Large N Analysis

For analyzing Uniform Dosage Units

Paul Vahey

Facilitator

PhARMA Expert Team

Dennis Sandell, PhD
PhRMA CM&C Statistics Expert Team, AstraZeneca, Lund, Sweden

Kim Vukovinsky
PhRMA CM&C Statistics Expert Team, Pfizer, Groton, CT

Myron Diener
PhRMA CM&C Statistics Expert Team, sanofi aventis Group, Kansas City, MO

Jeff Hofer
PhRMA CM&C Statistics Expert Team, Eli Lilly & Company, Indianapolis, IN

James Pazdan
PhRMA CM&C Statistics Expert Team, Novartis, East Hanover, NJ

Joep Timmermans, PhD
PhRMA PAT Expert Team, Pfizer, Morris Plains, NJ

CU Acceptance Testing for Large N

- An alternative to the current requirements
- Remove the disincentive to measure the product with large sample sizes, that exists in the current requirement.

The Issue

- Zero Tolerance - the harmonized pharmacopeial test for uniformity of dosage units (UDU) specifies that no result is allowed outside 75-125 %LC.

- This may be reasonable for small sample sizes (10-30), but is not suitable for for the large samples (> 100).

- Potential stopper for PAT ?

Product and Process Assumptions

- Mean = 100 %LC
- Normal Distribution of concentrations
- Manufacturing Target = 85 -115 %LC
- Individual Dosage Limit = 75 – 125 %LC

Plan from July ‘04 meeting w/ FDA

- Operating Characteristics (OC) acceptance curves intersecting with USP<905> at 50%
- Flexiblility wrt sample size needed
- Simple one-tiered test preferred
- Move away from zero tolerance
- Publish in peer-reviewed journal:
  Drug Information Journal (2006), vol **40**, pp 337-44.

Comparing Blend Uniformity Tests

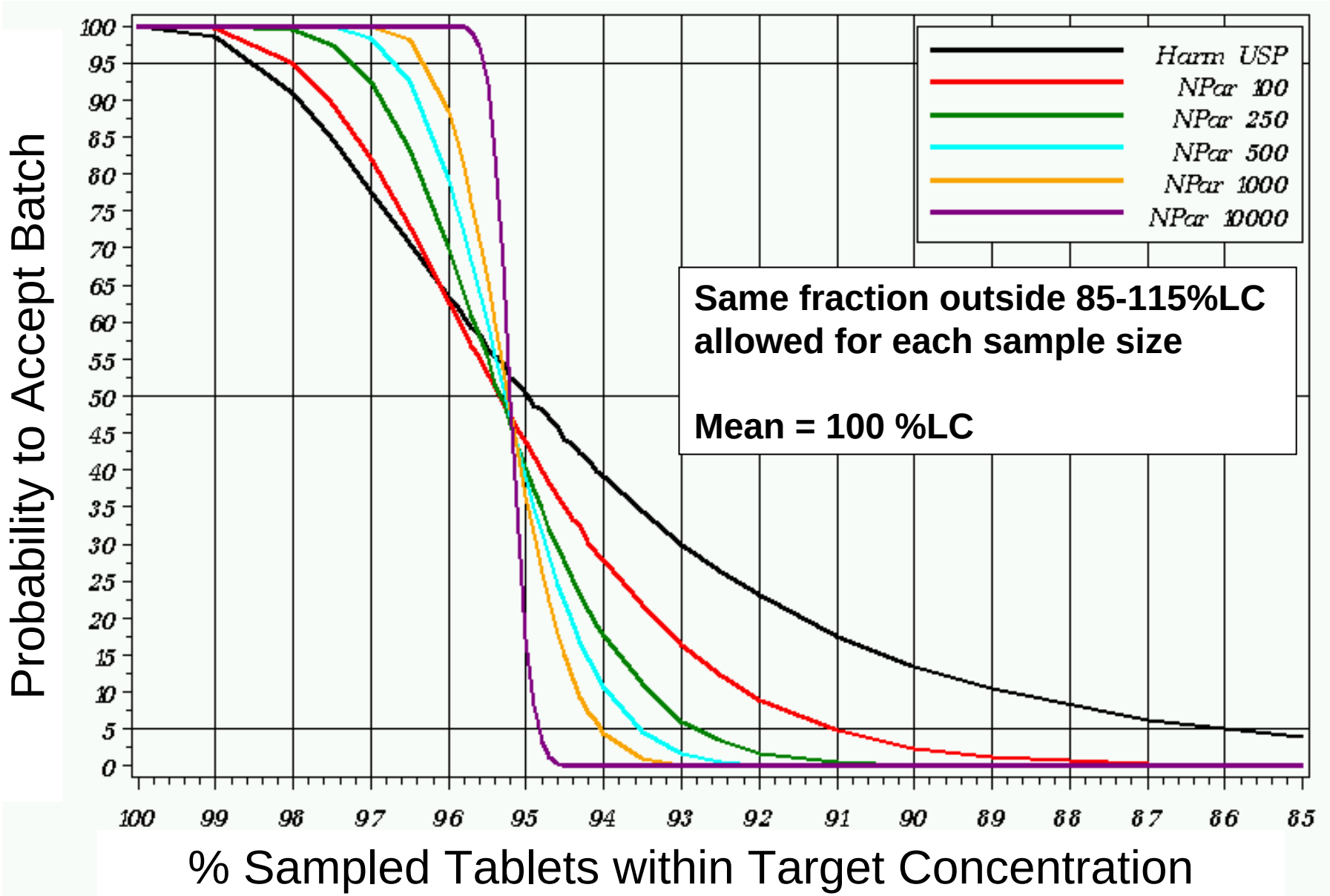
USP	PQRI	PhARMA
30 Tablets Randomly	7 Tablets x 20 Locations	N Tablets x Many Loc
Tier 1	**Tier 1**	**Tier 1**
10 Tablets Mean within Target All within Limits	60 Tablets Mean within Target All within Limits	All Sampled Units ≤ C outside Target
Tier 2	**Tier 2**	**Tier 2**
+ 20 Tablets Mean within Target All within Limits	+ 80 Tablets Mean within Target All within Limits	None

Proposed Test

- Collect the results for N dosage units
- Express each individual result in % Label Claim
- Count the number of results outside 85-115 %LC
- Batch complies if $\leq$ c units are outside 85-115 %LC

N	100	250	500	750	1000	2000	3000	4000	5000	10000
C	4	11	23	35	47	95	143	191	239	479

Vision for High N Sampling



Guidance for Industry: Investigating Out-of-Specification Test Results for Pharmaceutical Production – **CDER Oct. 2006**

Pg 12. Outlier tests have no applicability in cases where the variability in the product is what is being assessed, such as for content uniformity, dissolution, or release rate determinations. In these applications, a value perceived to be an outlier may in fact be an accurate result of a nonuniform product.

Pg 2. Process Analytical Technology (PAT) takes a different approach to quality assurance by using process controls and in-process data as the release specification instead of relying on single laboratory determinations to make batch acceptability decisions. **This guidance is not intended to address PAT approaches**, as routine in-process use of these methods might include other considerations.