USP Chapter <797>:
De-mystifying Beyond-Use Dating

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Special Thanks

- David W. Newton, PhD, FAPhA for his tutelage and forbearance regarding the establishment of beyond-use dating and the fundamentals of chemical drug stability.
- Since 2000, his leadership as the Chairman of the USP Sterile Compounding Committee has been instrumental in making patient care safer.
Disclaimer

“Although I am a member of the USP Sterile Compounding Expert Committee, I am speaking today in my individual capacity and not as a member of the Committee or as a USP representative.

The views and opinions presented are entirely my own. They do not necessarily reflect the views of USP, nor should they be construed as an official explanation or interpretation of <797>.”
Beyond-Use Dating (BUD)
USP <797> Risk Level

High Risk
Use non-sterile components
(ex: epidurals, alum)

Medium Risk
Uses multiple sterile components.
(ex: batch compounding, TPNs)

Low Risk
Simple, or single, sterile component mixing
(ex: one vial into one delivery container)

No Risk
(premixed or RTU single doses)
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
BUD: Microbiological Limits

- Must factor in chemical stability
- Extended storage of drugs not an initial consideration (greater than 2 weeks)
- Concern that microbial over-colonization of solutions would occur over time.
  - pH of solution is a consideration
    - Neutral (pH 6-8) favorable for microbial colonization
- Concern for proper storage conditions
  - Floor inspections and temperature checks
Ice-cold Milk

Enemies of the State: Time and Temperature

Milk Shelf Life

- Temperature Control Is Important
- Average Shelf-Life at 40°F is Ten Days
- Rapid Decrease in Shelf-Life at Higher Temperatures

Ideal

Enemies of the State: Time and Temperature


Fig. 1. Natural logarithm of the number of hours to reach 90% of original cefuroxime concentration, ln t90, versus temperature during first-order hydrolysis over the pH range of 4-7.3,4
Non-Visibility of Microbial Contamination

Numbers of Bacteria per mL in 1L bottles

Millipore Corp. Hospital Pharmacy Filtration Guide (Cat. No. MP801)
Bedford, MA; 1980:3
# Microbial Growth in PN solution

The results of incubating four microorganisms: *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, *Staphylococcus aureus*, *Bacillus subtilis*, and *Candida albicans*, (50 to 1000 cfu/mL) at undefined ambient room temperature (likely 20°-25°C or 68°-77°F) for 72 hours in 4.25% amino acids and 25% dextrose at pH 6.2

<table>
<thead>
<tr>
<th>Organism</th>
<th>Approximate Colony Forming Units per mL and % Change(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0 hour</td>
</tr>
<tr>
<td><em>Pseudomonas a</em></td>
<td>1000, 0%</td>
</tr>
<tr>
<td><em>Klebsiella p</em></td>
<td>300, 0%</td>
</tr>
<tr>
<td><em>Staphylococcus a</em></td>
<td>150, 0%</td>
</tr>
<tr>
<td><em>Bacillus s</em></td>
<td>1000, 0%</td>
</tr>
<tr>
<td><em>Candida a</em></td>
<td>30, 0%</td>
</tr>
</tbody>
</table>

\(^a\)Values estimated from graphed lines in Figure 1.

BUD: Microbiological Limits

- USP risk levels focus on microbial risk to patient
  - Principle source: breach of aseptic technique
- Vary in duration by risk Level
  - Greater # of aseptic manipulations, the greater the risk of microbial contamination, shorter the BUD
- Applied whenever an actual sterility test in accordance with USP Chapter <71> has not been performed
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. Thus, immediately after the date, a CSP is not always dangerous nor ineffective.

Contamination Events

- Basic tenets of proper hand hygiene and aseptic technique typically ignored
- Some of the “best” providers working in optimal environments have had incidences of CSP contamination
- All dosage forms have been contaminated
  - SDVs, MDVs, SVPs, LVPs and syringes
Pharmacy Urban Legend:

Chemotherapy drugs have an antimicrobial effect

- **Cisplatin**- Inhibits microbial growth (1)
- Cladribine- No antimicrobial effect (2)
- Cytarabine- No antimicrobial effect (3)
- Docetaxel- No antimicrobial effect (2)
- Doxorubicin HCl- No antimicrobial effect (4; 5)
- Etoposide phosphate- No antimicrobial effect (5; 6)
- Floxuridine- No antimicrobial effect (4)
- Fludarabine phosphate- No antimicrobial effect (2)
- **Fluorouracil**- Inhibits microbial growth (3; 7; 8)
- Gemcitabine HCl- No antimicrobial effect (2)
- Idarubicin HCl- No antimicrobial effect (2)
- Irinotecan HCl- No antimicrobial effect (6)
- Paclitaxel- No antimicrobial effect (2)
- Pentostatin- No antimicrobial effect (2)
- **Topotecan HCl**- Inhibits microbial growth (9)
References
7. Gaj E, Griffin RE. Evaluation of growth of six microorganisms in fluorouracil, bacteriostatic sodium chloride 0.9%, and sodium chloride 0.9% media. Hosp Pharm 1983; 18:348-49.
Expiration Date: History

- Under Section 501(a)(2)(B) of the federal Food, Drug and Cosmetic Act (FDCA), manufacturers of prescription drug products must establish controls for the manufacture, processing, packing, and holding of drug products to ensure their safety, identity, strength, quality, and purity.

- Requirements for these controls, also known as current good manufacturing practices (CGMPs), are established and monitored by the FDA.

- Expiration dates only apply when the drug product is stored in the manufacturer’s original, unopened container under defined conditions.
Expiration Date: History

- As part of the CGMP regulations, the FDA requires that drug products bear an expiration date determined by appropriate stability testing (21 CFR 211.137 and 211.166).

- The FDA defines an expiration date as “the date placed on the container/labels of a drug product designating the time during which a batch of the product is expected to remain within the approved shelf life specifications if stored under defined conditions, and after which it may not be used.”
Expiration Dates

- Applies to manufactured drug products
- Determined by multiple, scientifically valid, product/package-specific research studies
- Based on the Arrhenius Equation \( k = Ae^{-\frac{E_a}{RT}} \) with statistical analysis
  - Formula for rate of a chemical reaction
    - Oxidation, Hydrolysis and Reduction
- Strict, specific, and proven to be valid
- Approved by the FDA
- USP 24/NF 19, <795>, and <797> requires that the label of an official drug product bear an expiration date.
Svante August Arrhenius
Beyond-Use Dating

- Once the manufacturer’s container is opened and the drug product is transferred to another container for dispensing or repackaging, the expiration date no longer applies.
- The USP has developed recommendations for pharmacists to place a “beyond-use” date on the label of the new container.
- The “beyond-use” date can be no longer than the manufacturer’s expiration date and often may be shorter, i.e., one year for repackaged unit-dose orals.
- Unlike expiration dates, there is little scientific basis for beyond-use dating.
Beyond-Use Dating (BUD)

- The American Pharmacists Association (APhA) encourages, and 17 states require, that pharmacists place a “beyond-use” date on the label of the prescription container that is dispensed to the patient.

- Based on the BUD on the drug’s chemical stability in conjunction with microbiological limits for patient safety.
Microbial Populations in the Digestive Tract of Normal Humans

<table>
<thead>
<tr>
<th></th>
<th>Stomach</th>
<th>Jejunum</th>
<th>Ileum</th>
<th>Colon</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Viable bacteria per gram</strong></td>
<td>$0 - 10^3$</td>
<td>$0 - 10^4$</td>
<td>$10^5 - 10^8$</td>
<td>$10^{10} - 10^{12}$</td>
</tr>
<tr>
<td><strong>pH</strong></td>
<td>3.0</td>
<td>6.0-7.0</td>
<td>7.5</td>
<td>6.8-7.3</td>
</tr>
</tbody>
</table>

The gastrointestinal tract is sterile at birth, but colonization typically begins within a few hours of birth, starting in the small intestine and progressing caudally over a period of several days. In most circumstances, a "mature" microbial flora is established by 3 to 4 weeks of age.

http://www.vivo.colostate.edu/hbooks/pathphys/digestion/basics/gi_bugs.html
USP <797> Focus: People and Work Practices

- We are all microbially-contaminated and error-prone
- USP Chapter <797> notes that human transfer of microorganisms via direct contact is the principal cause of contaminated CSPs
- Poor work practices contaminate more CSPs than any other cause
- Britain’s NHS recognizes this with a new effort among staff to reduce hospital-acquired infections
  - No neckties, white coats, fake nails, or jewelry
  - Bare below the elbows
Direct Contact Contamination
Ideal Microbial Growth*

- Depending on the particular organism, ideal microbial growth factors feature, but are not limited to, presence of particular carbohydrate and protein nutrients, optimum pH range (6-8 for bacteria and 5-6 for fungi), optimum temperature range, and an oxygen-rich or carbon dioxide-rich environment.

- When introduced into a new and finite ideal environment, a population of bacteria and/or fungi exhibits four stages of growth, which are illustrated in Figure 1, and estimated in parts 1-4 below for a hypothetical 24-hour duration.

Ideal Microbial Growth

- Figure 1: Theoretical Rate Curve of Ideal Microbial Growth
Ideal Microbial Growth

- **Lag Phase**
  - Little to no increase in population.
  - Lag phase is longer in less than ideal environments.

- **Exponential or Logarithm Growth Phase**
  - The duration is micro-organism specific but range for 1-4 hours.
  - Binary cell population doubling or generation times range from 20 minutes for *Escherichia coli* to more than 20 hours for *Treponema pallidum* (syphilis) or *Mycobacterium tuberculosis*. 
Ideal Microbial Growth

- Figure 1: Theoretical Rate Curve of Ideal Microbial Growth
Ideal Microbial Growth

- **Stationary Phase:** All nutrients are exhausted in the finite environment. Duration 4-12 hours
- **Death Phase:** Microorganisms die rapidly from lack of nutrients. Begins after 6-20 hours.

Progression to cell death, also called Apoptosis
# Microbial Population Table

<table>
<thead>
<tr>
<th>Doubling Time, d</th>
<th>Growth Time, t</th>
<th>Approximate Cell Population Quantity^a</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>At Time = 0^b</td>
</tr>
<tr>
<td>20 minutes</td>
<td>1 hour</td>
<td>50</td>
</tr>
<tr>
<td>20 minutes</td>
<td>4 hours</td>
<td>10</td>
</tr>
<tr>
<td>4 hours</td>
<td>1 hours</td>
<td>50</td>
</tr>
<tr>
<td>4 hours</td>
<td>10 hours</td>
<td>10</td>
</tr>
</tbody>
</table>

^aThis quantity is typically described as the number of colony forming units, or cfu.

^bTheoretical quantities of microorganisms that may be introduced by inadvertent direct contact, e.g., human touch or secretions, into non-nutrient sterile solutions during clinical practice.

The table above illustrates population increases for two population doubling or generation times according to the equation, \( N_t = N_0 \times 2^{t/d} \), where \( N_t \) = cell population quantity at time, t; \( N_0 \) = cell population quantity at time of inoculation, t = time of cell population quantity measurement, and d = cell population doubling or generation time.
## Calculated Microbial Growth

<table>
<thead>
<tr>
<th>Time (Hours)</th>
<th>Microbial Count (CFU per mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>10</td>
</tr>
<tr>
<td>9</td>
<td>640</td>
</tr>
<tr>
<td>12</td>
<td>41,000</td>
</tr>
<tr>
<td>18</td>
<td>$1.7 \times 10^7$</td>
</tr>
<tr>
<td>24</td>
<td>$6.9 \times 10^9$</td>
</tr>
</tbody>
</table>

Cundell AM, USP Committee on Analytical Microbiology, Pharmacopeial Forum 2002; 28 (6) Stimuli to the Revision Process
Environment vs. Personnel

“*The most important variable affecting microbial contamination of admixtures was the aseptic technique of personnel, not the environment in which the drugs were compounded.*”

Compounding Personnel

- A person in a cleanroom is considered a broad spectrum particle generator enclosed by inefficient mechanical filters which may also be sources of particles.
- The human body harbors an average of 150-200 different classes of bacteria.
- Hands have an average of 100,000 organisms/sq mm.
- The body sheds 5 grams of skin fragments each day along with shedding 1 layer of skin every 5 days (size range 10 to 300 micron – 1000th of a mm).
- “Our greatest asset and also our biggest liability!”
Sources of Microbial Contamination in Aseptic Processing*

<table>
<thead>
<tr>
<th>Source</th>
<th>Ranks</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1986</td>
</tr>
<tr>
<td><strong>Personnel</strong></td>
<td>1</td>
</tr>
<tr>
<td>Human error</td>
<td>2</td>
</tr>
<tr>
<td>Aseptic assembly</td>
<td>4</td>
</tr>
<tr>
<td>Non-routine activity</td>
<td>3</td>
</tr>
<tr>
<td>Mechanical failure</td>
<td>5</td>
</tr>
<tr>
<td>Airborne contaminants</td>
<td>7</td>
</tr>
<tr>
<td>Improper sanitization</td>
<td>6</td>
</tr>
<tr>
<td>Surface contaminants</td>
<td>7</td>
</tr>
<tr>
<td>0.2 µm filter failure</td>
<td>8</td>
</tr>
<tr>
<td>HEPA failure</td>
<td>9</td>
</tr>
</tbody>
</table>

Medium-Risk Level Media Fill

- Evaluated 2 years of media fill tests of aseptic technique – over 600 tests
- Gowning and gloving not required
- 10-step complicated preparation
- A trainer provided guidance as to proper technique
- Contamination rate was found to be 5.2%!!!

Reducing the Contamination Rate by Changing Work Practices

- Evaluated 2 more years of media fill tests of aseptic technique using the same 10-step preparation

- Year 1:
  - Gowns and non-sterile gloves required
  - Reduced to about 1% contamination

- Year 2:
  - Sterile gloves with repeated 70% IPA wiping of gloves
  - Reduced to 0.3% contamination

# Microbiological Beyond-Use Dating

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>Room Temp</th>
<th>Refrigerator</th>
<th>Freezer (≤-10 °C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immediate Use</td>
<td>1 hour</td>
<td>1 hour</td>
<td>N/A</td>
</tr>
<tr>
<td>Low</td>
<td>48 hours</td>
<td>14 days</td>
<td>45 days</td>
</tr>
<tr>
<td>Low w/ 12-hr BUD</td>
<td>12 hours or less</td>
<td>12 hours or less</td>
<td>N/A</td>
</tr>
<tr>
<td>Medium</td>
<td>30 hours</td>
<td>9 days</td>
<td>45 days</td>
</tr>
<tr>
<td>High</td>
<td>24 hours</td>
<td>3 days</td>
<td>45 days</td>
</tr>
</tbody>
</table>
Putting it All Together

Risk Level

Beyond-Use Dating (point in time)

Chemical Stability ➔ Microbial Stability ➔ Aseptic technique

ASSUMPTION!
CSP is stored at its optimal temperature at all times
THINK MILK!
Making BUD work

- Reduce waste and rework in the sterile compounding area
  - Consider lean principles-PDSA
- Analyze current medication distribution system and location of medication storage areas
- Increase # of batches-JIT
- 64% reduction in rework and waste

Summary

- Meticulous aseptic technique is required.
- Proper garb and engineering controls are necessary.
- Time and temperature must be controlled throughout the entire life cycle of a CSP.
- USP <797> BUDs can be exceeded if sterility testing according to USP <71> is performed.
Thank you!

Keep it cold.