Prescription drug products' stability and expiration dates*

UTMB/NASA-JSC Aerospace Medicine Grand Rounds

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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			

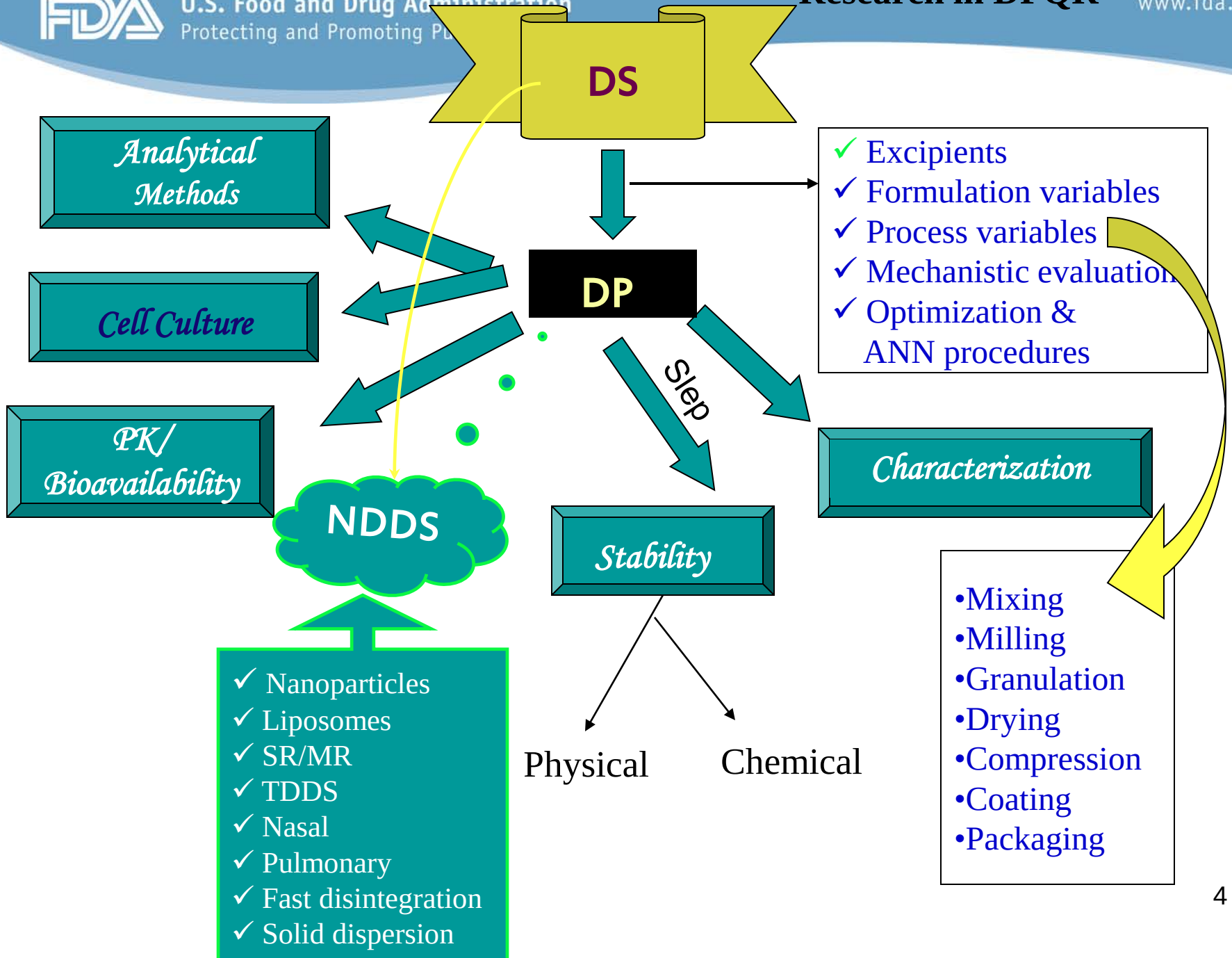
Combination products

Field Laboratories

Office of Biotech Laboratories

Office of Testing and Research Laboratories

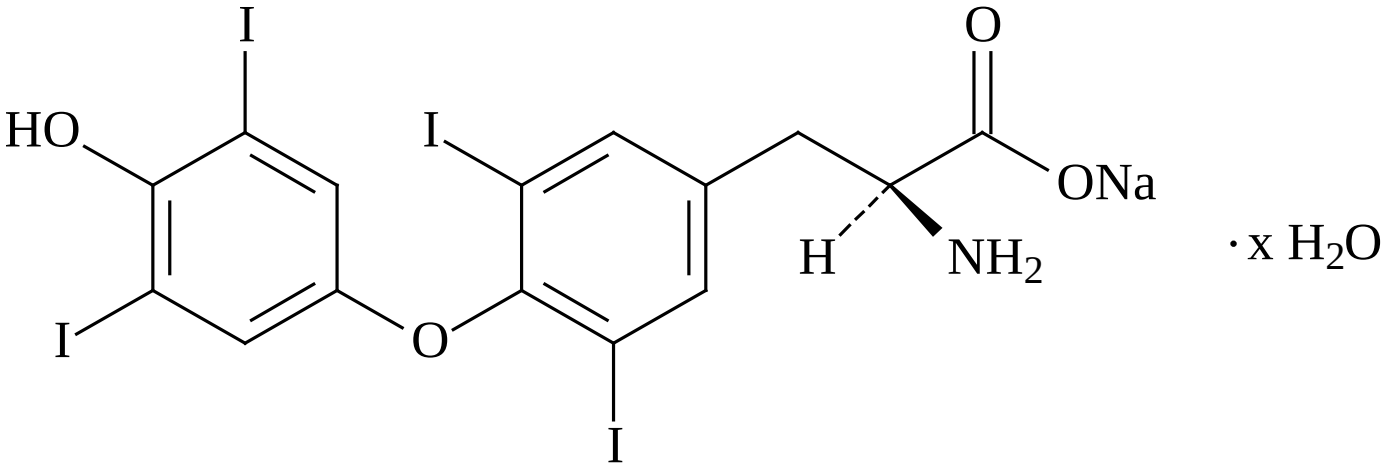
Research in DPQR



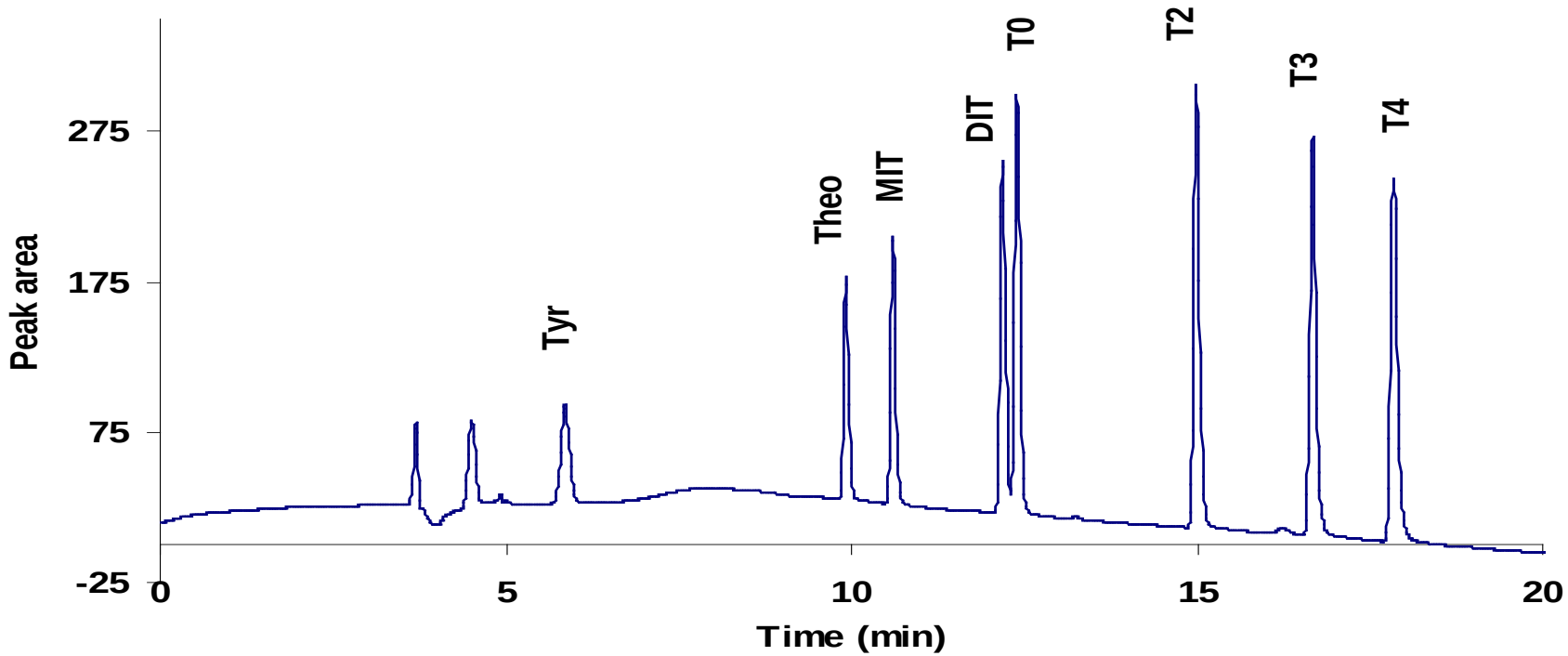
Stability, shelf-life, and expiration date

- 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*



International Journal of Pharmaceutics, 360:77-82, 2008.

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

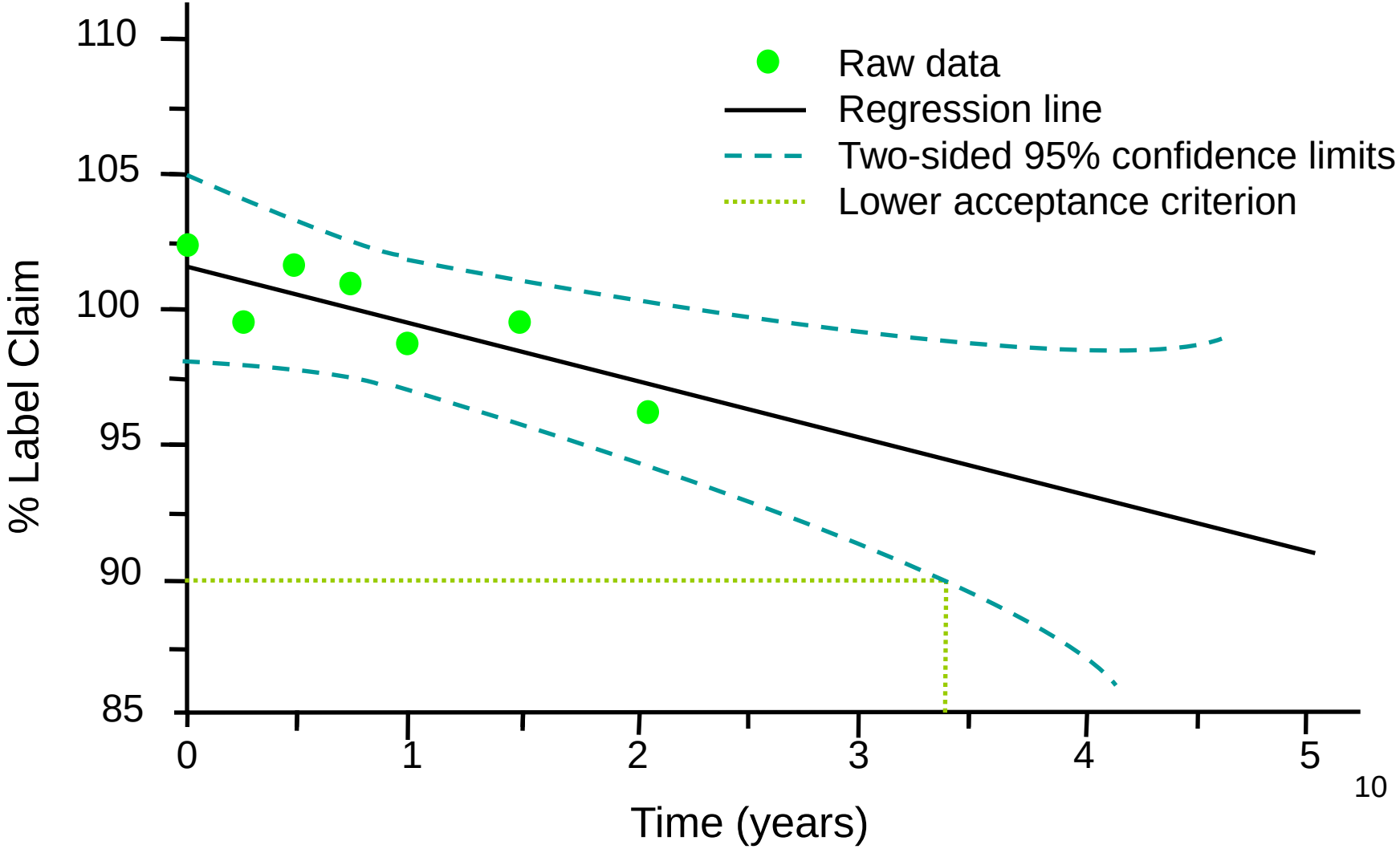
    *(Other stress conditions, e.g., light, acid, base, oxidant, for one-time testing)
  - Pull samples at predetermined intervals

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)



Stability Test Attributes

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

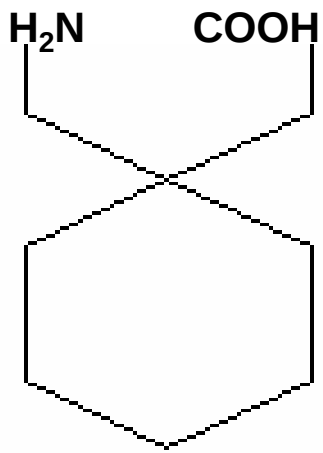
Injectables
- Potency Assay
- Impurities
- Preservatives
- pH
- Appearance
  - Color
  - Particulates

Powders
- Potency Assay
- pH
- Water Content
- Appearance

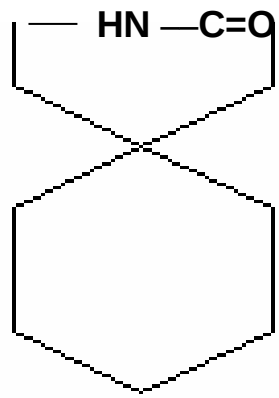
Creams/Ointments
- Potency Assay
- pH
- Appearance

Gabapentin

Example of a drug product impurity



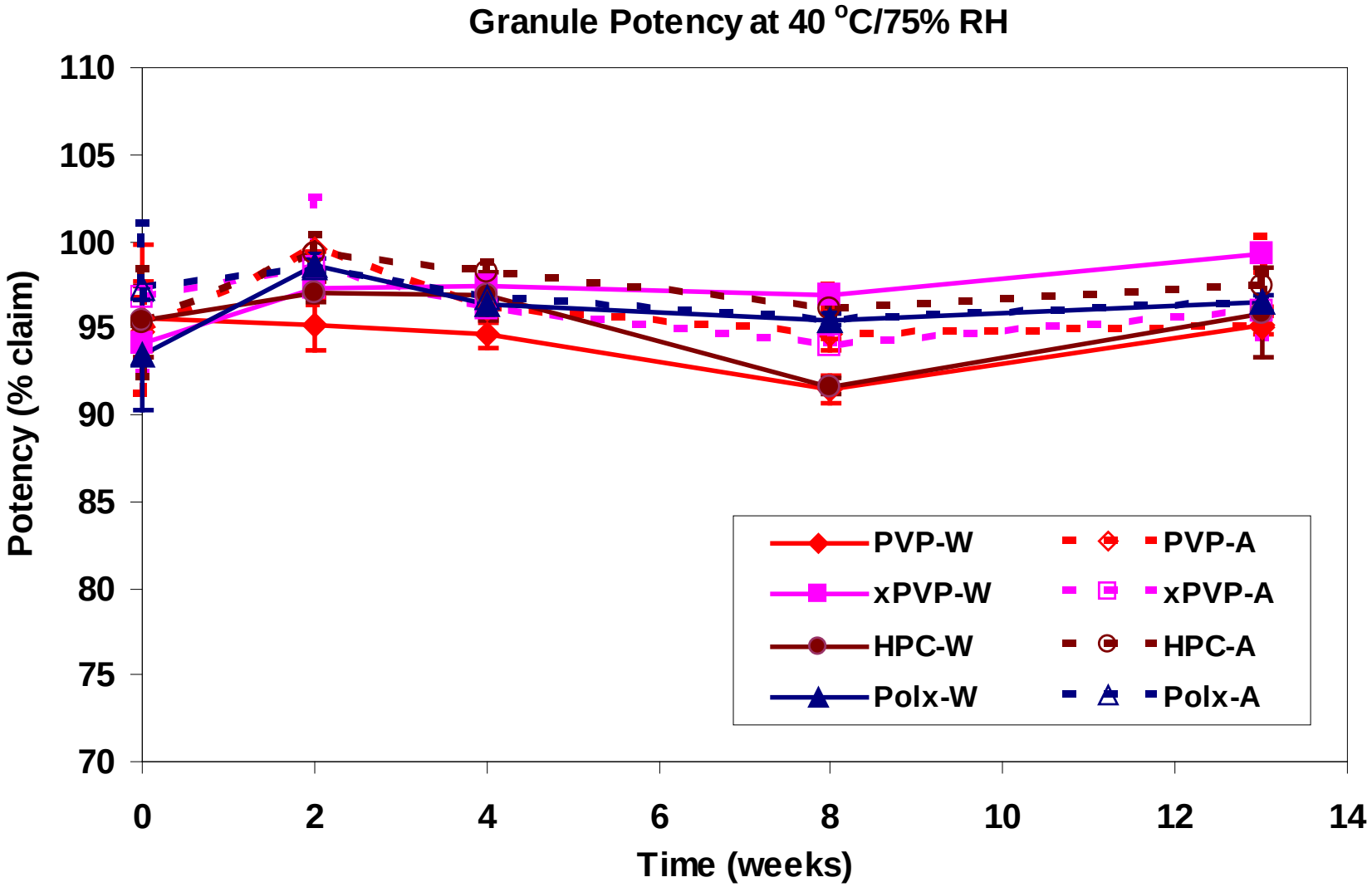
Gabapentin



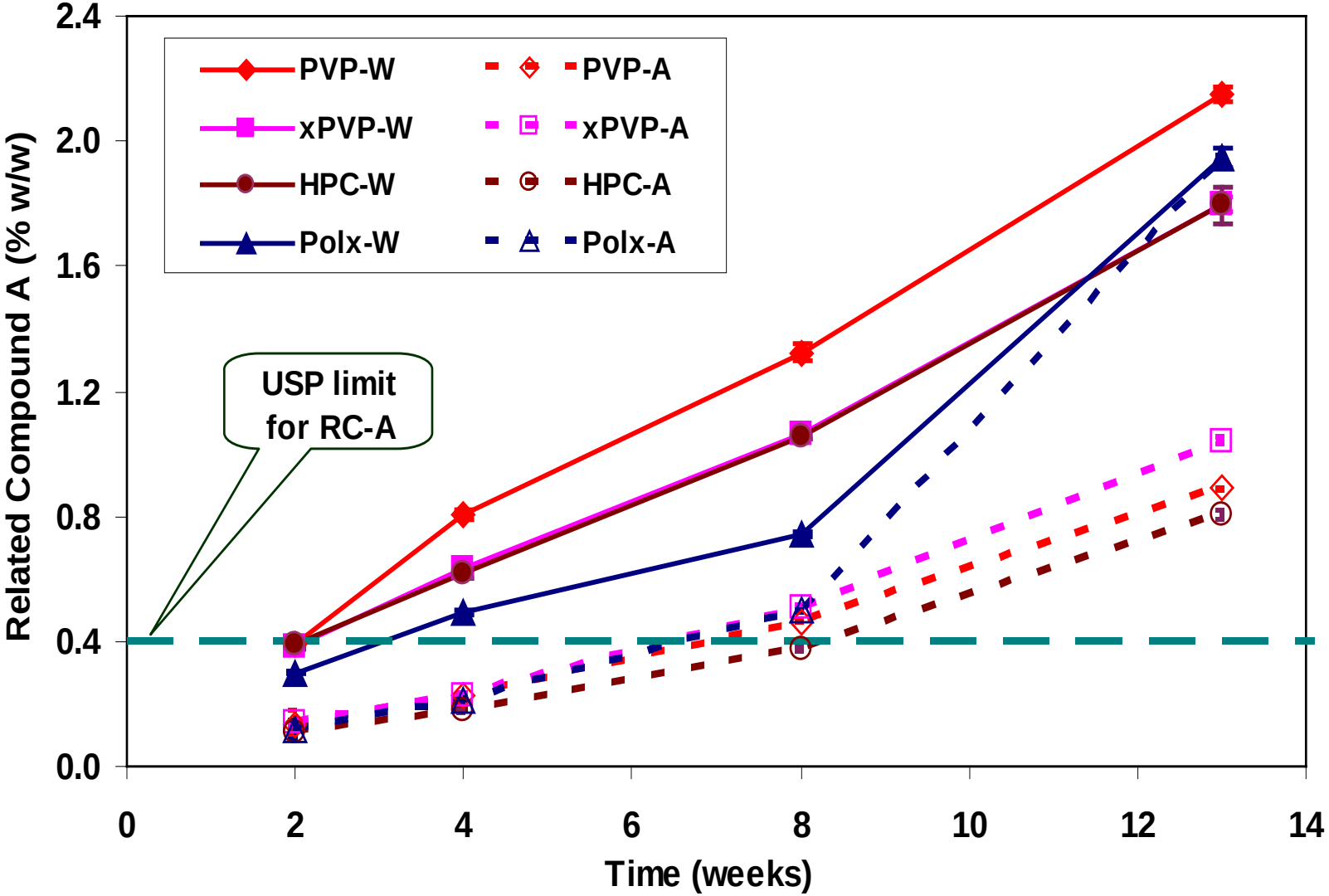
Lactam impurity

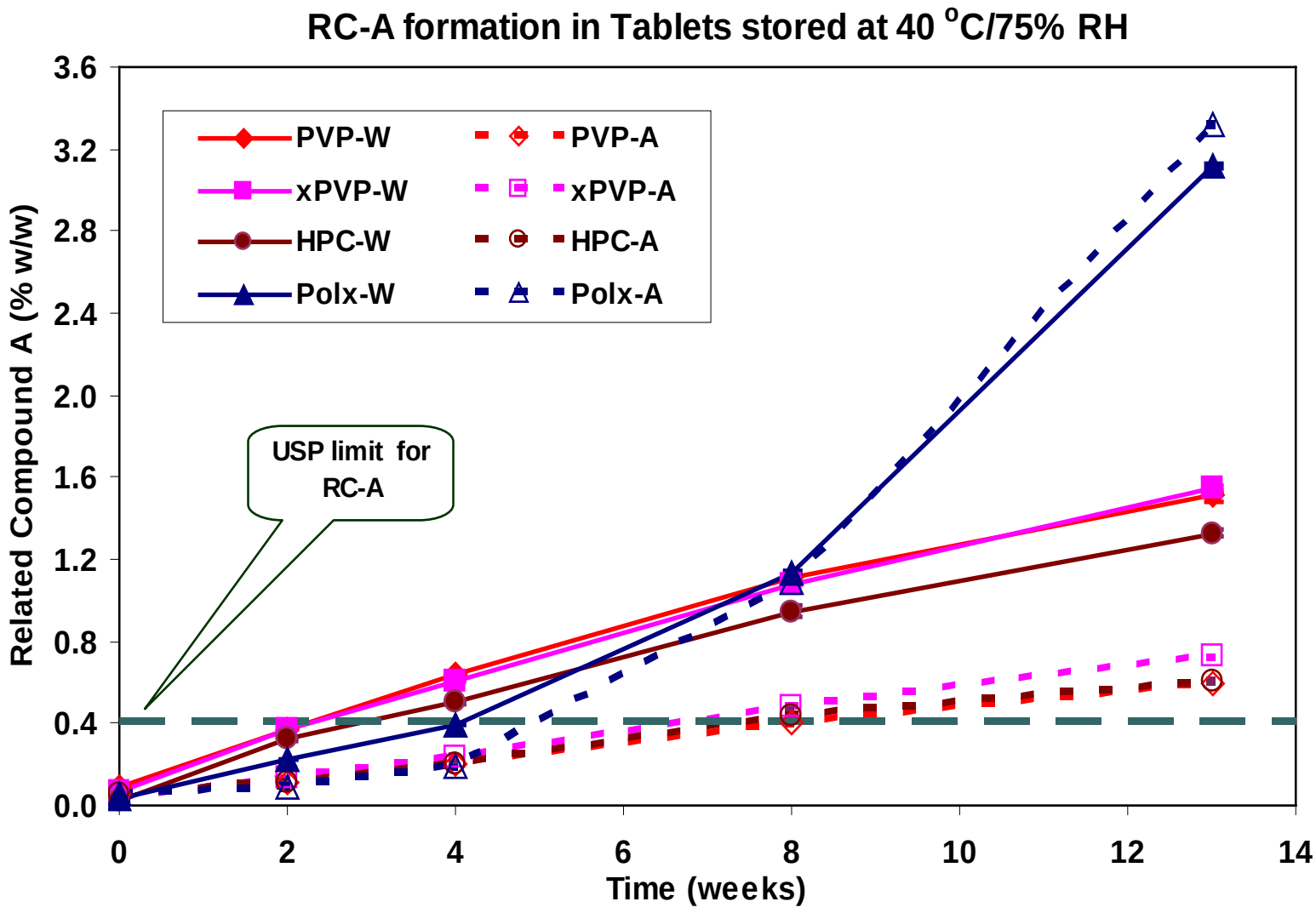
J. Pharm and Biomed. Analysis, 2008, 46, pp. 181-186.

* 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.


Granule Potency at 40 °C/75% RH
Potency (% claim)
110
105
100
95
90
85
80
75
70
0
2
4
6
8
10
12
14
Time (weeks)
PVP-W
PVP-A
xPVP-W
xPVP-A
HPC-W
HPC-A
Polx-W
Polx-A

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




RC-A formation in Tablets stored at 40 °C/75% RH
Related Compound A (% w/w)
3.6
3.2
2.8
2.4
2.0
1.6
1.2
0.8
0.4
0.0
0
2
4
6
8
10
12
14
Time (weeks)
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

Samples ↓ ↑ **New Expiration Date**

FDA Field Lab "Testing"

Samples →
← **Test Results**

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

Lyon et. al., J. Pharm. Sci., 2006, 95, 1549-1560.

Group 1A: Products with No Failures (≥ 10 lots tested)

Drug Product	Dosage Form	Tested	Mean
Amoxicllin Sodium	Tablets	21	23
Ciprofloxacin	Tablets	242	55
Diphenhydramine HCl	Syringe-Needle [a]	12	76
Doxycycline Hyclate	Capsules [b]	13	50
Doxycycline Hyclate	Powder [b]	31	27
Halothane	Liquid	12	67
Mannitol	Injection-Solution	10	66
Morphine Sulfate	Syringe-Needle [c]	13	89
Naloxone HCl	Injection-Solution	10	77
Oxacillin Sodium	Powder	13	56
Potassium Iodide	Tablets [d]	12	69
Sodium Bicarbonate	Injection-Solution	37	55
Sodium Chloride	Irrigation [e]	16	72
Sodium Nitrite	Injection-Solution	10	89
Sodium Thiosulfate	Injection-Solution	14	131

Cefoperazone Sodium	Powder	4	46	Assay
Cephapirin Sodium	Powder	13	74	Potency
Cimetidine HCl	Injection-Solution [c]	7	42	Assay
Dextrose (5%)	Injection-Solution	22	65	Assay; Appearance [i]
Flurazepam HCl	Capsules	3	35	Appearance
Morphine Sulfate	Autoinjector [d]	3	32	Degradant
Ophthalmic Irrigating	Solution	6	52	Low pH
Pancuronium Bromide	Injection-Solution	13	79	Assay (1)
Ringer's, Lactated and Dextrose	Injection-Solution	13	53	Assay [k] ; Assay, Appearance
Sodium Chloride	Injection-Solution [e]	41	50	Assay; pH
Sodium Polystyrene Sulfonate	Powder	3	55	Water Content
Sulfadiazine Silver	Cream	37	57	High pH & Assay
Tetracycline HCl	Capsules	11	50	Dissolution ; Degradant
Thiopental Sodium	Powder	12	54	Low pH ; Appearance

SLEP Participants

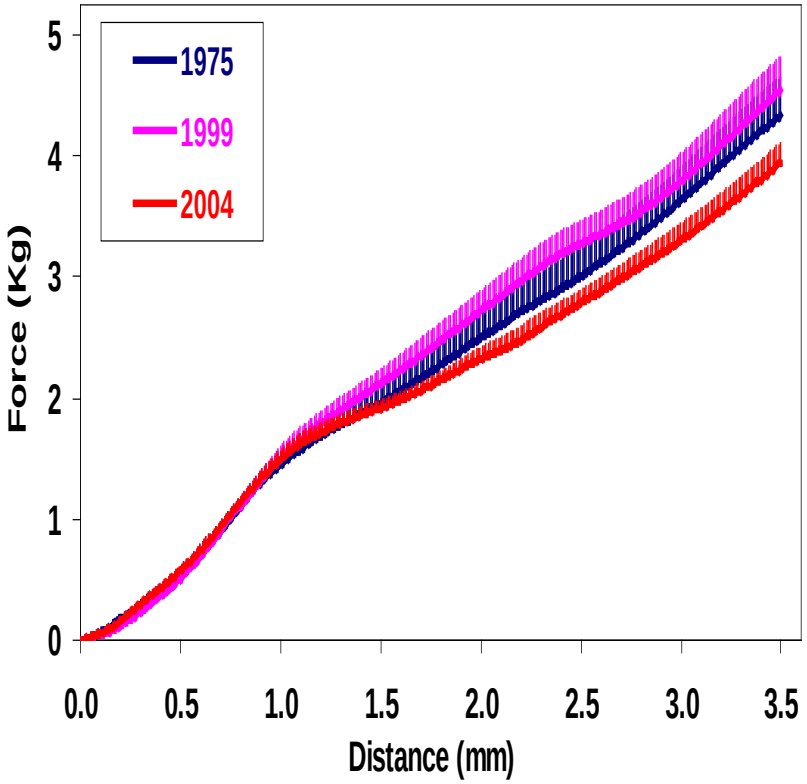
- Current DoD participants
  - US Army
  - US Air Force
  - US Navy
  - US Marines
- CDC/Strategic National Stockpile (SNS) – since 2004
- Dept. of Veterans Affairs (VA) – since 2005
- Only Federal agencies that sign an MOA with DOD may participate in SLEP

SLEP Challenges

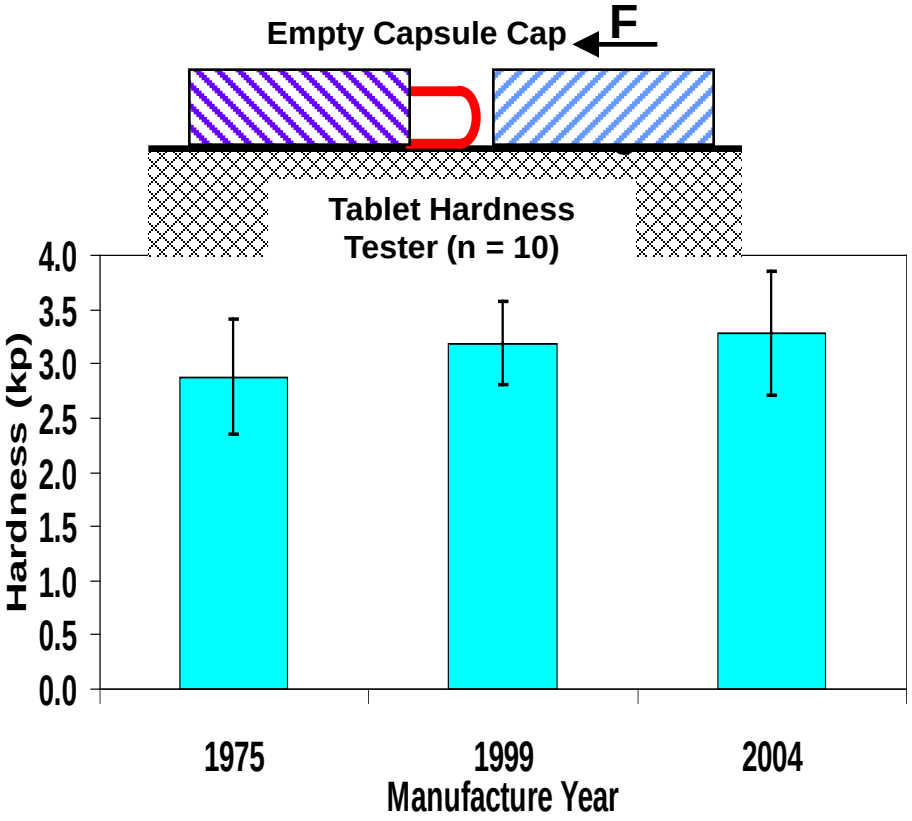
- Protocols/Procedures
- References standards
- Specialized equipment
- Lab research when needed
- Record keeping
- Knowledge Management

FDA Shelf Life Research Example

Force-Displacement



Cap Crushing Strength



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

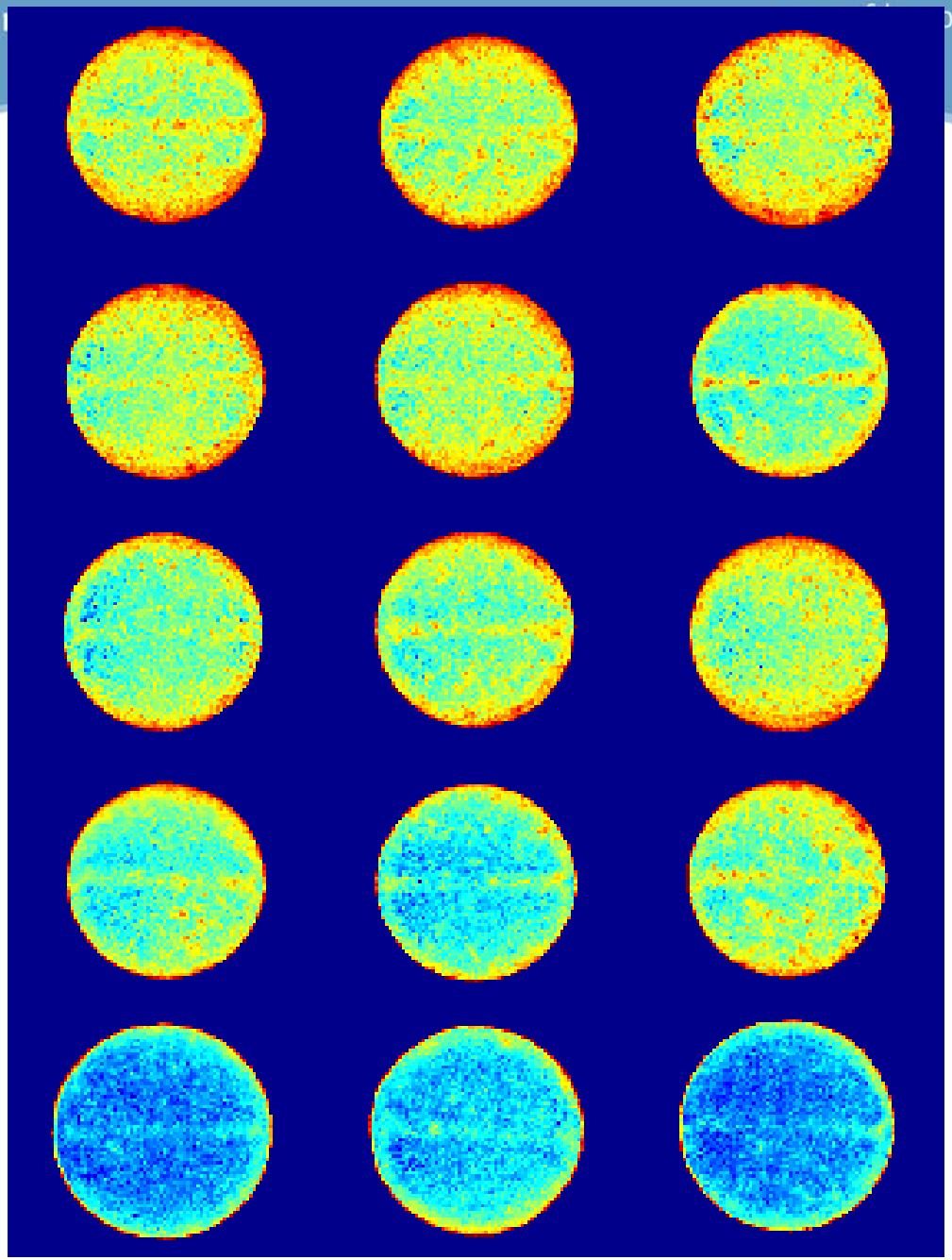
Original packaging tablets
Time 0

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