



Tablet Scoring: Discussion of Guidance and Compendial Development

ACPS-CP
August 9, 2012

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Introduction and Overview

- Historically, scoring is not a high regulatory priority in terms of risk management
 - Splitting is an atypical practice not regulated by FDA
- Flat pricing policies leads to more frequent splitting
 - It is apparently mandated in some instances
- FDA sees complaints and confusion from patients and pharmacists

Introduction and Overview

- FDA seeks and evaluates data, leading to Draft Guidance
- FDA also working with USP on a General Chapter building on other compendia such as European Pharmacopoeia (EP)

Introduction and Overview

- This can be topic of extremes
 - All segments must exactly meet all criteria for new strength
 - Likely not practical or appropriate, especially considering manual manipulation
 - It does not matter
 - Quality standard linked to demonstration of safety and efficacy
 - One standard for all brands and generics
- FDA strived for middle ground, building off QbD concepts
 - Bisect bar implies the tablet can be broken
 - A split bisected 20 mg tablet should approximately yield 2, 10 mg segments
- Desired some means to communicate to health care practitioners which products were evaluated to aid in their splitting decisions...
- Thus, the “functional score” concept and label was born

Agenda

- Tablet Scoring: Discussion of Guidance and Compendial Development
 - Russell Wesdyk (FDA)
- Tablet Scoring - Background
 - Anthony DeStefano (USP)
- Tablet Scoring – Current USP Status
 - Anthony DeStefano (USP)
- Testing of Functionally Scored Tablets – Statistical Considerations
 - Alex Viehmann (FDA)
- Overview of the FDA Draft Guidance
 - Russell Wesdyk (FDA)
- Topic Wrap-Up and Questions to ACPS-CP
 - Russell Wesdyk (FDA)



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Food and Drug Administration
Advisory Committee for Pharmaceutical
Sciences and Clinical Pharmacology
August 9, 2012

Tablet Scoring - Background

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- ▶ Tablets intended for oral use are the most common dosage form in the US and many bear score marks
- ▶ Patients split tablets for many reasons including to adjust the dose, to ease swallowing and to save money
- ▶ The presence of a score mark implies to a patient that a tablet can be split
 - Patients expect that the split tablet will provide the same quality, safety and efficacy profile as a whole tablet of equivalent dose
- ▶ Currently no standards for the performance of subdivisions of scored tablets



- ▶ Issues with compliance, drug acquisition costs and patient acceptance discussed in 1999
 - Relationship between tablet splitting and compliance, drug acquisition cost, and patient acceptance. Fawell, et al., *Am J Health Syst Pharm.* 1999;56(24):2542-2545
- ▶ Issues extensively considered in Europe by the Dutch National Institute for Public Health and the Environment (RIVM) and reviewed in a paper published in 2002
 - Breaking of scored tablets: a review. Van Santen et al., *Eur J Pharm Biopharm.* 2002;53:139-145)



- ▶ *Journal of the APhA*: March/April 2002
- ▶ Title
 - Lack of Medication Dose Uniformity in Commonly Split Tablets
- ▶ Authors
 - Jaja Teng, Clara Song, Roger Williams, James Polli
- ▶ Trained analyst used single edge razor blade to split tablets from 11 products and resulting uniformity studied



Results from the JAPhA Study – Uniformity Test

Quality Standards for Medicines, Dietary Supplements, and Food Ingredients

- ▶ Protocol
 - Select 30 tablets from each of 11 products (4 scored, 7 unscored)
 - Weigh 10 tablets
 - Split in half and weigh each half (razor blade)
 - Pass: At most one of 20 halves outside the range 85-115% (but within the range of 75-125%) of expected weight with a %RSD of 10% or less
 - If two outside of 85%-115% (but within 75%-125%), repeat with 20 more tablets. Pass: All 40 additional halves must be within 85%-115%, with %RSD for all 60 halves $\leq 10\%$
 - Fail if 3 of the first 20 halves were outside of 85%-115% or if any half tablet was outside the range of 75%-125%
- ▶ Result
 - 1 of 4 scored tablets passed the uniformity test
 - 2 of 7 unscored tablets passed
 - No correlation with scoring, tablet shape, or tablet surface flatness
 - Hand splitting of 3 scored tablets soft enough to do this was worse
- ▶ Conclusion: Strong suggestion that split tablets (scored or unscored) generally fail to meet expectations for weight variation



- ▶ USP Pharmacopeial Forum, Vol 35(6); Nov-Dec 2009, pp 1598-1611
- ▶ Title: *Pharmacopeial Standards for the Subdivision Characteristics of Scored Tablets*
- ▶ Authors: Geoff Green, Carolyn Berg, James Polli, Dirk Barends
- ▶ Top-line Observations
 - Presence of a score mark implies the tablet can be subdivided into smaller doses
 - Extensive literature showing scored tablets can be difficult to break and often display large variations in mass of the subdivided parts
 - In a Dutch study, 39% of patients dissatisfied with subdivision characteristics and poorly functioning score lines were perceived as a quality defect and could lead to reduced patient compliance with medication



- ▶ The available literature suggested three areas of importance
 - Accuracy of the splitting process
 - Ease of splitting scored tablets
 - Loss of mass of split scored tablets
- ▶ Criteria
 - Studies conducted in US laboratories
 - Included reports about measuring subdivision accuracy for scored tablets
- ▶ 8 studies satisfied both requirements
 - In 6 studies tablets were obtained commercially
 - In 1 study tablets were donated by the manufacturer
 - In 1 study professional samples were used



Accuracy of Subdivision

Quality Standards for Medicines, Dietary Supplements, and Food Ingredients

- ▶ 4 studies tested accuracy of subdivision using manual splitting
- ▶ 6 studies tested accuracy of subdivision using a splitting device
- ▶ 7 of 8 studies adapted USP Uniformity of Dosage Units <905> weight variation criteria: all within 85%-115% of label claim and %RSD \leq 6%
- ▶ Results
- ▶ Manually split – weight variation failed in 5 of 6 sets of tablets studied - % of parts >115% of target for these 5 ranged between 12% and 55%
- ▶ Splitter split – 18 of 37 tablet sets studied showed % of parts >115% of target ranged from 2% to 45%
- ▶ Conclusions
 - The situation is comparable to that reported in other parts of the world
 - For many tablets on the US market, significant variation can occur in the mass of subdivided tablet parts, regardless of the splitting method or person
 - Tablet splitter helps, but accuracy is still not acceptable for scored tablets – results vary widely depending on user and device
 - The presence of a score mark on a tablet does not necessarily imply the tablet can be split into accurate partial doses.



Accuracy – Manually Split – US Market

Quality Standards for Medicines, Dietary Supplements, and Food Ingredients

Reference	Panel	Products	Tablet Shape	Result (% Parts > 115% of ideal mass)
Matuschka and Graves 2001	Volunteers	Sertraline 100 mg	Capsule	0
Wilson et al. 2001	Elderly Diabetics	Micronized gluburide 3 mg	Oval	12
McDevitt et al. 2002	Volunteers	HydroDIURIL 25mg	Round	24
Teng, et al. 2002	Trained Pharmacy Student	HydroDIURIL 50 mg		40
		Gliburide 5 mg	Rectangle	15
		Oretic 50 mg	Round	55

Table 2. Accuracy of Subdivision of Scored Tablets on US Market Split by Splitter

Author	Panel and Splitting Device	Products	Tablet Shape(1)	Result (% of parts > 115% of ideal mass)	
Horn et al. 1999	Pharmacists	Catapres 0.1 mg	Round	12	
		Clonidine 0.1 mg	Round	43	
	EZ Dose tablet cutter	Capoten 12.5 mg	Capsule	2	
		Sertraline 50 mg	Capsule	3	
	Pharmacists	Tegretol 100 mg	Round	32	
		Catapres 0.1 mg	Round	22	
	Health Care Logistics tablet cutter	Clonidine 0.1 mg	Round	42	
		Capoten 12.5 mg	Capsule	26	
		Amlodipine 5 mg	Octagon (modified)	17	
		Tenormin 25 mg	Round	18	
	Matuschka and Graves 2001	Volunteers. LGS Health Products pill cutter	Sertraline 50 mg	Capsule	0
			Tegretol 100 mg	Round	9
Sertraline 100 mg			Capsule	0	
Rosenberg et al. 2002 (b)	Pharmacists Splitter not specified	Buspar 5 mg	Modified Rectangle	3	
		Captopril 6.25 mg	Capsule	13	
		Doxazosin (Apotex) 0.5 mg	Capsule	10	
		Cardura 2 mg	Round	0	
		Luvox 50 mg	Oval	0	
		Glipizide 2.5 mg	Round	13	
		Hydrochlorothiazide 12.5 mg	Round	0	

		Metoprolol (Caraco) 25 mg	Capsule	7
		Metoprolol (Mylan)	Round	0
		Toprol XL 25 mg	Oval	0
		Oxybutynin 2.5 mg	Round	13
		Zoloft 25 mg	Capsule	3
		Zoloft Sample A 50 mg	Capsule	0
		Zoloft Sample B 50 mg	Capsule	0
		Trazodone (Geneva) 25 mg	Round	14
		Trazodone (Mutual) 25 mg	Round	0
		Effexor 25 mg	Pentagon	45
		Coumadin 0.5 mg	Round	0
Teng et al. 2002	Trained pharmacy student	Hydrodiuril 50 mg	Round	15
		Glyburide 5 mg	Rectangle	15
		Oretic 25 mg	Round	45
		Oretic 50 mg	Round	20
	Razor blade	Zoloft 100 mg	Capsule	0
Polli et al. 2003	Trained pharmacy student	Coumadin 5 mg—orientation 1	Round	0
		Coumadin 5 mg—orientation 2	Round	0
	ACE-LIFE Pill Cutter	Furosemide 40 mg—orientation 1	Round	0
		Furosemide 40 mg—orientation 2	Round	0
		Glipizide 10 mg	Round	0
		Metoprolol 50 mg	Capsule	0
		Zoloft 100 mg	Capsule	0

Peek et al. 2002	Elderly patients using cutter A; brand not specified	Metoprolol 50 mg	Capsule	Tablet portions deviated 9% from their intended ideal mass
	Elderly patients using cutter A; brand not specified	Warfarin 5 mg	Round	Tablet portions deviated 9% from their intended ideal mass
	Elderly patients using cutter B; brand not specified	Metoprolol 50 mg	Capsule	Tablet portions deviated 20% from their intended ideal mass
	Elderly patients using cutter B; brand not specified	Warfarin 5 mg	Round	Tablet portions deviated 26% from their intended ideal mass

(a) All tablets single scored on one side only.

(b) Tablet mass reported for Rosenberg et al. in the "Products" column are the ideal half tablet mass.



- ▶ 4 of 8 studies reported data on loss of mass
- ▶ All tablets split in halves
- ▶ Loss of mass calculated by dividing total unaccounted for mass for all tablets split by the weight of all whole tablets
- ▶ Results:
 - Only 3 of 117 with average % loss of mass greater than 1%
- ▶ Conclusion
 - Consistent with other studies, most tablets, on average, lost less than 1% of the intact tablet mass upon subdivision

Table 3: Loss of Mass on Subdivision of Scored Tablets on US Market

Author	Panel	Splitting method (a)	Product	Percent Loss of Mass (b) (Range)
McDevitt et al. 1998	Volunteers	Manual	Hydrochlorothiazide 25 mg	1.06 (0 to 19.4)
Matuschka and Graves 2001	Volunteers	LGS Health Products Cutter	Sertraline 100 mg	0.08 (NR)
	Volunteers	Manual	Sertraline 100 mg	0.06 (NR)
Polli et al. 2003	Trained pharmacy student	ACE-LIFE tablet cutter	Coumadin 5 mg—orientation 1	0.0 (NR to 0.18)
			Coumadin 5 mg—orientation 2	0.5 (NR to 1.4)
			Furosemide 40 mg—orientation 1	0.8 (NR to 1.7)
			Furosemide 40 mg—orientation 2	1.3 (NR to 7.3)
			Glipizide 10 mg	0.08 (NR to 0.95)
			Metoprolol 50 mg	0.1 (NR to 0.4)
			Zoloft 100 mg	0.1 (NR to 0.3)
Teng et al. 2002	Trained individual in laboratory conditions	Razor blade	Zoloft (sertraline) 100 mg	0.4 (NR to 1.2)
			Glyburide 5 mg	2.6 (NR to 6.7)
			Hydrodiuril (hydrochlorothiazide) 50 mg	0.8 (NR to 3.0)
	Trained individual in laboratory conditions	Manu	Oretic (hydrochlorothiazide) 50 mg	0.8 (NR to 2.0)
			Glyburide 5 mg	0.4 (NR to 1.2)
			Hydrodiuril (hydrochlorothiazide) 50 mg	0.3 (NR to 0.7)
			Oretic (hydrochlorothiazide) 50 mg	0.4 (NR to 0.5)

(a) All tablets split into halves

 (b) Mean loss of mass calculated by dividing the total unaccounted mass for all tablets split by the sum of theoretical weight of all whole tablets.
 NR = Not reported.



- ▶ Assessment of individuals' ability to subdivide tablets regardless of accuracy or loss of mass
- ▶ Studied in detail by RIVM research group but only 2 of 8 US studies included this attribute
- ▶ Results
 - Wilson, et. al., elderly diabetics split glyburide tablets: 7.7 on 10 point visual analog scale
 - Teng et al., 50-mg hydrochlorothiazide tablets were “hard to split”
 - Net – very limited US data

- ▶ Shaynan W. Hill, Andrew S. Varker, Kelly Karlage and Paul B. Myrdal, *Journal of Managed Care Pharmacy*, 15(3), 2000; 253-261
- ▶ Examined drug content uniformity (HPLC Assay) and weight variation for six commonly split medications
 - Warfarin Na 5 mg, scored
 - Simvastatin 80 mg, not scored
 - Metoprolol succinate 200 mg, not scored
 - Metoprolol tartrate 25 mg, scored
 - Citalopram 40 mg, scored
 - Lisinopril 40 mg, not scored
- ▶ All split with tablet splitter



- ▶ Whole tablets all fell within USP accuracy and %RSD range
- ▶ Drug Content
 - 43 of 180 half-tablets (23.9%) out of USP drug content range. All %RSD less than 10.5%
 - 5 of 180 (2.78%) out of drug target range on a weight adjusted basis
- ▶ Weight Variation
 - 23 of 180 (12.8%) half-tablets fell out of USP weight variation range. Mean weight loss - 5 of 6 <0.6%
- ▶ Scored vs. Nonscored – little difference -
 - Drug Content: 20 of 90 out of range scored, 23 of 90 nonscored - wider range
 - Weight Variation: 10 of 90 scored 13 of 90 nonscored
- ▶ Key Conclusions:
 - Weight variation is a good surrogate for content uniformity
 - Dose is primarily determined by ability to split the tablet



- ▶ The European Pharmacopoeia has studied this issue for a number of years
- ▶ Presented pharmacopoeial standards for subdivision performance in 2002.
- ▶ Currently presents standards for accuracy of subdivision but not ease of subdivision or loss or mass



Tablets may bear a break-mark or break-marks and may be subdivided in parts, either to ease the intake of the medicinal product or to comply with the posology. In the latter case, subdivision must be assessed and authorised by the competent authority. In order to ensure that the patient will receive the intended dose, the efficacy of the break-mark(s) must be assessed during the development of the product, in respect of uniformity of mass of the subdivided parts. Each authorised dose must be tested using the following test.



Take 30 tablets at random, break them by hand and, from all the parts obtained from 1 tablet, take 1 part for the test and reject the other part(s). Weigh each of the 30 parts individually and calculate the average mass. The tablets comply with the test if not more than 1 individual mass is outside the limits of 85 per cent to 115 per cent of the average mass. The tablets fail to comply with the test if more than 1 individual mass is outside these limits, or if 1 individual mass is outside the limits of 75 per cent to 125 per cent of the average mass.



- ▶ Draft Guidance for Industry – Tablet Scoring: Nomenclature, Labeling, and Data for Evaluation – Issued August, 2011
- ▶ Provides guidelines and criteria for assessing characteristics of scored tablets during development
- ▶ Proposes the nomenclature “functional score” for tablets meeting the criteria
- ▶ Consistent with European Pharmacopoeia guideline – contains drug development guidelines and acceptance criteria
- ▶ FDA Guidance provides a pathway for manufacturers to demonstrate functionality of scoring
 - QbD risk-based approach



- ▶ Develop post-release testing requirements for tablets labeled “Functional Score” to show they perform as expected throughout their shelf life
 - Provide a means to confirm quality of functional scoring
 - Specific tests
 - Acceptance criteria
- ▶ Application of USP standard will be triggered by FDA approved labeling



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Tablet Scoring – Current USP Status

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- ▶ USP and FDA
- ▶ Expert Committee Deliberations
- ▶ Assumptions
- ▶ Current Focus
- ▶ USP Process – Next Steps



- **1820** USP – independent, national pharmacopeia
- **1906** Food & Drugs ‘Wiley’ Act
 - Feds can act if adulterated or misbranded
 - USP *strength, quality & purity*
- **1938** Federal Food, Drug, and Cosmetic Act (FD&C Act)
 - FDA application – safety – but **no preapproval**
 - USP *identity* (drug named in official compendium)
USP *packaging & labeling*
- **1962** FD&C Drug Amendments
 - FDA **pre-market approval authority**; safety & *efficacy*
 - FDA authority to require manufacturing controls:
GMPs - assure safety + identity, strength, quality & purity
- **1997** FDA Modernization Act Amendments
 - USP *Positron Emission Tomography (PET) standards*



- USP has produced uniform voluntary drug quality standards for over 190 years
 - At first, recipes for **compounding** pharmacists.
 - Later, focus shifted to chemical formulations, identifications and assays, for drug ingredients and finished drug products, to foster conformity in **manufacturing** and dispensing drug products
- Roles of USP and FDA have changed over time, along with changing medical science and public policy
 - Today, FDA enforces USP’s public standards (failure to satisfy USP standards can cause article to be deemed “adulterated” or “misbranded”)
 - FDA also enforces manufacturers’ private specifications in approved drug applications (NDAs and BLAs), and GMPs



- Russ Wesdyk, FDA, discussed the work of an Office of Pharmaceutical Science Working Group on Tablet Scoring
- Increase in scored tablets through the years
- Consumer expectation that a scored tablet
 - Was meant to be split
 - Split portions would have key quality attributes similar to those of whole tablets of the same nominal dose
- FDA Guidance under development
- QbD approach for requirements (content uniformity, other) to support label statement (functional score)
- Guidance would be a “going forward” document and apply only to those products that would be labeled as “Functionally Scored”



- 820 expert volunteers serving on 22 Expert Committees and 67 Expert Panels
- 350 Expert Committee members
- 362 Expert Panel members*
- 103 FDA Liaisons

* This number does not include Expert Committee members also serving on Expert Panels.



2010–2015 USP Council of Experts

Quality Standards for Medicines, Dietary Supplements, and Food Ingredients

Council of Experts/Executive Committee R. Williams

<i>USP Medicines Compendium</i>	<i>United States Pharmacopeia</i>		<i>National Formulary</i>	<i>Dietary Supplements Compendium</i>	<i>Food Chemicals Codex</i>	<i>USP on Compounding</i>
V. Srinivasan	Chemicals: K. Russo		C. Sheehan	G. Giancaspro	M. Lipp	S. Becker
S. Asia (Chemicals) A.R. Gomas	Small Molecules Monographs 1 G. Van Buskirk	Small Molecules Monographs 2 E. Parente	Excipients L. Block	Dietary Supplements D. Gorecki	Food Ingredients A. Ebert	Compounding G. Davidson
E. Asia (Excipients) J. Tu						
L. America (Chemicals) I. Santoro	Small Molecules Monographs 3 B. Olsen	Small Molecules Monographs 4 M. Cutrera				
Biologics D. Patankar	Biologics: T. Morris					
E. Europe (Chemicals)	B&B Monographs 1 M. Mulkerrin	B&B Monographs 2 J. Huxsoll				
MENA (Chemicals)						
TBD						
TBD						

General Chapters and Cross-Cutting Expert Committees

S. Becker	General Chapters: A. DeStefano				W. Hauck/M. Pitluck
Nomenclature, Safety, and Labeling T. Reinders	Chemical Analysis T. Wozniak	Biological Analysis W. Workman	Microbiology J. Akers	Statistics R. Singer	Reference Standards M. Borer
	Physical Analysis G. Amidon	Dosage Forms J. DeMuth	Packaging M. Foster	Toxicology R. Osterberg	

Questions

- ▶ Should the standard address quality attributes for any tablet that has been subdivided, whether scored or not or should it mirror the FDA Guidance?

- ▶ Should the chapter be:
 - Written as a guideline for information only (numbered above <1000>) or
 - Required when called for in a USP product monograph (numbered below <1000>)?

 - Should the full monograph standard be applied to the split tablets?

 - If not the full standard, which procedures and criteria should be applied?

- ▶ Should the standard address quality attributes for any tablet that has been subdivided, whether scored or not?
 - Unscored tablets are being split
 - Would manufacturer be held accountable for actions of patients and practitioners that are not addressed in the labeling?
 - FDA draft Guidance provides basis for expectations of products with approved labeling that indicates functional scoring

- ▶ Should the chapter be informational (numbered above <1000>) or required if referenced in the drug product monograph (numbered below <1000>)?

- ▶ An informational chapter can be broader in scope
 - Address issues identified in the literature such as ease of splitting
 - Provide guidelines but these would not be required
 - FDA Guidance and literature already provide substantial background

- Below 1000 would require limitation of scope
 - Specific tests (procedures and criteria)
 - What would trigger application (e.g., the approval of the “Functionally Scored” designation)?



- ▶ Should the full monograph standard be applied to the split tablets?
 - The going-in assumption is that the intact tablet meets all its USP monograph requirements
 - From the FDA Guidance: split portions meet same testing requirements as whole tablet of same strength
 - Avoid redundant testing requirements such as impurities, identification, and assay (content uniformity for the split pieces)
 - Concentrate on attributes that may be affected by splitting (e.g., dissolution and weight variation)



- ▶ What procedures and criteria should be applied? The draft Guidance serves as a starting point.
 - USP <905> Uniformity of Dosage Forms
 - What is the appropriate sample size?
 - What aspects of uniformity are of interest?
 - Dissolution is specifically mentioned in the FDA draft Guidance
 - Approaches for immediate and modified release tablets
 - Immediate release by appropriate monograph test
 - Modified release testing by monograph test or profile comparison with similarity factor (f_2) criteria
 - 12 split portions serve as the sample



- ▶ Tablets labeled as functionally scored have been reviewed by the FDA based on expectations detailed in the draft guidance
 - Subdivided portions shown to meet same testing requirements as intact tablets of the same strength
 - Demonstrated 90-day stability for subdivided portions
 - <905> Uniformity of Dosage Units
 - Weight variation in place of Content Uniformity (if split portion meets ≥ 25 mg AND $\geq 25\%$ requirement)

- ▶ Uniformity
 - As an attribute of the functional scoring

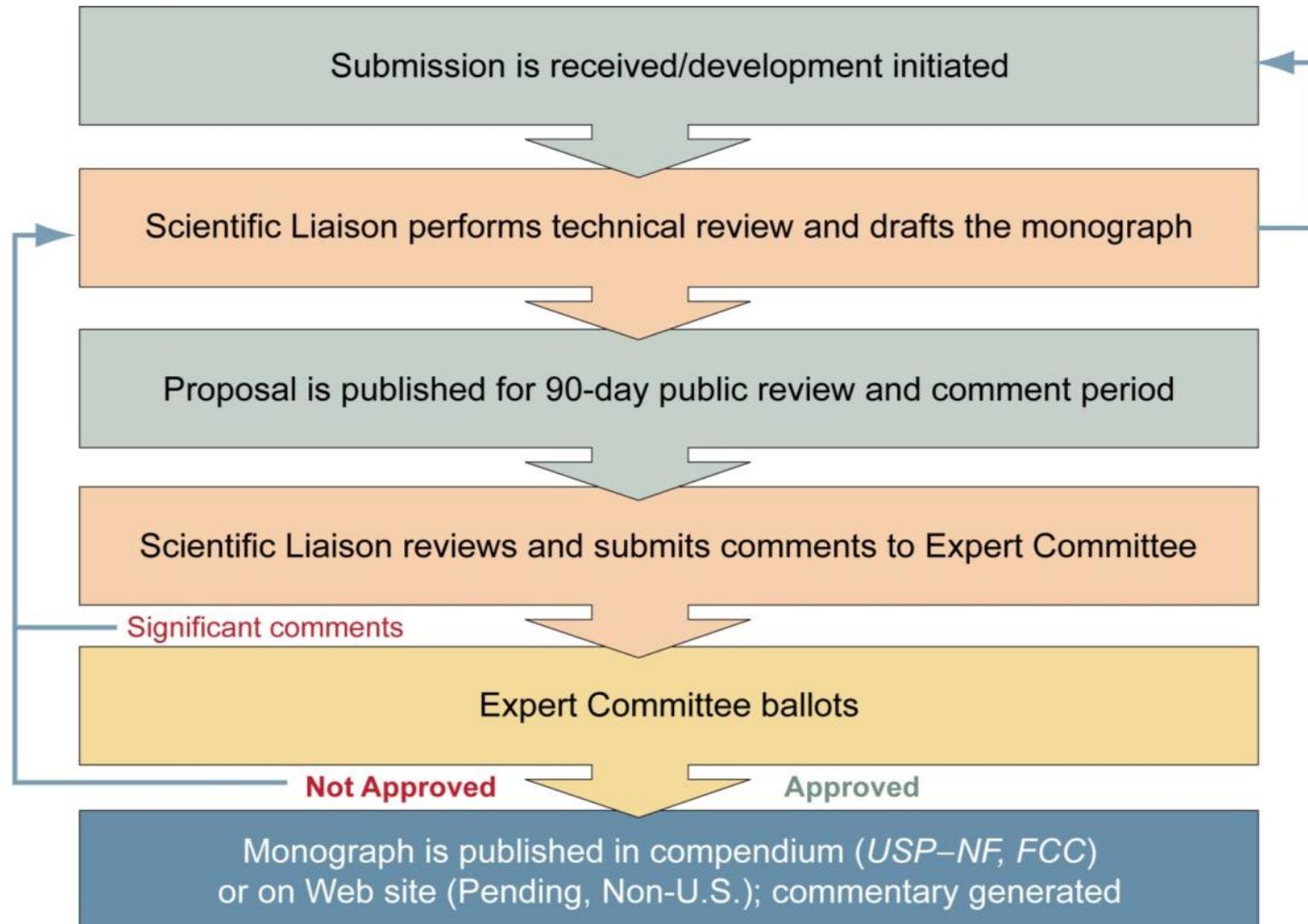
- ▶ Dissolution

- ▶ Disintegration (when used as a surrogate for dissolution)



- ▶ USP standard will provide means to confirm quality of functional score for drug products throughout the shelf life of the product
 - Specific tests
 - Acceptance criteria

- ▶ Application of USP standard will be triggered by FDA approved labeling and referenced in the product monograph



- ▶ All proposed revisions required to be published in *Pharmacopeial Forum (PF)* for public review and comment
 - 90-day comment period
 - Second round of notice and comment in *PF* can occur if changes require substantial new compendial requirements beyond proposal, or if the EC or CoE Chairperson determines reprinting is necessary due to the significance of comments received or changes made
- ▶ *PF* is a free, on-line only publication



- ▶ Discussion within Expert Committee
 - In conjunction with the appropriate FDA Liaisons, the committee will reach conclusions on the issues outlined in the presentation and any others that arise during their deliberations.
- ▶ Publish Draft Chapter and PF Stimuli Article in the same issue of Pharmacopeial Forum
 - Stimuli article to provide background and rationale (the “why”)
 - Draft chapter to provide procedures and criteria (the “what”)
 - 90 day public comment period but will likely be posted on the USP web site prior to official publication in PF to provide additional time
 - Comments are all addressed by the committee before the standard becomes official
 - Additional information gathering tools (e.g., webinars) if needed
- ▶ Timing – Target publication is first half of calendar 2013.



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Testing of Functionally Scored Tablets

Statistical Considerations

ACPS-CP
August 9, 2012

Alex Viehmann
FDA/CDER/OPS

Introduction and Objective

- How to test functionally scored tablets?
- Is the Uniformity of Dosage Units test appropriate for assessing functionally scored tablets ability to split?
- Create a statistically valid sampling plan that characterizes functionally scored tablets ability to split

Committee Considerations

- USP <905> Uniformity of Dosage Units
 - Two sided tolerance interval
 - Controls for a proportion to be within specified limits
- Two one-sided tolerance interval approach
 - Controls for a proportion of lot to be above a lower limit
 - Controls for a proportion of lot to be below an upper limit
- Attribute sampling plan
 - Go / no-go decision on each unit
 - Acceptable Quality Level (AQL) and an Unacceptable Quality Level (UQL).

USP <905>

Table 1. Uniformity of Dosage Units Test Procedure

All measurements of dosage units and criteria values are in percentage label claim (% LC).

At each stage calculate the sample average, \bar{X} , and the sample standard deviation s .

Stage	Number tested	Pass stage if:
S ₁	10	$ M - \bar{X} + 2.4s \leq 15.0$, where M is defined below.
S ₂	20	i) $ M - \bar{X} + 2.0s \leq 15.0$ using all 30 results (S ₁ + S ₂) ii) No dosage unit is outside the maximum allowed range of 0.75*M to 1.25*M.

M is defined as follows:

If T is less than or equal to 101.5%LC, and

- (i) If \bar{X} is less than 98.5%LC, then $M = 98.5\%LC$.
- (ii) If \bar{X} is between 98.5 and 101.5%LC, then $M = \bar{X}$.
- (iii) If \bar{X} is greater than 101.5%LC, then $M = 101.5\%LC$.

If T is greater than 101.5%LC, and

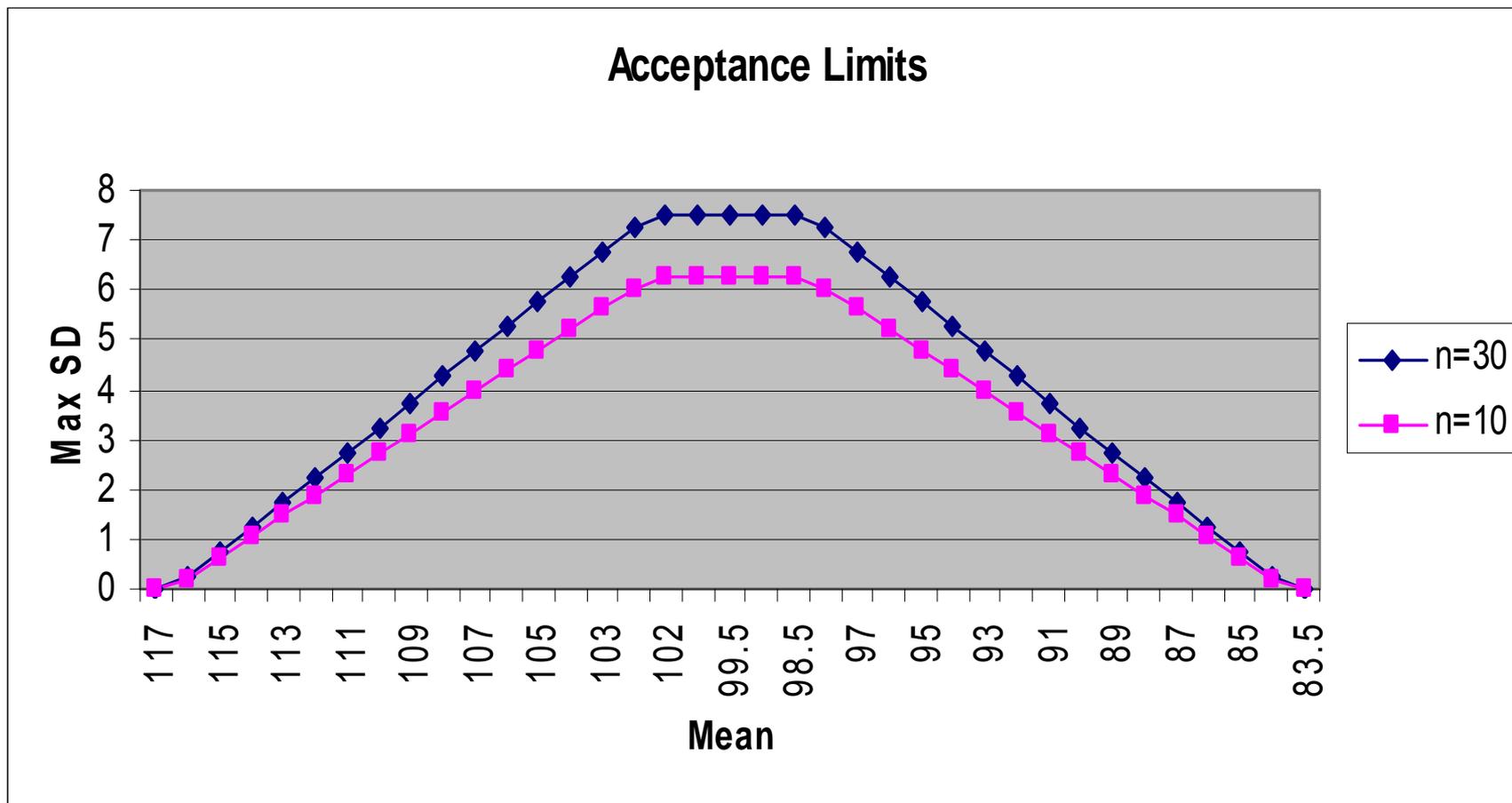
- (i) If \bar{X} is less than 98.5%LC, then $M = 98.5\%LC$.
- (ii) If \bar{X} is between 98.5 and T, then $M = \bar{X}$.
- (iii) If \bar{X} is greater than T, then $M = T$.

T is the Target content per dosage unit at the time of manufacture, expressed as percentage label claim. Unless otherwise specified in the individual monograph, T is 100.0%LC.

USP <905>

- Apply current procedure to tablet segments
 - Example: Bi-sect 15 tablets; analyst has no less than 30 tablet segments
- The current procedure allows for a +/- 1.5% indifference zone.
- The procedure is based on a two-sided tolerance interval approach.
 - An interval that contains p percent of the population measurements
 - $N=10 / k_2=2.4$
 - $N=30 / k_2=2.0$
 - k_2 is a tolerance interval factor that is affected by sample size, desired confidence, and coverage (k_2 is specific to a two sided tolerance interval)
 - K_2 is determined so that the interval covers at least a proportion p of the population with a confidence c
- Based upon the criteria of the test (k_2 value), the metrics provided are – 87% confident that 91% of the population lies between 83.5-116.5%; this is due to the 1.5% indifference zone
- The second aspect of the procedure is no tablet will be outside ~ 73.9-126.9%

USP <905> Acceptance Limits



Two One-Sided Tolerance Interval

- Ensures that p percent of population measurements will not fall below a lower limit
 - Lower limit is pre-determined (lower specification)
 - $X_L = \bar{X} - k_1 * s$ (lower tolerance limit)
- Ensures that p percent of population measurements will not fall above an upper limit
 - Upper limit is pre-determined (upper specification)
 - $X_U = \bar{X} + k_1 * s$ (upper tolerance limit)
- k_1 is a tolerance interval factor that is affected by sample size, desired confidence, and coverage (k_1 is specific to a one sided tolerance interval)
- k_1 is determined so that the interval covers at least a proportion p of the population with a confidence c

Two One-Sided Tolerance Interval

- Compare upper specification to upper tolerance limit (X_U)
- Compare lower specification to lower tolerance limit (X_L)
- If lower tolerance limit $>$ lower specification and upper tolerance limit $<$ upper specification
 - Y% confidence that at least P% of population lies below upper specification
 - Y% confidence that at least P% of population lies above lower specification

Two One-Sided Tolerance Interval

Example Stage 1

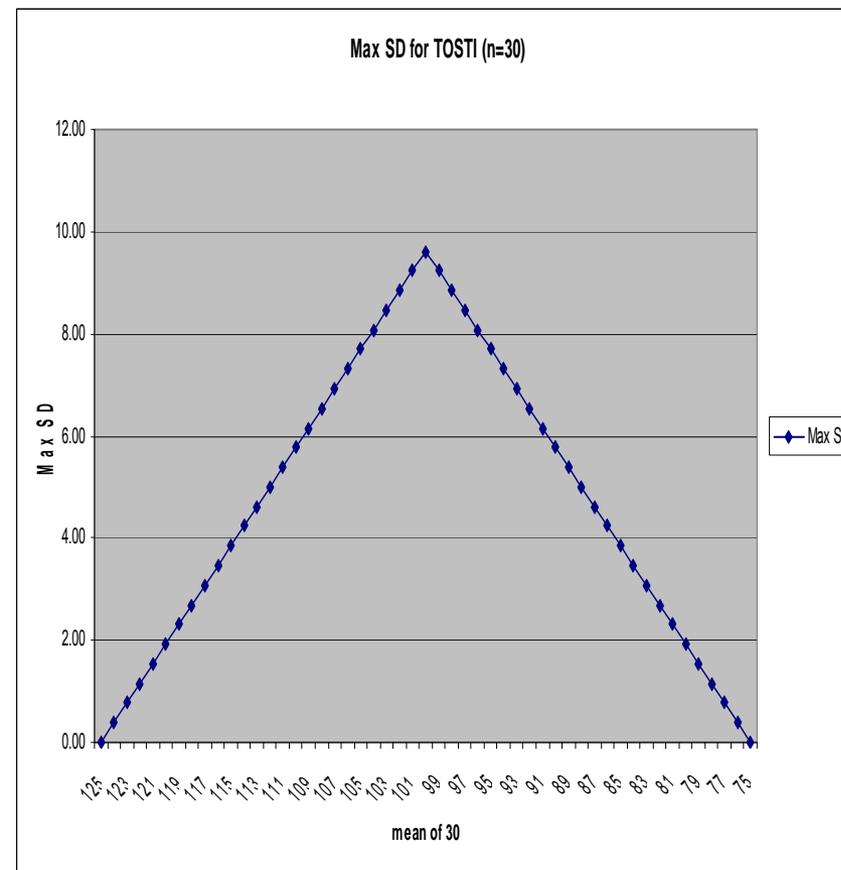
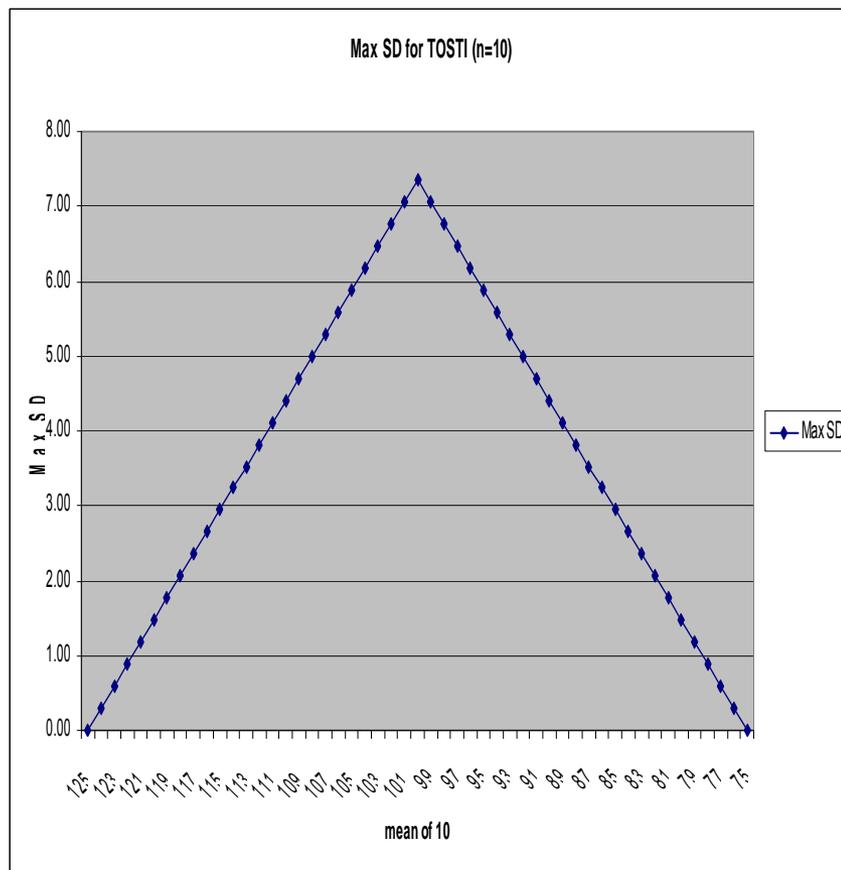
- Take no more than 15 tablets and split accordingly; this will leave analyst with no less than 30 units.
 - Take a random sample of 10 units.
 - Calculate Mean and Standard Deviation
 - Calculate Lower Tolerance Limit
 - $\bar{X} - k_1 \cdot s$
 - $K_1=3.4$ (95% confident that 97.5% of population lies above Lower Tolerance Limit based on sample size of 10)
 - Lower Tolerance Limit $\geq 75\%$
 - Calculate Upper Tolerance Limit
 - $\bar{X} + k_1 \cdot s$
 - $K_1=3.4$ (95% confident that 97.5% of population lies below Upper Tolerance Limit based on sample size of 10)
 - Upper Tolerance Limit $\leq 125\%$
 - If original 10 fail, move to Stage 2
- If lot complies at Stage 1; analyst is 95% confident that at least 97.5% of lot lies above 75%LC and 95% confident that at least 97.5% of lot lies below 125% LC.
- THIS IS AN EXAMPLE ONLY – SPECIFICATION / % CONFIDENCE / PROPORTION CAN BE ALTERED

Two One-Sided Tolerance Interval

Example Stage 2

- Analyze remaining 20 units (30 total; Stage 1 + Stage 2)
 - Calculate Mean and Standard Deviation of all 30 units
 - Calculate Lower Tolerance Limit
 - $\bar{X} - k_1 * s$
 - $K_1=2.6$ (95% confident that 97.5% of population lies above Lower Tolerance Limit based on sample size of 30)
 - Lower Tolerance Limit $\geq 75\%$
 - Calculate Upper Tolerance Limit
 - $\bar{X} + k_1 * s$
 - $K_1=2.6$ (95% confident that 97.5% of population lies below Upper Tolerance Limit based on sample size of 30)
 - Upper Tolerance Limit $\leq 125\%$
- If lot complies at Stage 1; analyst is 95% confident that at least 97.5% of lot lies above 75%LC and 95% confident that at least 97.5% of lot lies below 125% LC.
- THIS IS AN EXAMPLE ONLY – SPECIFICATION / % CONFIDENCE / PROPORTION CAN BE ALTERED

Two One-Sided Tolerance Interval *Acceptance Limits*



Tolerance Interval

Concerns

- Parametric
 - Assume the data follow a normal distribution
- Analyst bi-sects tablet and one segment is crushed in to powder
 - Each granule of powder in crushed segment must be considered a segment in the random sample
 - Probability of passing becomes nearly impossible

Attribute Sampling Plan

Why?

- Easy to implement
 - Counting test
- Non parametric
 - Does not assume tablet segments follow a specific distribution
- Crushing one tablet segment will not guarantee failure

Attribute Sampling Plan *Development Questions?*

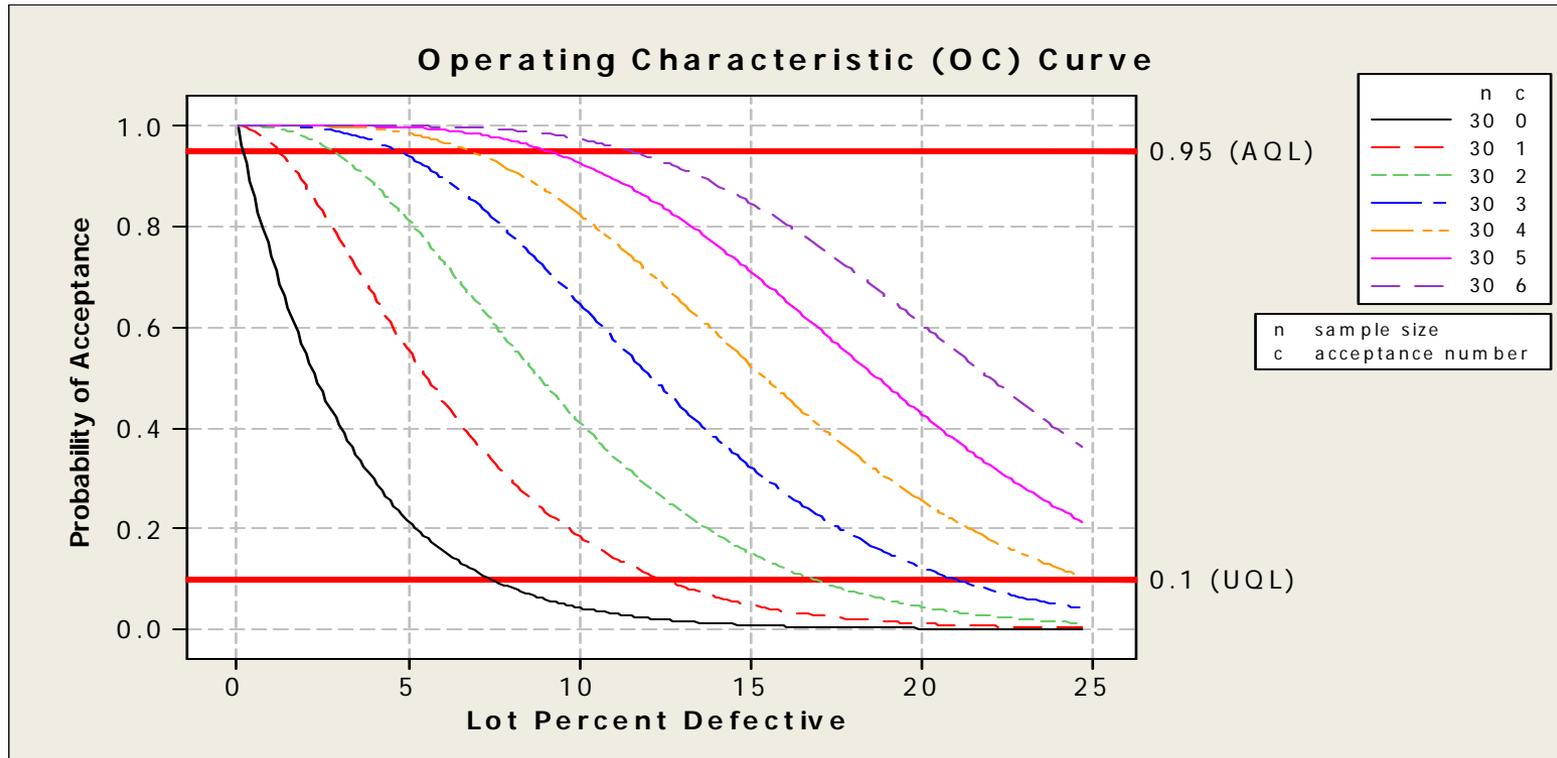
- What is the desired attribute?
- What is the sample size?
- What is the acceptance/rejection criteria?
- What is the Acceptable Quality Level (AQL)?
 - Percent Defective that is the base line requirement for the quality of the producer's product. There is a high probability (e.g. 95%) of accepting a lot that has a defect level less than or equal to the AQL.
 - Type I error (α risk): probability of rejecting a lot that has a defect level equal to the AQL.
- What is the Unacceptable Quality Level (UQL)?
 - High defect level that would be unacceptable. There is a low probability (e.g. 10%) of accepting a lot with a defect level as high as the UQL.
 - Type II error (β risk): The probability of accepting a lot with a defect level equal to the UQL.

Attribute Sampling Plan

- Attribute
 - Functionally-scored tablet breaks into the desired number of segments, each segment containing +/- 25% LC
 - Accounts for all segments of the tablet
- Sample size
 - Random sample of 30 tablets (legacy number)
- Acceptance criteria
 - A range of acceptance numbers (A_c) were investigated
 - 0,1,2,3,4,5,6

Operating Characteristic Curves

- Plots the probability of accepting the lot (Y-axis) versus the lot percent defectives (X-axis)



AQL / UQL

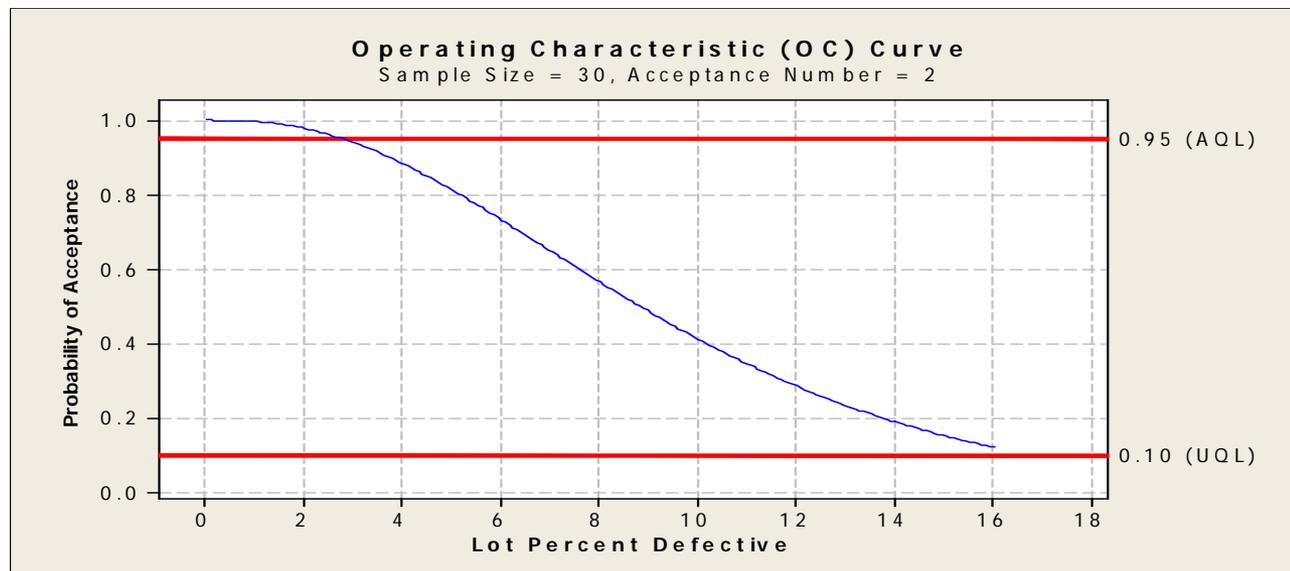
<i>Ac</i>	<i>AQL (95% Pa)</i>	<i>UQL (10% Pa; 90% confident defect level does not exceed)</i>
0	0.18%	7.47%
1	1.2%	12.28%
2	2.88%	16.7%
3	4.75%	21%
4	6.78%	24.7%
5	9.2%	28.8%
6	11.22%	32.5%

Example – Analysis by Weight

1. Take a random sample of 30 units
2. Accurately weigh each tablet and record its weight
3. For each tablet, determine the expected weight of the split portions by dividing the whole-tablet weight by the designed number of split portions indicated on the labeling.
4. Manually break each tablet into the designed number of split portions and weigh each split portion.
5. For each tablet, determine the percent of the expected weight represented by each of the split portion
 - *An acceptable tablet breaks into the designed number of segments, with each split portion having not less than 75% and not more than 125% of the expected weight of the split tablet portion*

Acceptance Criteria: Not less than 28 of the 30 tablets are acceptable.

Statistical Metrics



- AQL = 2.88% (95% probability a lot with 2.88% defects will be accepted)
- UQL = 16.7% (10% probability a lot with 16.7% defects will be accepted; 90% confident the lot contains no more than 16.7% defects)
 - Defect: A tablet that does not break in to the desired number of segments, with each segment containing +/- 25% LC.

Conclusions

- Parametric and Nonparametric methodologies' are being investigated
 - Nonparametric approach (attribute sampling plan) was identified as a viable option
 - No distribution assumption
 - Easy implementation
- Attribute sampling plan is a valid statistical approach
 - Provides level of assurance on un-tested units ability to split

Overview of the FDA Draft Guidance

ACPS-CP

August 9, 2012

Russell Wesdyk

Scientific Coordinator

FDA/CDER/OPS/IO

Agenda

- Guidance as drafted
- Overview of comments received
- Areas of potential evolution
- Rationale

Draft Guidance

- Three principles
 - Consistent approach to CMC evaluation of scored products
 - Consistency of nomenclature (scored, bisected, etc...)
 - Provide information through labeling or other means to health care providers
- Generally meet the specified requirements of the sub-divided segment
- Label product as “functional score”...
- Provides health care practitioners with information relevant to splitting decisions
- Focused on development and validation data; not end product release requirements

Draft Guidance - Guidelines

- Not scored if
 - Below MTD
 - Not safe to handle
 - Release mechanism compromised by splitting
- Stability on segments in pharmacy dispensing containers at controlled room temperature (CRT) for 90 days
- Risk assessment for justifying testing criteria
- Testing using patient (manually) and mechanically split products

Draft Guidance - Criteria

- UDU USP <905>
- Loss on Mass (LOM); less than 3%
- Friability
- Dissolution
 - Staged for IR, MR (matrix), MR (coated, compressed components)

Comments on Draft Guidance

- Approximately 20 comments to the docket
- Broadly supportive of need for guidance
 - Brand, generic, provider
- Comments both supportive and opposed to allowing non-functional scores
 - Two opposed, one in favor
- Multiple concerned re industry segment gaming
 - FDA comfortable tools exists to address this

Specific Comments on Draft Guidance

- Approximately 11 comments on specific guidance aspects
- Stability (reduced requirements or clarifying questions)
- Friability (elimination)
- Burden of patient segment splitting guideline
- LOM (elimination)
- Dissolution (reduced requirements)

FDA Tablet Scoring Working Group

- Membership from ONDQA, OGD, OC, OTR, and OPS/IO
- Functional representation includes chemists, field investigators, industrial pharmacists, practicing (community) pharmacists, and medical officers
- Considered the comments received to the docket

Draft Guidance – Stability & Friability

- Clarification of stability requirements recommended
 - Use of pharmacy container with no seal or desiccant
- Recommended maintaining 90-day segment stability guideline
 - Short term prescription dispensed with minimal downstream handling
 - Reports of 3 months supply being dispensed
 - Chronic drugs / mail order
 - Further shipment or extensive handling
- Recommended maintaining friability guideline also based on potential for downstream handling/shipment

Draft Guidance – Other Specific Comments

- Recommended modifying guideline to not use indicated patient segment, but maintain guideline to test non-mechanically split segments (as well as those mechanically split)
 - Patient segment data could be requested when justified by risk assessment
- Recommended maintaining LOM guideline
 - May be subsumed in UDU, USP <905>
 - Potentially a deciding data set if non-functional scores allowed
- Recommended dissolution guidelines remain unchanged



THANK YOU