Prescription drug products’ stability and expiration dates*

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Mansoor A. Khan, R.Ph., Ph.D.
Director, FDA/CDER/Division of Product Quality Research

Views are my own and does not represent the official policy of the Agency
Outline

• Introduction to FDA and DPQR
• Drug product shelf life & expiration date
• Shelf-Life Extension Program (SLEP)
• Repackaged products
Food and Drug Administration

ORA

CDER  CBER  CDRH  CVM  CFSAN  NCTR

Drugs  Biologics  Devices
Combination products

Field Laboratories
Office of Biotech Laboratories
Office of Testing and Research Laboratories
Research in DPQR

- Excipients
- Formulation variables
- Process variables
- Mechanistic evaluations
- Optimization & ANN procedures

Analytical Methods

Cell Culture

PK/Bioavailability

NDDS

- Nanoparticles
- Liposomes
- SR/MR
- TDDS
- Nasal
- Pulmonary
- Fast disintegration
- Solid dispersion

Characterization

DP

Physical
- Mixing
- Milling
- Granulation
- Drying
- Compression
- Coating
- Packaging

Chemical

Stability

DS

Process variables

Mechanistic evaluations

Optimization &

ANN procedures

Mixing

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Nasal

Pulmonary

Fast disintegration

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Physical

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NDDS

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Analytical Methods

Research in DPQR
Stability, shelf-life, and expiration date

- Drug substance and products could degrade by oxidation, hydrolysis, racemization etc.

- Factors such as temperature, humidity, light, pH, ionic strength, buffer strength could enhance the degradation.

- It is expected that a well designed formulation and packaging protects the product from degradation

- A “shelf-life” generally means a product will retain approved specs in the final packaged container, in stated storage conditions, when tested by validated methods

- An “expiration date” must be placed on container label (21 CFR 201.17).
Levothyroxine Sodium
Levothyroxine Stability Indicating Method*

How is Shelf Life Established?

- **Applicant** conducts systematic stability testing (21 CFR 211.166) according to a prescribed protocol
  - Select samples from representative batches
  - Store samples at defined storage conditions*
    - Accelerated (40ºC/75% relative humidity or RH)
    - Long-term (25ºC/60% RH)
    - Intermediate (30ºC/65% RH), if needed
  *(Other stress conditions, e.g., light, acid, base, oxidant, for one-time testing)*
  - Pull samples at predetermined intervals
How is Shelf Life Established?

– Test samples for product attributes susceptible to change during storage and shipping and likely to influence quality, safety, and/or efficacy
  • Physical attributes, e.g., appearance, particle size
  • Chemical attributes, e.g., assay, degradants, pH
  • In vitro drug release rate, e.g., dissolution
  • Biological, e.g., bioassay, and microbiological attributes

– Analyze data for each attribute as a function of time against proposed acceptance criteria

– Determine if the proposed shelf life can be supported by available data
How is Shelf Life Established?

Perform regression analysis (if needed)

- Raw data
- Regression line
- Two-sided 95% confidence limits
- Lower acceptance criterion

% Label Claim vs. Time (years) graph
Stability Test Attributes

Solid Orals
- Potency Assay
- Impurities
- Dissolution
- Water Content
- Appearance

Injectables
- Potency Assay
- Impurities
- Preservatives
- pH
- Appearance
  - Color
  - Particulates

Powders
- Potency Assay
- pH
- Water Content
- Appearance

Creams/Ointments
- Potency Assay
- pH
- Appearance
Gabapentin

Example of a drug product impurity

\[\text{H}_2\text{N}\quad \text{COOH}\]

\[\text{HN} \quad \text{C}=\text{O}\]

Gabapentin

Lactam impurity

* Laboratory efforts: Understand all the variables and their interactions that enhance the impurity level. DOE experiments to obtain a design space of a unit operation. Drying and granulation process monitored by Near IR and chemical imaging.

RC-A formation in Granules stored at 40°C/75% RH

- **PVP-W**
- **PVP-A**
- **xPVP-W**
- **xPVP-A**
- **HPC-W**
- **HPC-A**
- **Polx-W**
- **Polx-A**

**USP limit for RC-A**
RC-A formation in Tablets stored at 40 °C/75% RH

Related Compound A (% w/w)

- PVP-W
- PVP-A
- xPVP-W
- xPVP-A
- HPC-W
- HPC-A
- Polx-W
- Polx-A

USP limit for RC-A
SLEP: Program Operation

Drug Lot Stored in Military/SNS/VA Stockpile → Samples → SLEP Military/SNS/VA Contact

FDA Field Lab “Testing” → Samples → FDA SLEP Coordinator

FDA SLEP Coordinator

Tests/Test methods/Location of standards/procedures/research (when needed) → Data Evaluation, Analysis, and Estimations of New Expiration Date

FDA CDER Chemist Analysis

<table>
<thead>
<tr>
<th>Drug Product</th>
<th>Dosage Form</th>
<th>Tested</th>
<th>Mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amoxicillin Sodium</td>
<td>Tablets</td>
<td>21</td>
<td>23</td>
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<tr>
<td>Ciprofloxacin</td>
<td>Tablets</td>
<td>242</td>
<td>55</td>
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<tr>
<td>Diphenhydramine HCl</td>
<td>Syringe-Needle a</td>
<td>12</td>
<td>76</td>
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<tr>
<td>Doxycycline Hyclate</td>
<td>Capsules b</td>
<td>13</td>
<td>50</td>
</tr>
<tr>
<td>Doxycycline Hyclate</td>
<td>Powder b</td>
<td>31</td>
<td>27</td>
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<tr>
<td>Halothane</td>
<td>Liquid</td>
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<td>67</td>
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<tr>
<td>Mannitol</td>
<td>Injection-Solution</td>
<td>10</td>
<td>66</td>
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<tr>
<td>Morphine Sulfate</td>
<td>Syringe-Needle c</td>
<td>13</td>
<td>89</td>
</tr>
<tr>
<td>Naloxone HCl</td>
<td>Injection-Solution</td>
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<tr>
<td>Oxacillin Sodium</td>
<td>Powder</td>
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<tr>
<td>Potassium Iodide</td>
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<tr>
<td>Sodium Bicarbonate</td>
<td>Injection-Solution</td>
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<tr>
<td>Sodium Chloride</td>
<td>Irrigation e</td>
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<tr>
<td>Sodium Nitrite</td>
<td>Injection-Solution</td>
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<tr>
<td>Sodium Thiosulfate</td>
<td>Injection-Solution</td>
<td>14</td>
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<tr>
<td>Product</td>
<td>Formulation</td>
<td>Assay 1</td>
<td>Assay 2</td>
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<tr>
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<tr>
<td>Cefoperazone Sodium Powder</td>
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<tr>
<td>Cephapirin Sodium Powder</td>
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<tr>
<td>Cimetidine HCl Injection-Solution</td>
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<tr>
<td>Dextrose (5%) Injection-Solution</td>
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<tr>
<td>Flurazepam HCl Capsules</td>
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<td>Morphine Sulfate Autoinjector</td>
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<td>Ophthalmic Irrigating Solution</td>
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<td>Pancuronium Bromide Injection-Solution</td>
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<td>Ringer’s, Lactated and Dextrose Injection-Solution</td>
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<td>Sodium Chloride Injection-Solution e</td>
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<tr>
<td>Sodium Polystyrene Sulfonate Powder</td>
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<td>Sulfadiazine Silver Cream</td>
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<td>Tetracycline HCl Capsules</td>
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<tr>
<td>Thiopental Sodium Powder</td>
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<td>12</td>
<td>54</td>
</tr>
</tbody>
</table>
SLEP Participants

- Current DoD participants
  - US Army
  - US Air Force
  - US Navy
  - US Marines

- CDC/Strategic National Stockpile (SNS) – since 2004

- Dept. of Veterans Affairs (VA) – since 2005

- Only Federal agencies that sign an MOA with DOD may participate in SLEP
SLEP Challenges

• Protocols/Procedures
• References standards
• Specialized equipment
• Lab research when needed
• Record keeping
• Knowledge Management
FDA Shelf Life Research Example

Force-Displacement Cap Crushing Strength

- Force-Displacement Curves for Empty Capsule Caps and Tablets
  - 1975
  - 1999
  - 2004

- Manufacture Year:
  - 1975
  - 1999
  - 2004

- Hardness (kp) vs. Manufacture Year

- Tablet Hardness Tester (n = 10)
Research Lessons

• Actual shelf life may be much longer than indicated by expiration date on the product original label.
• Shelf life varies greatly between lots.
• Continued testing and systematic evaluation is required to ensure product quality.
• Analyses of the successes and failures can help in applying this information to new product development.
Repackaged Product Background

• The draft guidance, CPG 7132.b11, specifies conditions where it may be possible to assign up to 12 months expiration dating to non-sterile solid and liquid oral dosage form drug products repackaged into unit dose containers for Class A, without conducting new stability studies.

• According to USP,
  – a unit dose container is designated Class A if not more than 1 of 10 containers exceed 0.5 mg/day in moisture permeation rate, and none exceeds 1 mg/day.
  – a unit dose container is designated Class B if not more than 1 of 10 containers exceed 5 mg/day in moisture permeation rate, and none exceeds 10 mg/day.
Two repackaging firms say a draft FDA guidance should be revised to allow one year dating on open dose packages using Class B material. (http://www.fdaweb.com/start.php?sa=v&aid=D5100826&cate=&stid=4LnsBWacYRN0k')

FDA Webview, Sept 12, 2005
Unit Dose Products Selected

- Ranitidine HCl Syrup, 15 mg/mL
- Metoprolol tartrate tablets, USP – 50 mg
- Phenytoin sodium suspension, USP – 125 mg/5 mL
- Gabapentin capsules, 300 mg
- Furosemide tablets, USP, 40 mg
Original packaging tablets
Time 0

Original packaging tablets
Stored at 25°C 60%RH for 4 Weeks

Original packaging tablets
Stored at 40°C 75%RH for 4 Weeks

Repackaged tablets
Stored at 25°C 60%RH for 4 Weeks

Repackaged tablets
Stored at 40°C 75%RH for 4 Weeks
Overall Conclusions

• Drug product degrade by several different type of reactions

• It is important to monitor several product attributes in addition to the amount of main drug

• The stability of a product beyond expiration is not evaluated. Some product could be dangerous if used after expiration

• SLEP program is restricted to certain federal agencies at this time

• Repackaged metoprolol tartrate tablets – Product integrity compromised at accelerated conditions.

• Repackaged Phenytoin Sodium Suspension – Product uniformity, potency, and dissolution compromised at initial time point itself

• Repackaged Ranitidine HCl Syrup, Furosemide Tablets, and Gabapentin Capsules – no stability issues in the conditions of experiment