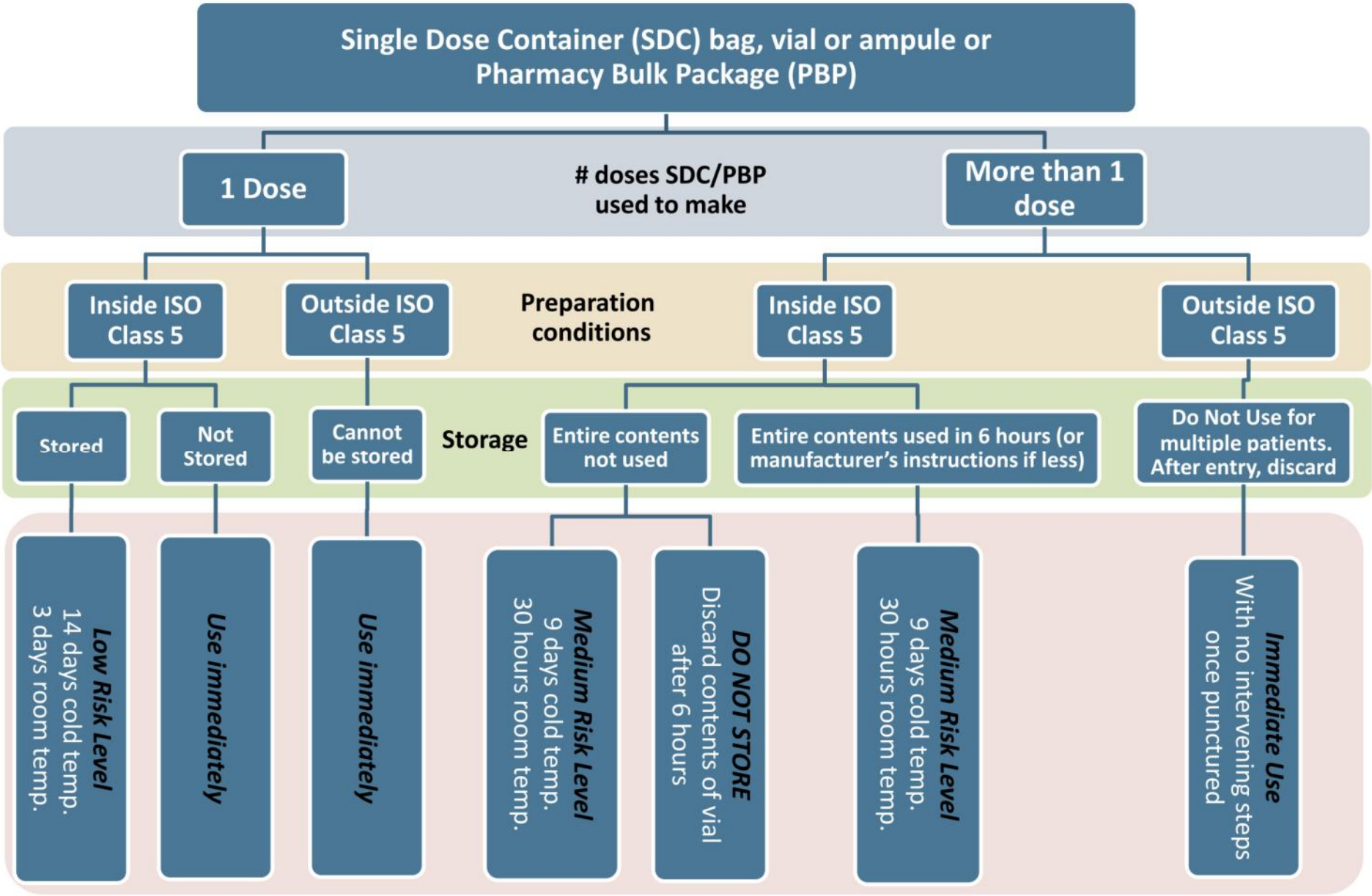
You are inspecting a pharmacy that is compounding hydration bags (in a LAFW inside a cleanroom) for a patient. They are adding electrolytes to liter bags of D5%/0.45%NS. Though they are only dispensing enough bags for 1 week at a time, you notice the label bears instructions to refrigerate and a “do not use after” date that is 2 weeks from the date compounded. What is your concern?

1. No concern. It is acceptable for low risk level CSPs to have a storage time of 14 days refrigerated.
2. Medium risk level BUDs refrigerated are only 9 days.

Microbiological Beyond Use Dating

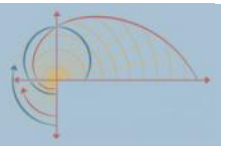
Beyond-use dating for CSPs according to Risk-Level			
Risk Level	BUD at Room Temperature (20 to 25° C)	BUD under Refrigeration (2° to 8° C)	BUD with Frozen Storage (-25 to -10° C)
Immediate Use	1 hour	N/A	N/A
Low Risk with 12h BUD	12 hours	12 hours	N/A
Low Risk	48 hours	14 days	45 days
Medium Risk	30 hours	9 days	45 days
High Risk	24 hours	3 days	45 days

Assigning Beyond Use Dating for Batch Prepared CSPs



CLINICAL IQ

Summary of Risk Level and Assignment of BUD



- It is important that consistent approach be established and uniformly applied when establishing and assigning BUDs to CSPs.
- It is strongly recommended that pharmacies establish a standardized compounding methodology for each CSP they compound.
- That methodology and all elements are best memorialized in a master compounding worksheet.
- With a standardized methodology, the microbial risk level is always the same each time the CSP is compounded.
- The risk level AND stability together determine BUD limited by whichever is shorter.
- Sterility testing according is the requirement of USP Chapter <71> are required when the default BUDs in the chapter for all risk levels are exceeded.