



U.S. PHARMACOPEIA  
*The Standard of Quality*<sup>SM</sup>



# Sample Sizes in Uniformity Measurements – The Role of USP

Anthony J. DeStefano, Ph.D.  
Vice President, General Chapters  
US Pharmacopeia

Walter W. Hauck, Ph.D.  
Sr. Scientific Fellow  
US Pharmacopeia



## Part 1 - USP Overview (Tony)

- ▶ Standard-setting Process
- ▶ Role of General Chapters
- ▶ Observations on USP <905> and other Uniformity Chapters

## Part 2 – Statistics – And Ideas on Ways Forward (Walter)

- ▶ Concepts of Uniformity
- ▶ Test by Value (Parametric) vs. Test by Attribute (Counts)
- ▶ Accommodating Large N
- ▶ Possible Way Forward



# USP – An Overview

Quality Standards for Medicines, Dietary Supplements, and Food Ingredients

- ▶ Since 1820, nonprofit, private, independent, and self-funded
- ▶ Headquartered in Rockville, Maryland; 600+ employees; facilities in India, China, Switzerland, Brazil
- ▶ Establishes public standards and related programs that help ensure the quality, safety, and benefit of medicines and foods
- ▶ Expert volunteers are scientific decision-makers
- ▶ 21 Expert Committees with associated sub-committees and Expert Panels encompassing general chapters, small and large molecule monographs in the USP as well as committees for excipients (NF), dietary supplements and the Foods Chemical Codex. Approximately 650 volunteers involved with these efforts.

- 1) Industry or other interested parties (including Ad Hoc Advisory Panels) work with USP scientific staff expert to draft proposal. 
- 2) Scientific staff approves item for publication  
*Pharmacopeial Forum* for public review and comment 
- 3) Public comments received 
- 4) USP Scientific Liaison review and submits comments to the USP Expert Committee 
- 5) If no further revisions are need, Expert Committee ballots for official adoption 
- 6) Revised Standard Appears in the USP, NF, Supplement, or other official publication



# Required General Chapters (Below <1000>)

Quality Standards for Medicines, Dietary Supplements, and Food Ingredients

- ▶ When referenced in monographs, are procedures used by the FDA to demonstrate compliance to a specification
- ▶ Typically are procedures referenced in multiple monographs
  - Chapter status avoids duplication and simplifies updating
- ▶ Typically consist of method and procedure
  - Acceptance criteria – in the General Chapter or the monograph
- ▶ Can apply to monographs even if not specifically called out in the monograph
- ▶ Tests need to be verified by users for their applications



# Informational General Chapters (<1xxx>)

Quality Standards for Medicines, Dietary Supplements, and Food Ingredients

- ▶ Provide information or guidance
- ▶ Are not intended to be enforced by regulatory agencies
  - Some countries enforce the entire *USP–NF*
  - FDA reserves the right to enforce if appropriate
- ▶ Should be devoid of acceptance criteria to minimize misunderstandings
- ▶ May become required if referenced without disclaimer in a monograph or General Chapter numbered below <1000>



# General Notices, General Chapters, and Monographs

Quality Standards for Medicines, Dietary Supplements, and Food Ingredients

- ▶ General Notices contain requirements applicable throughout *USP–NF* unless superseded by a chapter or monograph
- ▶ General Chapters numbered below 1000 contain requirements applicable to monographs to which they apply
  - General Chapter requirements supersede General Notice requirements in case of conflict
- ▶ Monograph requirements are specific to the monograph in which they appear
  - Monograph requirements supersede General Notice and General Chapter requirements in case of conflict



- ▶ USP develops public standards.
- ▶ USP is typically silent on if, when, or how frequently to test.
- ▶ If tested - must pass – for its entire shelf life.
- ▶ USP, through its informational general chapters, can speak broadly to standards development.
  - Through PDG this can be harmonized
  - Help develop broad, globally-acceptable standards or best practices
  - Process-related (e.g., large N) issues are consistent with this approach – pharmacopeias can provide harmonized best practice approaches



- ▶ All are, and need to continue to be, public standards that can assess product quality throughout the drug's lifetime.
- ▶ Statistics in many cases are inconsistent, and some, like uniformity of dosage units, are compromises rather than best statistical approaches.
- ▶ The pharmaceutical industry could benefit from well-founded statistics that work for any sample size.
- ▶ The pharmacopeias could help provide a global approach for these statistics to increase consistency across the industry.



# Uniformity of Dosage Units – An Example

Quality Standards for Medicines, Dietary Supplements, and Food Ingredients

- ▶ A harmonized chapter across USP, EP and JP.
- ▶ A compromise in operating characteristics curves between a previous USP chapter and a Japanese proposal published in 1997.
- ▶ Indifference zone introduced as part of the compromise – no statistical rationale.
- ▶ Result is a harmonized chapter that is difficult to understand, probably overly complex, and doesn't scale to large sample size.
- ▶ FDA stimuli article in *Pharmaceutical Forum* 37(1) Jan/Feb 2011 recommends updating.



- ▶ USP is in the process of consolidating our statistical approaches across the pharmacopeia.
- ▶ UDU is clearly an outlier that should be addressed.
- ▶ Statistics that are consistent from small N (public standard) to large N (process control) would make sense.
- ▶ USP's goal:
  - Help enable good process control by embracing statistics that encourage the collection of more data rather than penalizing for it.
  - Harmonize the approach to the extent possible to minimize rework.



## Part II – Some Ideas On a Way Forward

Quality Standards for Medicines, Dietary Supplements, and Food Ingredients

- ▶ Some issues to discuss
- ▶ What does USP currently have for uniformity assessment
- ▶ A way forward?



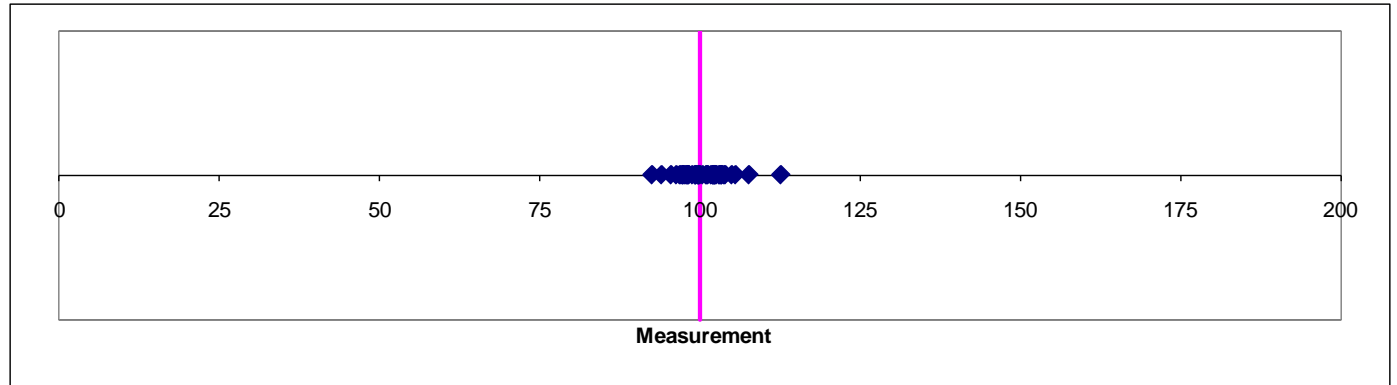
# Q1: Sample or Batch?

- ▶ USP standards apply to the sample
  - Inference to properties of the batch is not intended
  - All samples must meet requirements if tested
- ▶ Batch release is not in USP's purview
  - Company's responsibility to determine batch release criteria so potential samples have a sufficiently high probability of meeting USP standards should they be tested
- ▶ Regardless, it seems impossible to talk about and decide on compendial requirements without considering the operating characteristics of the compendial decision rule, a batch characteristic

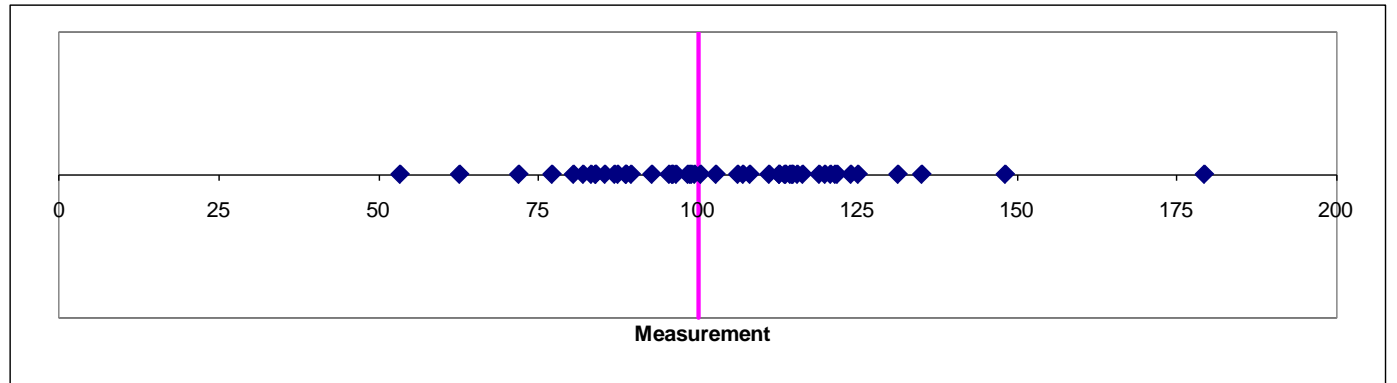


# Q2: What Do We Mean by “Uniformity”?

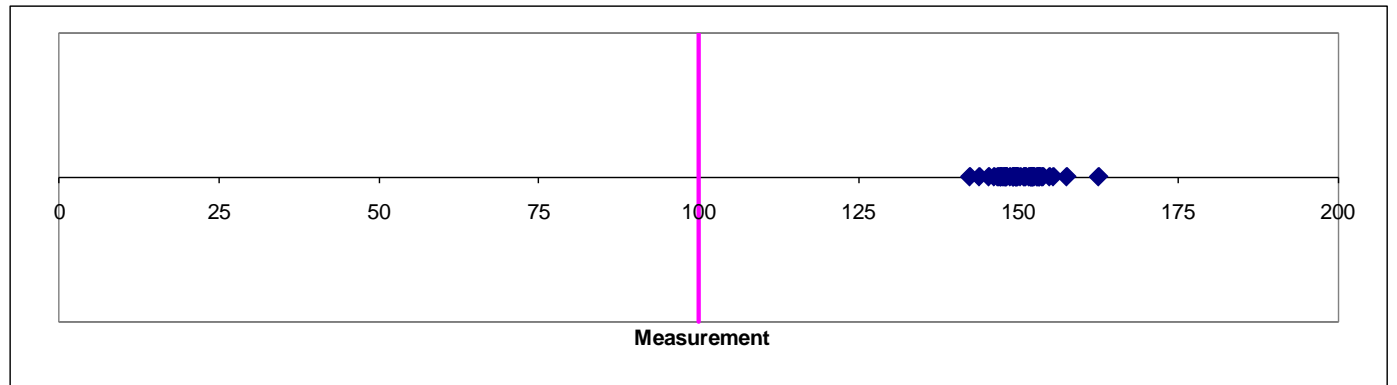
## 1. Ideal



## 2. Probably not OK



## 3. What about this?





1. Should Uniformity mean “consistency about the target” or just “consistency”?
2. Can choose “just consistency” if another part of the specification addresses whether on target or not
  - Want to avoid redundancy of tests
3. USP and EP approaches are all consistency about the target
  - Exception: EP for aerosols (just consistency)
4. For within-container uniformity, where there is less precedent within *USP-NF*, so “just consistency” could be an option going forward



## Q3: Within or Between?

1. Between: Examines uniformity of content of entire unit
  - Tablets and capsules are usual example
  - Can be content of entire bottle or canister
2. Within: Examines uniformity of content within a unit
  - Applicable to multi-dose containers
3. Combination of between and within: If take multiple samples from multiple multi-dose containers
  - This can be treated as Within if the between container-variability is small relative to within-container variability



## Q4: Parametric or Nonparametric (counts)?

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1. Parametric: Test by Value – use actual value of results
  - a. Mean and variance separate
  - b. Mean and variance combined  
Involves a mean-variance tradeoff  
e.g., parametric tolerance intervals (PTI),  
the basis for criteria in <905>
  
2. Nonparametric: Test by Attribute – use only whether in specified intervals
  - a. Counts within intervals about target  
Related to nonparametric tolerance intervals
  - b. Test by attribute makes less good use of the data than test by value  
Consequence is requirement for larger sample sizes for given properties
  
3. *USP-NF* also has mixtures of these



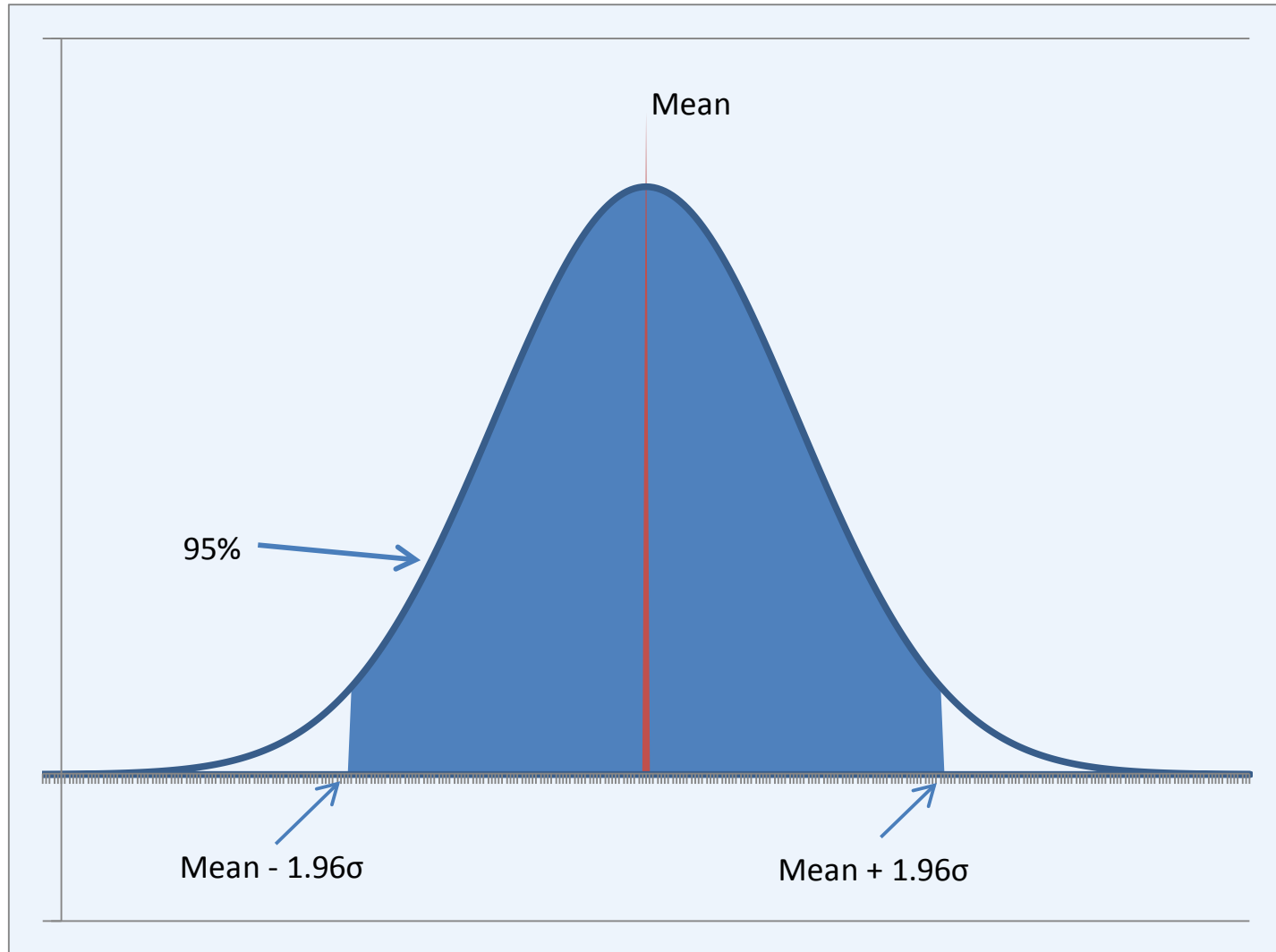
# What is a Tolerance Interval?

1. An estimate of an interval that covers a specified proportion of the underlying distribution the data came from
2. For normal distribution, general form of PTI is  $\bar{X} \pm kS$
3.  $k$  depends on sample size, confidence and coverage
  - Coverage – What % of the distribution to be covered
  - Confidence – how confident in the statement that are coverage the stated percentage of the distribution
  - $k$  will decrease, as  $N$  gets large, to normal values (e.g., 1.96 for 95% coverage)



# What is Being Estimated by a Tolerance Interval

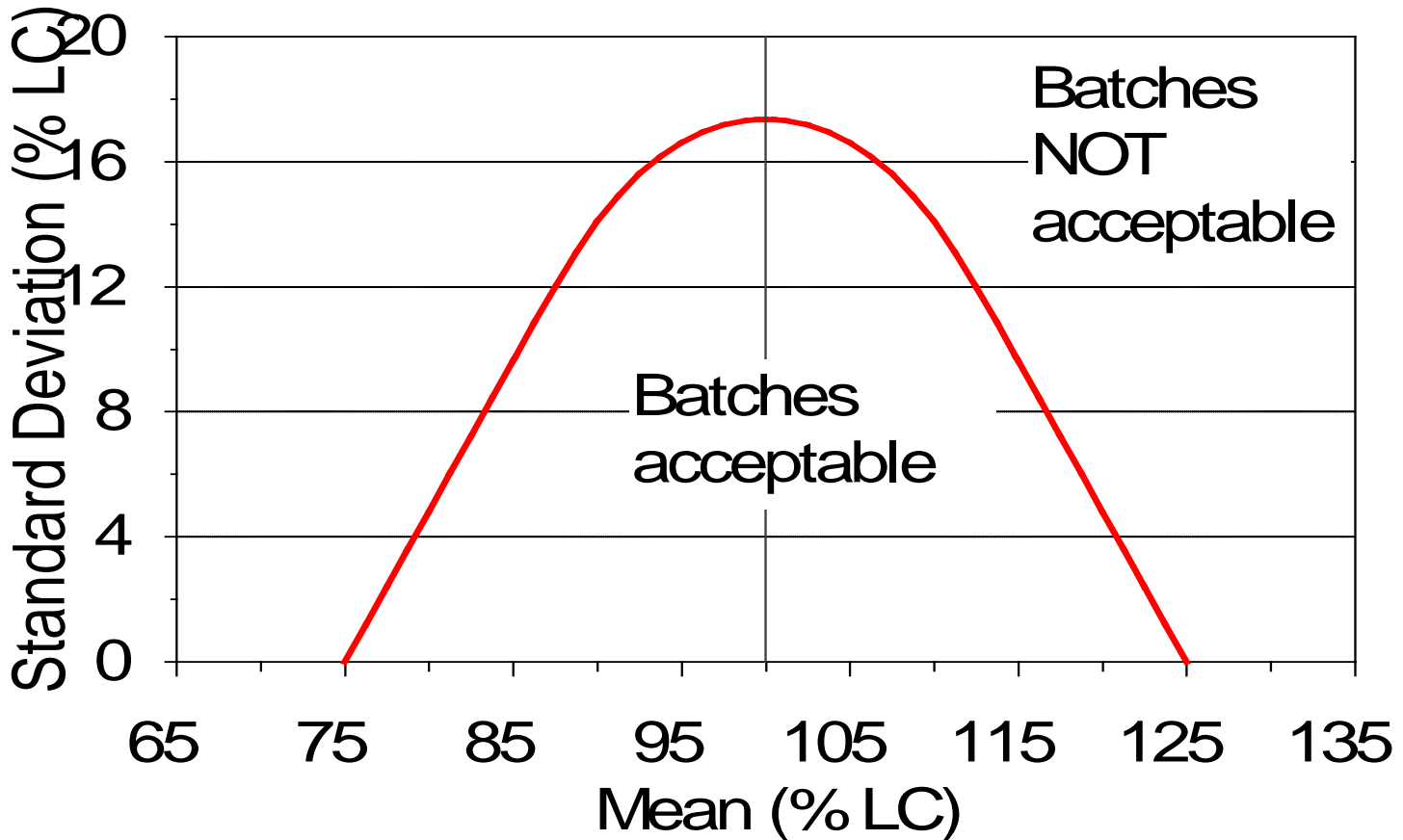
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# Example of Mean-Variance Tradeoff

85% coverage within 75%/125% of label claim





## Q5: Include a Zero-Tolerance Criterion (ZTC)?

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1. ZTC – no values permitted outside some interval
2. Example of ZTC from <3>:  
“No Assay result is outside the range 90% - 110% of the product label claim ...”
3. ZTC cause problems for companies as they can be held to these even when not testing to compendial compliance
4. General principle – Avoid approaches that penalize collection of additional data
5. Recommendations for ZTC
  - a. DON'T use to control variability
  - b. DO use to control for values that would be unacceptable if got to a patient
  - c. Can also think of it as limiting occurrence of values that should be rare (as opposed to never)



# What Does USP/NF Currently Contain?

Quality Standards for Medicines, Dietary Supplements, and Food Ingredients

Chapter		T or C?	B or W?	Criterion	ZTC?
<3> proposed	Tubes	Both	Both	%CV	Yes
<601>	Delivered Dose (DDU ) (MDI/DPI)	T	B	Count	Yes
<601>	DDU (nasal spray)	T	Both	Count	Yes
<601>	DDU (over entire contents)	T	Both	Count	Yes
<698>	Deliverable Volume	T	B	Count + Mean	Yes
<905>	Tablets, capsules, etc.	T	B	PTI	Yes
<909> proposed	Bottles	T	Both	PTI	TBD

T or C: About Target of just Consistency?

B or W: Between or Within?

ZTC: Includes a zero tolerance criterion? (in addition to Criterion)



# Accommodating Large N

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1. A variety of approaches have been suggested based on PTI and counting tests
2. General idea is to fix some property of the test and vary the acceptance criteria with N
3. For example, for PTI, EP proposal retains 84% confidence and 91% coverage (approximate properties of <905> PTI test)
  - a. Single stage test
  - b.  $k$  decreases with N; e.g.,  $k = 1.70$  at  $N = 10,000$
4. Replace ZTC with a criterion for “rare” that allows some occurrences for large N
  - May still mean 0 occurrences for compendial sample sizes



# A Possible Way Forward for USP

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1. Decide on an approach to be used consistently for all tests for between-container uniformity
  - e.g., PTI
2. Decide on an approach to be used consistently for all tests for within-container uniformity
  - e.g., %CV
3. The chosen approaches can be:
  - One or two stage
  - Can keep a criterion for “rare” values;  
i.e., allows for some values outside limits for large N
4. Prepare a >1000 chapter that covers the acceptance criteria for both approaches for a range of sample sizes
  - Range to include values used in Chapters
5. Rewrite existing <1000 chapters (public standards) using uniformity tests to match with the new chapter



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*Thank You*