

Mylan's Unique Formulation and Process for the Consistent Production of a Potent, Uniform and Stable Levothyroxine Sodium Product

**David J. Wargo, R.Ph., Ph.D.
Senior Director, Product Development
Mylan Pharmaceuticals, Inc.**

October 4, 2006



MYLAN®

Federal Register Notice (62 FR 43535)

- Levothyroxine Sodium products declared “new drugs” August 14, 1997.
 - Medically necessary NTI drug with no alternative therapeutic drug substitute.
 - Purported problems with existing products.
 - AEs with same brands or after switching brands
 - Sub- and Super-potency potential
 - Multiple instances of low potency/stability failures
 - Formulation changes

New Product Quality Requirements

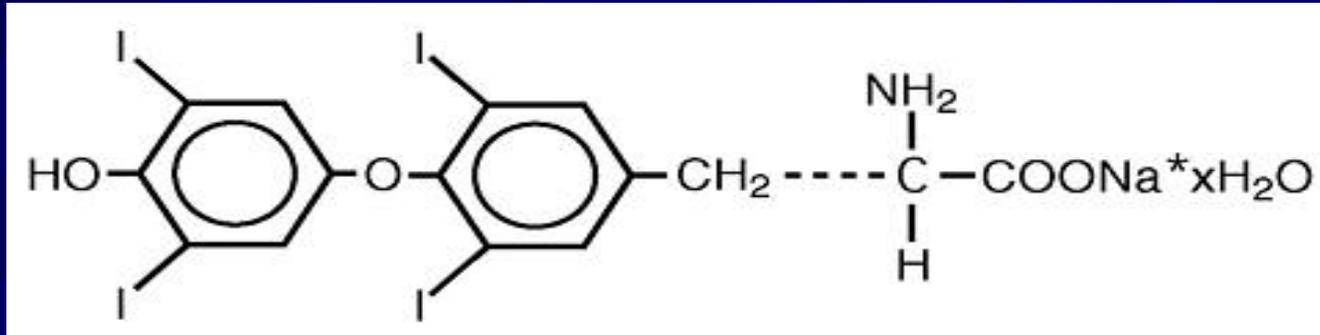
- **Potency**

- Target 100% of labeled potency
- Intra- and Inter- Lot-to-Lot Consistency
- Specifications for Content Uniformity
- Overlapping strengths

- **Stability**

- Maintained throughout product shelf-life

Levothyroxine Sodium



- Degrades quickly upon exposure to:
 - Light
 - Moisture
 - Oxygen
 - Carbohydrate excipients
- Low Dose / NTI Drug
 - “Guidance for Industry - Levothyroxine Sodium Tablets -- In Vivo Pharmacokinetic and Bioavailability Studies and In Vitro Dissolution Testing.” CDER, FDA. Feb 2001.

Development Goals

- Devise a robust formula and manufacturing process that:
 - Targets 100% of Label Claim Potency
 - Ensures Consistent Content Uniformity
 - Demonstrates Acceptable Stability
 - Potency
 - Purity
 - Water content

Mylan's Intellectual Property

- “Storage stable thyroxine active drug formulations and methods for their production”
(Inventors: David J. Wargo & Dwight D. Hanshew)
- U.S. Patent Numbers
 - 7,052,717
 - 6,936,274
 - 6,645,526
- provides a storage-stable dosage form of a thyroxine active drug composition which exhibits improved stability

Potency

July 1, 2003 – June 30, 2005

- 125 production batches manufactured
 - 11 strengths – 25 mcg to 300 mcg
 - Average potency: 99.2% (RSD 0.9%)
 - Potency Range: 95.8% – 104.6%
 - USP Limit: 90.0% - 110.0%
 - Mylan Proposed Limit: 95.0% - 105.0%

Potency

July 1, 2003 – June 30, 2005

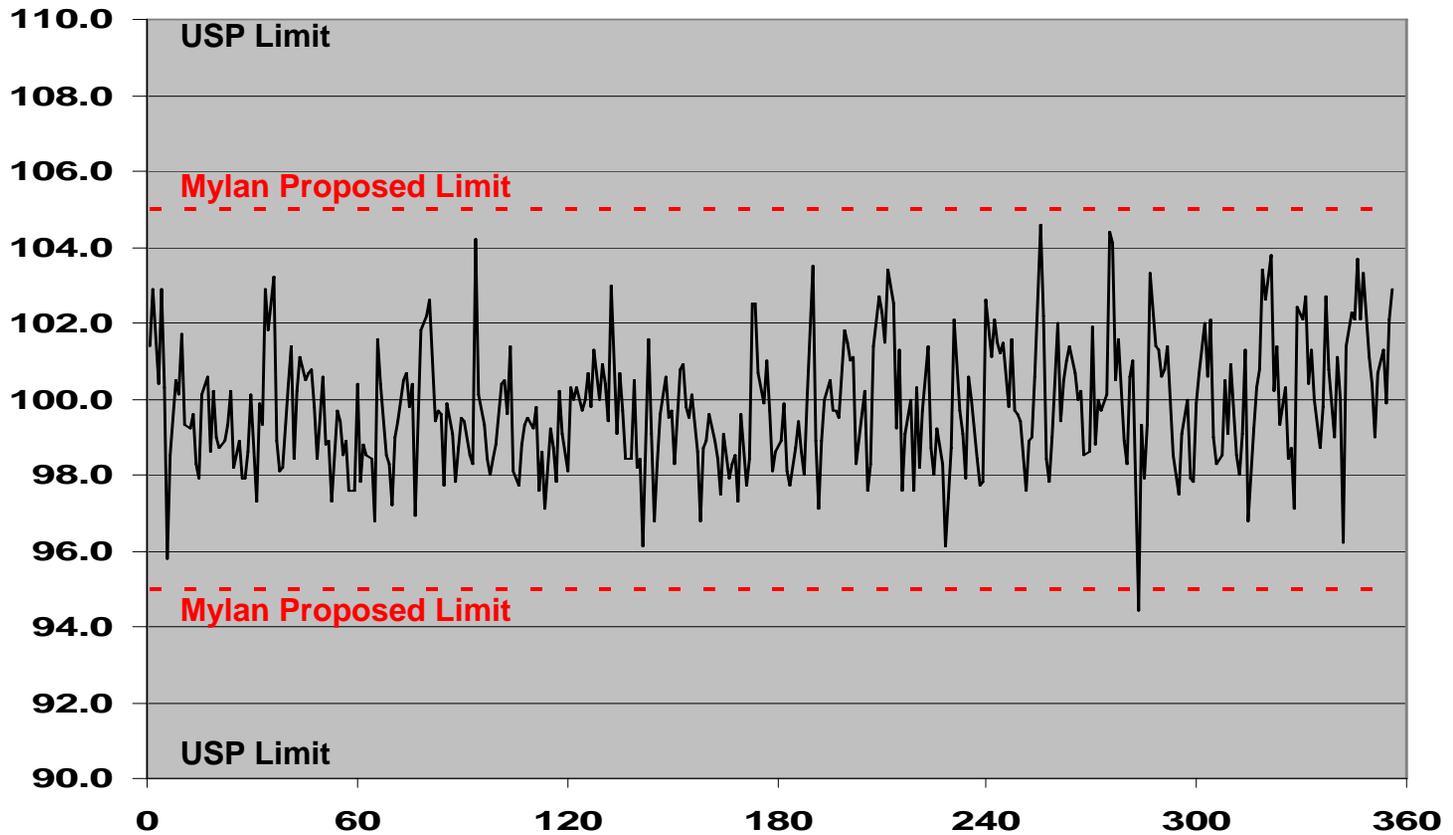
Strength (mcg)	# Lots	Assay 90.0% to 110.0%	
		Average	Range of Averages
25	11	99.2	95.8 - 101.7
50	23	99.4	97.3 - 101.4
75	15	99.2	97.7 - 101.4
88	6	98.4	96.1 - 101.6
100	18	99.4	97.3 - 102.5
112	10	98.7	96.1 - 102.1
125	13	99.9	97.6 - 104.6
150	9	100.6	97.9 - 103.3
175	5	98.9	96.8 - 101.3
200	6	100.2	97.1 - 102.7
300	9	101.4	96.2 - 103.7
	Total 125		



Potency

All Commercial Lots

Percent Assay



Batches Manufactured to Date



MYLAN®

Content Uniformity

July 1, 2003 – June 30, 2005

- 125 production batches manufactured
 - 11 strengths – 25 mcg to 300 mcg
 - Uniformity Mean: 100.6%
 - Mean Range of RSDs: 1.3% - 1.9%

Content Uniformity

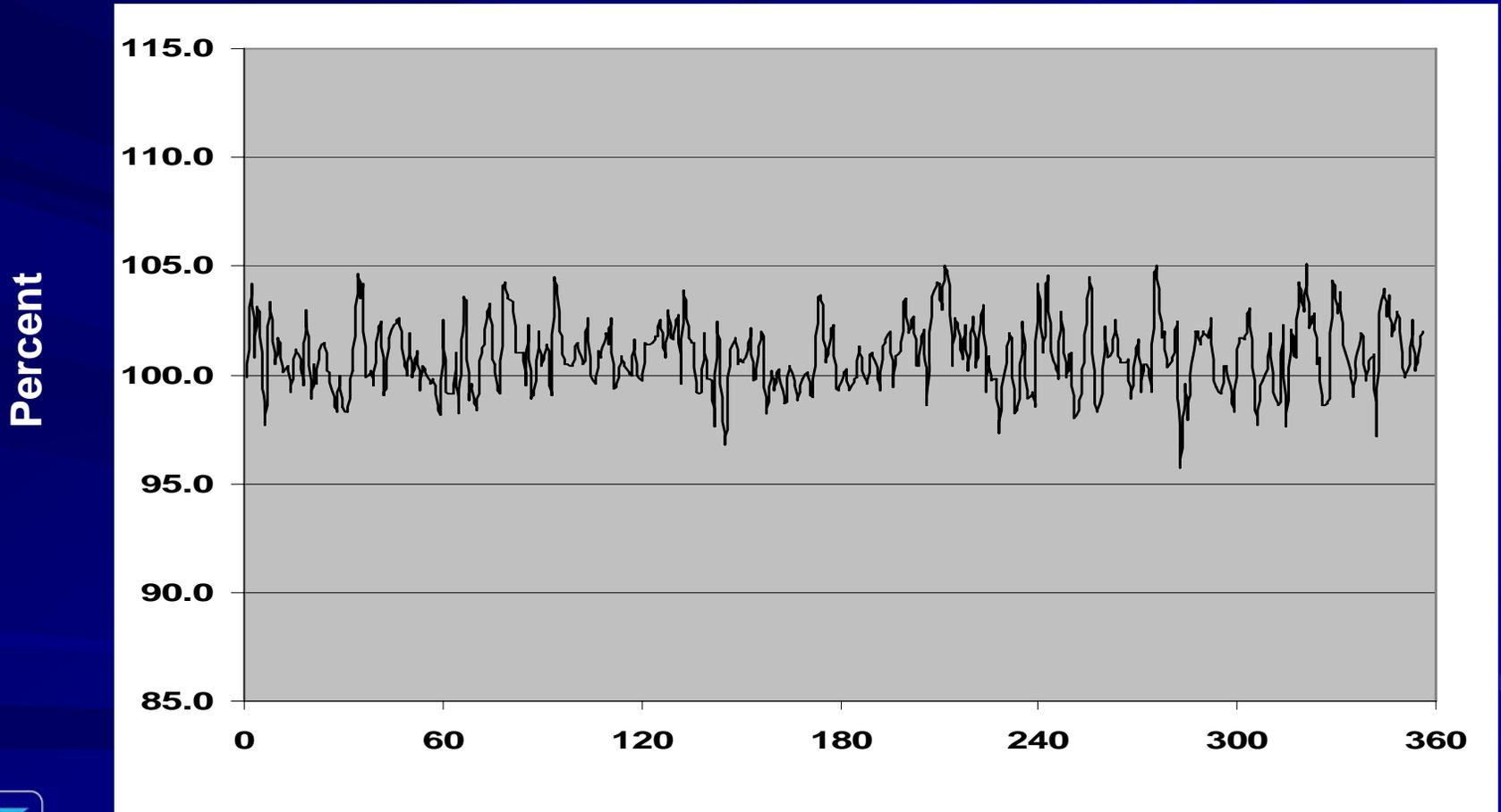
July 1, 2003 – June 30, 2005

Strength (mcg)	# Lots	Content Uniformity 85.0% to 115.0%; RSD NMT 6.0%			
		Mean %	Range of Means %	Mean RSD %	Range of RSDs %
25	11	100.6	97.8 - 103.4	1.7	0.9 - 2.7
50	23	100.7	98.2 - 102.6	1.4	0.7 - 2.3
75	15	101.0	99.6 - 102.6	1.3	0.8 - 2.0
88	6	99.3	96.8 - 102.4	1.8	0.7 - 3.2
100	18	100.7	99.0 - 103.7	1.6	1.2 - 2.7
112	10	99.9	97.3 - 101.9	1.6	1.0 - 2.2
125	13	100.5	98.1 - 104.5	1.5	1.0 - 2.2
150	9	101.0	97.9 - 102.5	1.6	0.9 - 2.4
175	5	99.9	97.6 - 102.3	1.5	1.1 - 1.9
200	6	101.3	98.6 - 104.3	1.5	0.9 - 2.6
300	9	101.9	97.2 - 104.0	1.9	1.2 - 3.3
	Total 125				



Content Uniformity

All Commercial Lots



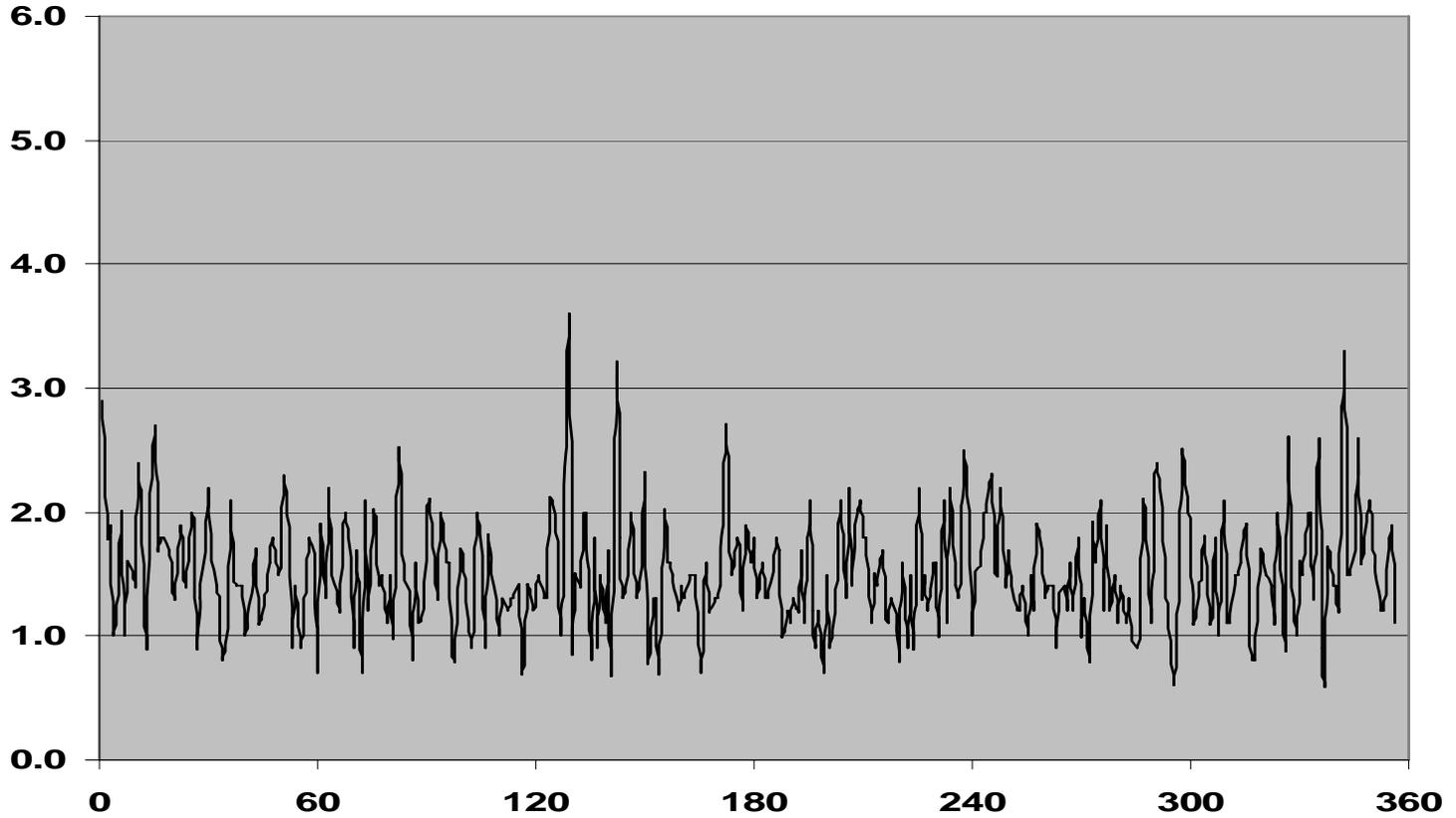
Batches Manufactured to Date



MYLAN®

Content Uniformity All Commercial Lots

% RSD



Batches Manufactured to Date



MYLAN®

Stability

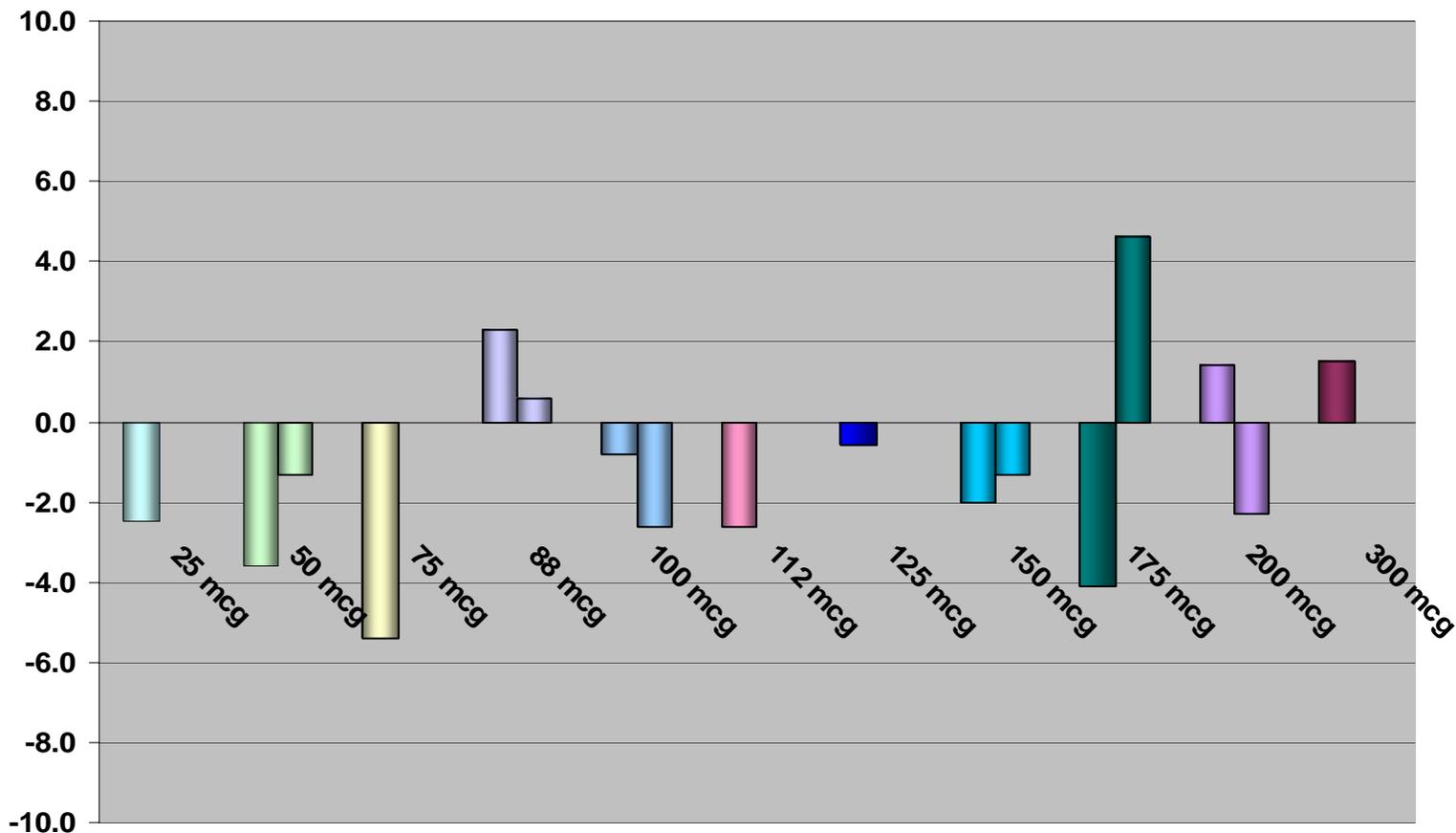
July 1, 2003 – June 30, 2005

- 125 production batches manufactured between July 1, 2003 and June 30, 2005
- 41 batches placed into a long term stability program
 - ICH storage conditions of 25°C and 60% RH
 - USP Limit: 90.0% - 110.0%
 - Mylan Proposed Limit: 93.0% - 107.0%

Change in Potency at 18 Months

July 1, 2003 – June 30, 2005

% Change from Initial Potency



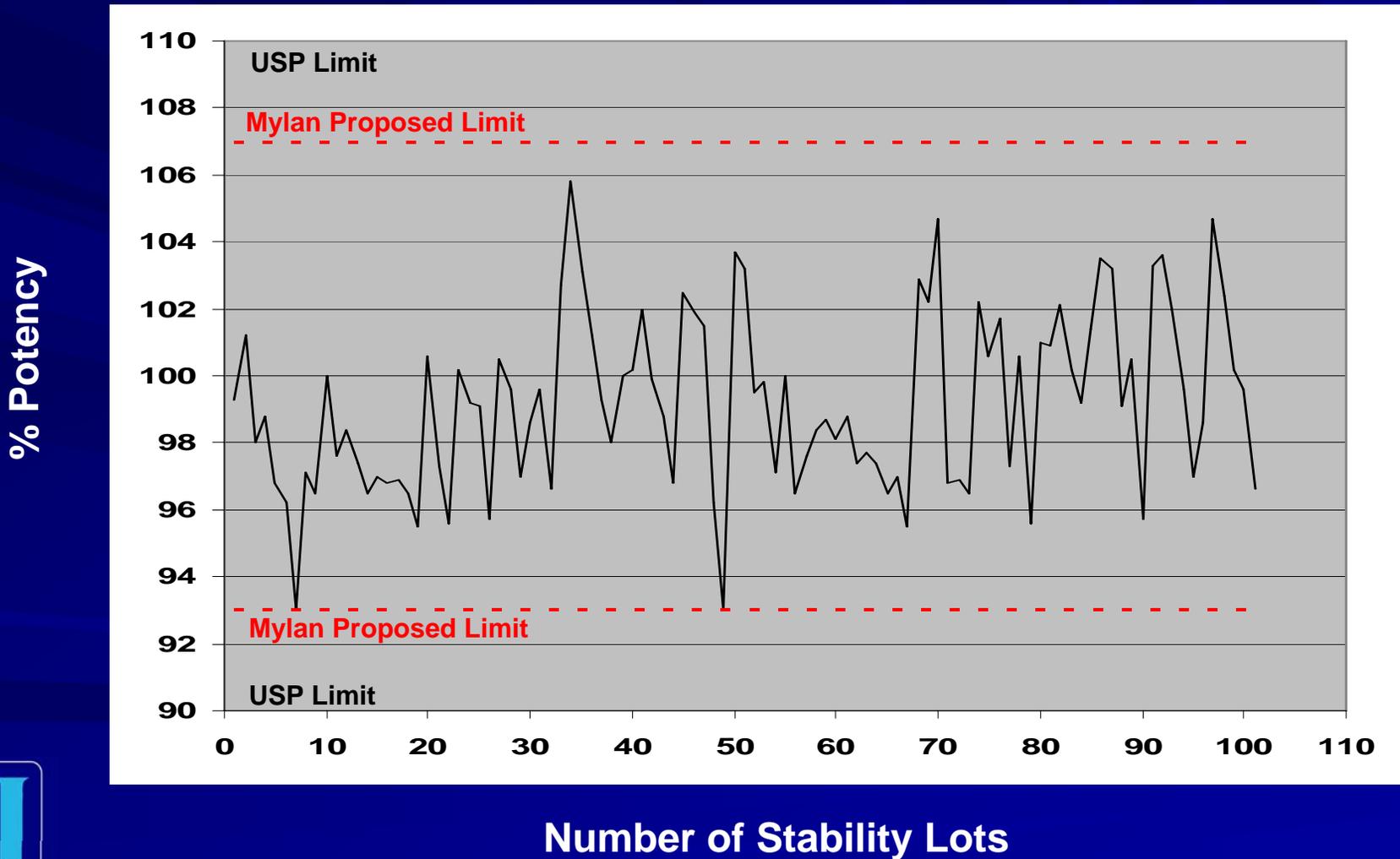
Tablet Strength



MYLAN®

Potency at 18 Months

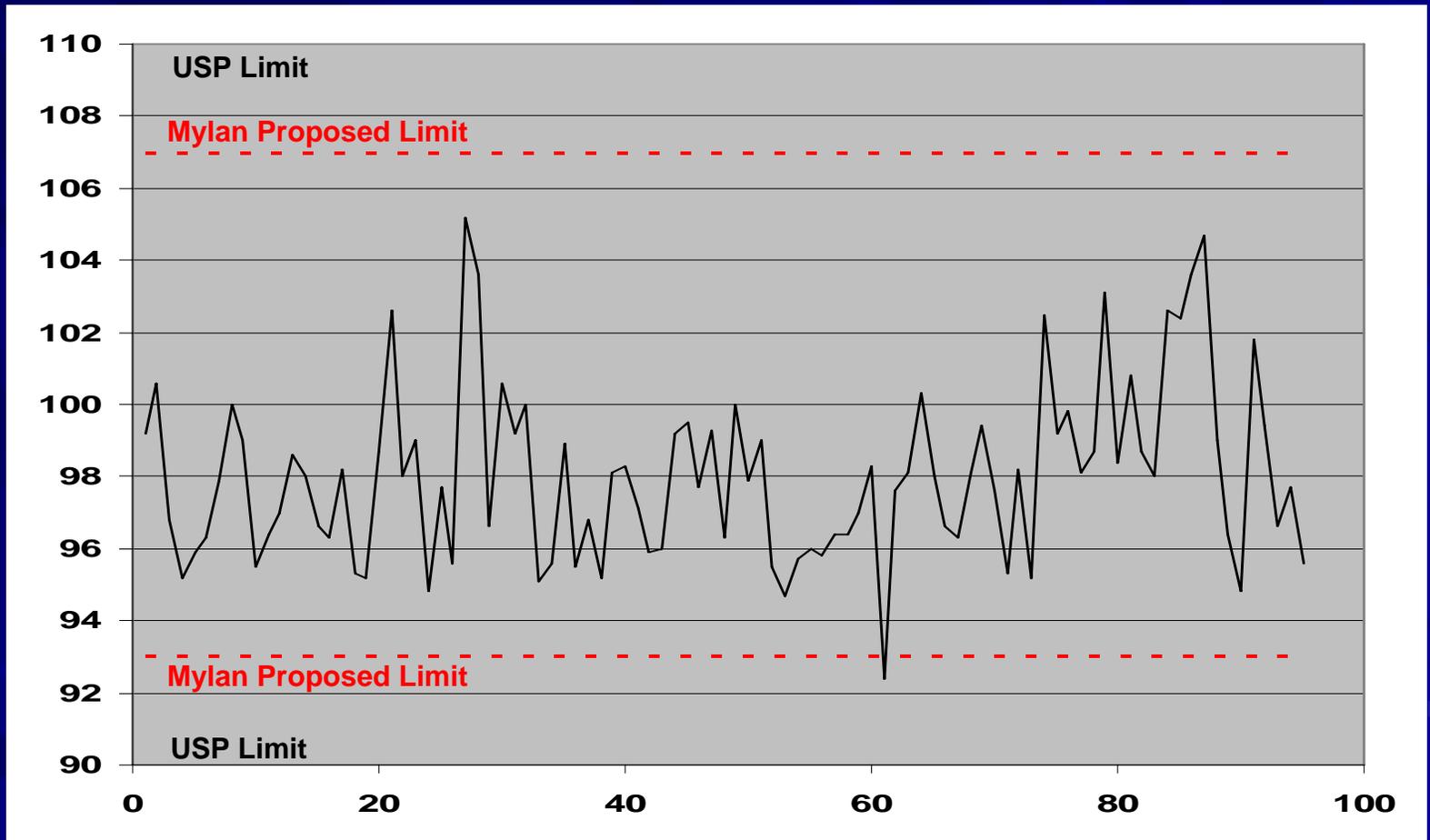
All Commercial Stability Lots



Potency at 24 Months

All Commercial Stability Lots

% Potency



Number of Stability Lots



MYLAN®

Mylan's Complaint History for Levothyroxine Sodium Tablets

Complaint Type	# Cases (% Total Cases)	# Cases as a Percent of TRx (% TRx)
	through June 2006	TRx = 18,993,463* through June 2006
Total # Cases	130	0.00068%
AEs only	77 (59.2%)	0.00041%
QCs only	48 (36.9%)	0.00025%
SAEs	7 (5.4%)	0.00004%
Deaths	0	0

*IMS monthly data for Total Prescriptions Dispensed for Mylan Levothyroxine from product approval through June 2006.



Summary

- A significant body of data demonstrates Mylan's ability to consistently produce Levothyroxine Sodium Tablets that are **potent**, **uniform** and **stable** via a controlled manufacturing process.
- Mylan agrees that all Levothyroxine Sodium Products should be held to high standards for these quality attributes.

Mylan Recommendations to FDA

- Mylan proposes that all approved Levothyroxine Sodium Products should comply with:
 - 95.0% - 105.0% potency specification at time of release.
 - 93.0% - 107.0% potency specification during shelf life.
 - Minimum 18 month shelf life.