

Pharmacopeial Standards for the Subdivision Characteristics of Scored Tablets

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ABSTRACT The practice of tablet splitting as a way to reduce prescription medication costs has become increasingly prevalent. The United States Pharmacopeial Convention (USPC) has no standards for the subdivision characteristics of scored tablets. Literature results show that many tablets on the US market exhibit unacceptable subdivision characteristics. The *European Pharmacopoeia (EP)* provides requirements for subdivision accuracy of scored tablets, if subdivision is indicated in order to comply with the product label. This *Stimuli* article provides a rationale for why standards should be included in *USP* to address the accuracy of subdivision, as well as to account for loss of mass upon subdivision. We propose that for accuracy of subdivision current *EP* standards be adopted, applicable only to any tablet that bears a score mark. For loss of mass, we propose an average of $\leq 3\%$ of the intact tablet mass. From data reported in the literature we estimate that as many as half of the scored tablets on the US market would be in compliance with these standards. Generally, we do not advocate such standards be tested on a batch-to-batch basis but rather that the testing should be conducted as part of the development process before marketing approval. We also discuss a third, related, quality attribute: ease of subdivision. Although future research and discussion in this area are warranted, we believe that not only should scored tablets break into accurate partial doses with minimal loss of mass, but also that the tablets should be breakable by a representative sample of the population, including the elderly.

INTRODUCTION

Tablets intended for oral administration are the most common pharmaceutical dosage form in the US, and many tablets bear score mark(s) (1). The presence of a score mark implies that the tablet can be subdivided into smaller doses. Patients split tablets for a variety of reasons, including to adjust the dose, to ease swallowing, and to save money. As healthcare costs rise, tablet splitting to save money has become more prevalent in the US. Because some manufacturers have established the same or similar prices for different strengths of tablets of the same medication, consumers can purchase double the strength needed and divide the tablets in half for twice the number of doses (2). This has led many healthcare plans to establish mandatory tablet splitting policies as a means to reduce costs, a practice that has drawn opposition from several organizations, including the American Society of Consultant Pharmacists, the American Medical Association, and the American Pharmacists Association. The opposition stems from concerns about the potential for unpredictable dosing, particularly for the elderly (3–5).

The most important advantage of score lines, however, is dose flexibility—the ability to adjust a dose up or down in response to medication effects or to comply with the labeled dosage and administration instructions (posology). Dose flexibility can be especially important for medications that typically are titrated to achieve a therapeutic goal or for those that have a narrow therapeutic index, such as warfarin or levothyroxine.

Therefore, scored tablets play an important role in providing dose flexibility, among other benefits. Many studies have shown that scored tablets can be difficult—or even impossible—to break and often display large variations in the mass of the subdivided parts (6–8). A research group of the Dutch National Institute for Public Health and the Environment (RIVM) conducted a comprehensive literature review of articles that investigated the subdivision performance of scored tablets and identified several studies that reported unacceptable subdivision characteristics (9). Problems included large variations in the mass of the subdivided parts when split by hand, tablet splitter, or other means (9). A later study published by the same research group investigated patients' experiences and perceptions with breaking scored tablets. This study reported that 39% of patients were in some way dissatisfied with the subdivision characteristics of their scored tablets and that poorly functioning score lines were perceived as a quality defect. The authors concluded that the subdivision performance of scored tablets cannot be interpreted as a purely technical quality attribute and that badly performing score lines may lead to reduced patient compliance with medication.

Based on available literature, this *Stimuli* article examines: a) the ease or lack thereof in splitting scored tablets, b) the accuracy of the splitting process, and c) the loss of mass of split scored tablets sold in the US. The *Stimuli* article then proposes *USP* standards for the subdivision of scored tablets.

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SUBDIVISION PERFORMANCE OF SCORED TABLETS ON THE US MARKET

The RIVM research group concluded that the performance of score lines should be defined by the following three quality attributes: accuracy of subdivision (i.e., uniformity of the mass of the subdivided tablets), ease of breaking, and loss of mass resulting from subdivision (9). We follow the same classification to explore the subdivision performance of scored tablets on the US market.

We reviewed published studies that were selected according to the following criteria: (a) the research was conducted in US laboratories or institutions, which presumably supported the assumption of probability that the tablets studied were approved by FDA and marketed in the US, and (b) the research included reports about the measuring subdivision accuracy for scored tablets. Eight studies (“US studies”) satisfied both requirements (10–17). In six of the eight US studies, the tablets were obtained from commercial suppliers. One of the studies used tablets donated by the manufacturer (15), and one study used professional samples (16).

Accuracy of Subdivision

Each of the US studies focused on assessing subdivision accuracy by measuring the whole tablet and the subsequent subdivided tablets’ mass as a surrogate for estimating the content uniformity of a split tablet (see General Chapter *Uniformity of Dosage Units* (905) for information about relying on mass as a surrogate for content). Four of the US studies tested the accuracy of subdivision of scored tablets from manual splitting (Table 1), and six tested tablet splitting accuracy using a tablet-splitting device (Table 2). Of the six studies involving a tablet splitter, four cited cost containment as the rationale for testing the accuracy of tablet splitters; one study reported concern about obtaining accurate pediatric doses; and one study involved obtaining nonmarketed doses of a popular anti-hypertensive drug. In the absence of FDA and/or USP standards for uniformity of mass of the subdivided parts, seven of eight (88%) US studies adapted and applied the USP 24 criteria for the uniformity of dosage units (11). The term *uniformity of dosage unit* is defined as the degree of uniformity in the amount of the drug substance among dosage units. This USP criterion states all units tested must be within 85.0% to 115.0% of label claim and no units outside the range of 75.0% to 125.0% of label claim with a maximum batch standard deviation (SD) no greater than 6%.

Results of the US studies are comparable to those previously summarized and reported in the RIVM review (9). A comparison of Tables 1 and 2 shows that a tablet-splitting device may improve the accuracy of subdivision—but not in all cases—and accuracy varies with different devices, users, and tablet shapes. In general, oblong-shaped tablets performed slightly better, but this also depended on the user and device.

With respect to the subdivision accuracy of scored tablets putatively on the US market, we conclude: (a) the situation is comparable to that reported in other parts of

the world; (b) 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; (c) although tablet splitters somewhat improve subdivision accuracy, this accuracy is still unacceptable for scored tablets, and the results can vary widely depending on the device and the user; and (d) the presence of a score mark on a tablet does not necessarily imply that the tablet can be split into accurate partial doses.

Loss of Mass

Four of the eight US studies reported data on the loss of tablet mass upon subdivision (Table 3). Of the scored tablets tested, the largest mean percent loss of mass occurred when users split glyburide tablets with a razor blade. In this case the loss was 2.6%, which was approximately 6.5 times higher than the loss of glyburide tablet mass after manual splitting (14). McDevitt et al. reported a maximum loss of mass from manually splitting hydrochlorothiazide tablets (nearly 20%, with an average of 1.06%) (13). Sertraline tablets split manually and with a tablet splitter showed comparable loss of mass (0.08% using a tablet splitter compared to 0.06% when split manually) (16). Although there are limited data available for US-marketed products, the results of these US studies are consistent with those reported by the RIVM review, in which the authors concluded that most tablets, on average, lost less than 1% of the intact tablet mass upon subdivision (9).

Ease of Subdivision

Another quality attribute that researchers should consider when assessing the efficacy of a score mark is ease of subdivision (9), that is, individuals’ ability to subdivide tablets regardless of accuracy or loss of mass. Although this attribute has been studied in some detail by the RIVM research group, including the development of an *in vivo* test, only two of the eight US studies included this attribute in their splitting accuracy studies (10, 14). Wilson et al. asked elderly diabetic patients to manually subdivide micronized glyburide tablets and to rate the degree of splitting difficulty using a visual analog scale. On average, the rating was 7.7 on a scale of 1 to 10 where 10 was considered the most difficult (10). Teng et al. reported that because of their hardness 50-mg hydrochlorothiazide tablets were “difficult to split by hand” (14).

PHARMACOPEIAL STANDARDS FOR THE SUBDIVISION PERFORMANCE OF SCORED TABLETS

In 2002, EP presented pharmacopeial standards for the subdivision performance of scored tablets (12). This marked the first time a pharmacopeial requirement for the functioning of a score mark was established. Since that date, several proposals for revision to that standard have been published (6, 13–18). Some of these proposals were adopted in subsequent revisions, e.g., in EP 5.0 (19) and in Supplement EP 5.5 (20). The text of EP 5.5 remained unchanged until EP 6.4, which is now cur-

rent (21). A historical overview of proposed standards and enforced *EP* standards relative to scored dosage forms is depicted in *Table 4*. With the exception of the proposed revisions in December 2006, which called for the adoption of additional tests and standards for ease of breaking and loss of mass, accuracy of subdivision was the only quality attribute addressed. In other words, *EP* currently presents standards for accuracy of subdivision of scored tablets but has not yet adopted standards for ease of subdivision nor for loss of mass upon subdivision.

PROPOSED STANDARD FOR ACCURACY OF SUBDIVISION FOR SCORED TABLETS

Among the two quality attributes for which standards are being proposed, we view splitting accuracy as primary in importance. If sufficient accuracy is not achievable even under ideal conditions, other aspects become less important because splitting is no longer a viable option for dose adjustment. With respect to accuracy of subdivision, several questions arise:

- (a) Which standards should be set?
- (b) Which test methods should be used?
- (c) Should all scored tablets be forced to comply with these standards?

Answering question (a) suggests two very different approaches that can be taken. The first is that the subdivided tablet parts should conform to uniformity of mass or weight variation standards. In this respect, the (905) standards currently in place for whole dosage forms could be adapted and applied to subdivided tablet parts. Many of the researchers of the US studies adapted a variation of these standards to the studies in *Tables 1* and *2*. Or one could adopt the current enforced *EP* standard for uniformity of mass of subdivided parts of scored tablets. The advantage of adopting the *EP* standard is the ability to leverage the considerable work, research, debate, and discussion that have already taken place.

A second approach to answering question (a) would be to apply the uniformity of content standards where the amount of drug substance within the subdivided tablet parts is assayed. Interestingly, both approaches were adopted in the first *EP* standard, which stated that subdivided tablet parts should comply with "... either Uniformity of Mass (2.9.5) or Uniformity of Content (2.9.6), as appropriate," leaving it up to regulatory authorities to decide which test to apply (12). This first *EP* standard for scored tablets proved to be insufficient because it raised a number of questions such as whether or not chemical analyses were necessary for uniformity of mass studies, whether the uniformity of content standards could be used with the uniformity of mass test, and how the tablets should be subdivided (i.e., manually or by a tablet cutter).

Gradually, the standard for uniformity of content variability was dropped by *EP*, perhaps because very few scored tablets could comply with that standard, and the requirement of mass determinations replaced the requirement of chemical analyses. Later, *EP* introduced a provision stating that only one part from every subdivided tablet should be allowed in the final test.

The current *EP* requirement for subdivision accuracy (6.4) has been unchanged for a number of years and appears to work well in practice. This requirement specifies subdivision by hand, using only one part of each subdivided tablet, and limits deviations to $\pm 15\%$ of the average mass of the subdivided parts. Thus, questions (a) and (b) are answered by the current *EP* standard.

We recognize that the present *EP* standards for accuracy of subdivision evolved from a long process and seem to reflect both the interest of the patient in receiving the correct dose while taking into account current technological/manufacturing capabilities. Also, from the point of view of pharmacopeial harmonization, it is sensible to adopt the present *EP* standards for accuracy of subdivision.

With respect to question (c), Should all scored tablets be forced to comply with these standards? We do not support the restricted applicability of the current *EP* standards that require that only tablets with break marks need to comply with labeling (posology) and should be tested for uniformity of mass. To "comply with posology" means that the tablet must be subdivided to arrive at a dose stated in the Product Information Leaflet (PIL), or Package Insert (PI) as it is referred to in the US, for some indications, conditions, and/or patients. We do not support this restricted applicability of the *EP* standard in scored tablets for the reasons outlined below.

First, the presence of a score line in a tablet implies the tablet is meant to be subdivided. Thus, no matter what the reason for subdividing, the score line should perform well. Patients perceive badly functioning score lines as a quality defect, regardless of the reason for the subdivision (7). Second, from a practical point of view it is unusual and cumbersome to make the applicability of pharmacopeial standards depend on dosage schemes in the PI. In such a situation, any decision to declare an article either in compliance or out of compliance can be made only in combination with an interpretation of the current PI of that particular drug. Third, the criterion of tablets that "may be subdivided in parts to comply with posology" appears not to be entirely objective (6). Fourth, off-label use of drug products is common, particularly for pediatric and geriatric patients. Hence, the PI of those medications may not reflect dosing instructions for those patient groups and, therefore, those tablets will not be subject to the compendial subdivision requirements and thus will not be tested for compliance. In practice, standards are needed most for these particular medications because doses for pediatric and geriatric patients are frequently adjusted, and a lack of standards could potentially compromise patients who receive an incorrect dose based on the characteristics of tablet subdivision.

In summary, we recommend that USP adopt the present *EP* standards for accuracy of subdivision but enforce these standards for all scored tablets. *Table 5* depicts our proposals for *USP* standards.

PROPOSED STANDARD FOR LOSS OF MASS FOR SCORED TABLETS

No pharmacopeial standard exists today for loss of mass upon tablet subdivision. A standard of $\leq 1\%$ average loss of mass compared to the mass of the intact tablet was proposed in December of 2006, although this standard has not been adopted at the time of this writing (6). This proposed standard was tested by the RIVM research group for 29 scored tablets on the European market, and 25 products (86%) were in compliance. Products that exceeded the 1% threshold had a loss of mass of 1.10%, 1.14%, 1.21%, and 2.68%, and all were round, single scored, and between 5.9 and 9.0 mm in diameter. Based on the data from the US studies in Table 3 and the European data, we propose a limit of $\leq 3\%$. The proposed standard and test method can be found in Table 5. The test method mandates subdivision by hand and calculating the loss of mass for each of the subdivided tablets. As in the case for the accuracy of subdivision standard, the loss of mass standard should apply to all scored tablets.

ATTAINABILITY OF THESE STANDARDS

Because the eight US studies were conducted using a variety of methodologies and criteria, one finds it difficult to make any conclusions how many products on the US market would be in compliance if the proposed standards for accuracy of subdivision were adopted. However, in 2006, the RIVM research group conducted a market surveillance study applying the enforced *EP* standards at the time to tablets available in the European market. They concluded that 7 of the 29 (24%) products tested complied with the proposed standards of accuracy of subdivision. Four of the seven products were oblong, and three were round (6). For the proposed *USP* loss of mass standard ($\leq 3\%$), all 29 products tested in the RIVM research study complied.

It seems reasonable to assume that the attainability rate for scored tablets on the US market would be comparable to that observed in RIVM research study.

FREQUENCY OF TESTING OF PROPOSED PHARMACOPEIAL STANDARDS

A related question is "Under what situations should the two standards be tested?" We advocate that all scored tablets be characterized in terms of accuracy and loss of mass during registrations in a New Drug Application (NDA) or Abbreviated New Drug Application (ANDA). Further, both accuracy and loss of mass should be pharmacopeial standards that are tested during registration and under scale-up and post-approval change (SUPAC) situations when such changes may influence splitting performance. We recognize that not all SUPAC situations would trigger the need for accuracy and loss of mass testing, but it currently may not be easy to discern when testing is needed and when testing is not needed. We suspect that tests for accuracy and loss of mass need not be performed for each batch, although we are not aware of batch-to-batch data that suggests otherwise.

Pharmacopeial standards are not necessarily batch-to-batch tests. Until May 2009, *USP*'s General Notices stated that

every compendial article in commerce shall be so constituted that when examined . . . it meets all the requirements in the monograph defining it. However, it is not to be inferred that the application of every analytical procedure in the monograph to samples from every production batch is necessarily a prerequisite for ensuring compliance with pharmacopeial standards before the batch is released for distribution. Data derived from manufacturing *process validation* studies and from *in-process controls* may provide greater assurance that a batch meets a particular monograph requirement than analytical data derived from an examination of finished units drawn from that batch. On the basis of such assurances, the analytical procedures in the monograph may be omitted by the manufacturer in judging compliance of the batch with the Pharmacopeial standards (22).

Thus, the standards proposed in Table 5 can be enforced as pharmacopeial without necessarily implying the need for batch-to-batch testing. However, even in the absence of batch-to-batch testing, each batch should be compliant.

IN VIVO TEST PROCEDURES FOR EASE OF SUBDIVISION

We do not propose a standard at this time for the ease of subdivision but do advocate further research on this topic. To date, pharmacopeial standards for ease of subdivision have not been adopted in any country/region. However, in view of the unsatisfactory performance of scored tablets previously presented in The Netherlands by the RIVM research group with respect to ease of subdivision (6, 8, 9) and the data available in the US studies (10, 14), we believe *USP* should consider adopting a standard for this attribute. As stated previously, patients perceive poorly breaking tablets to have a quality defect, which may lead to reduced patient compliance (7). Thus, we hold the view that *USP* could and should take the lead in enforcing standards for this attribute.

Until recently, very few tests to evaluate the ease of breaking of scored tablets have been proposed. The RIVM published an *in vivo* test using a panel of elderly volunteers who manually split scored tablets (8). This ease of breaking test subsequently was applied in the 2006 market surveillance study in The Netherlands, and it concluded that the proposed test procedure for ease of subdivision was workable (6).

Depending on the statistical power required, between 39% and 52% of the tested tablets were in compliance. Of note, 100% of all oblong tablets were considered to be in compliance based on the proposed criteria (6). The published test procedure proposed that no less than 80% of the elderly panelists be able to break the tablet, with a minimum confidence level of 90%, one sided (8). The authors also concluded that large panels are sometimes needed to meet the minimum statistical power.

It is uncommon to define the statistical power of a pharmacopeial test, but it is not uncommon to define the sample size. Consequently, we reworked this test into a more common two-tier test (*Table 6*). In the first tier, 10 elderly panelists break one tablet each. In order to comply, all 10 tablets must be deemed breakable by hand. At a 90% confidence level, this requirement corresponds to at least 79% of the elderly population being able to break that tablet. If the tablets do not comply with the first-tier test, the elderly panel is expanded from 10 to 30 for the second tier. When a total of 30 tablets have been tested, at least 27 tablets (78%) must be deemed breakable by hand. With a 90% confidence level this corresponds to a minimum of 81% of the elderly population being able to break the tablet.

Although we believe that for the time being, a testing method for the ease of breaking of scored tablets requires additional study, the RIVM research group in The Netherlands has proposed this quality attribute be considered for inclusion within the *EP* standards. In the US, 51.6% of the population > 65 years takes three or more prescription drugs, and by the year 2020 the age group will consume 40% of all prescription drugs. The number of persons 75 years and older will increase from 18.1 million in 2005 to 33.5 million in the year 2030. Thus, a criterion of a mean age \geq 75 years and none < 65 years is representative of the US population that consumes the largest portion of pharmaceutical tablets (23). Other procedures, such as panel participants breaking the tablets by hand without having a tryout of the tablet to be tested, stem from real-world experiences. Patients would rarely be able to practice breaking tablets and discarding those that do not break well without jeopardizing the duration of their prescription. Also, breaking by hand is the most common situation. The test anticipates that 20% of the elderly panel will be incapable of subdividing the tablet by hand, so for this subset, use of a tablet splitter may be indicated.

In summary, the standard and criteria proposed by the RIVM research group for ease of subdivision appears to be workable but will need to be validated in future US studies. Although we do not study it in this *Stimuli* article, the authors suggest that any future ease of subdivision testing by the panel of elderly would be unworkable for batch-to-batch testing. The RIVM research group already concluded that this test typically should be performed only once, i.e., during the development phase of a tablet (8).

CONCLUSIONS AND RECOMMENDATIONS

In (905), *USP* provides content uniformity requirements for drug products where applicable to ensure that patients receive an accurate dose with minimal variability. However, no such standards or tests are mandated for the subdivided parts of tablets that bear score marks. Upon subdivision, such tablets have shown significant variability in the mass of the subdivided parts. By inference, this should be interpreted as variability in dose, a result contrary to the intent of the whole dosage form standards developed by *USP*. In an increasingly cost-conscious environment when patients are frequently subdivi-

ding dosage forms, we see considerable risk related to unpredictable dosing resulting from inaccurate splitting and the loss of mass. Therefore, we propose that *USP* should adopt the current *EP* standards, but *USP* should make the standards applicable to all scored tablets. The purpose of this proposal would be to ensure adequate content uniformity for divided tablets with a score. For loss of mass, we propose a limit of \leq 3% of the intact tablet mass. We do not believe such standards generally should be tested on a batch-to-batch basis but rather should be determined as part of the development and registration processes. These proposed standards for accuracy of subdivision and loss of mass are attainable both from a pharmaceutical and a technological point of view. We advocate future investigation of the ability of representative populations to demonstrate ease of splitting scored tablets.

ACKNOWLEDGEMENTS

The authors acknowledge Koos Van der Steen and Kik Groot of RIVM for critically reading the manuscript.

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APPENDIX

Table 1. Accuracy of Subdivision of Scored Tablets on US Market Split Manually

Reference	Panel	Products	Tablet Shape ^a	Result (% of parts >115% of ideal mass)
Matuschka and Graves 2001	Volunteers	Sertraline 100 mg	Capsule	0
Wilson et al. 2001	Elderly diabetics	Micronized glyburide 3 mg	Oval	12
McDevitt et al. 2002	Volunteers	HydroDIURIL 25 mg	Round	24
Teng et al. 2002	Trained pharmacy student	HydroDIURIL 50 mg	Round	40
		Glyburide 5 mg	Rectangle	15
		Oretic 50 mg	Round	55

^a All tablets single-scored on one side only.

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

Author	Panel and Splitting device	Products	Tablet Shape ^a	Result (% of parts > 115% of ideal mass)	
Horn et al. 1999	Pharmacists	Catapres 0.1 mg	Round	12	
		EZ Dose tablet cutter	Clonidine 0.1 mg	Round	43
			Capoten 12.5 mg	Capsule	2
			Sertraline 50 mg	Capsule	3
			Tegretol 100 mg	Round	32
	Pharmacists Health Care Logistics tablet cutter	Catapres 0.1 mg	Round	22	
		Clonidine 0.1 mg	Round	42	
		Capoten 12.5 mg	Capsule	26	
		Amlodipine 5 mg	O c t a g o n (modified)	17	
		Tenormin 25 mg	Round	18	
		Sertraline 50 mg	Capsule	0	
		Tegretol 100 mg	Round	9	

^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.

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

Author	Panel and Splitting device	Products	Tablet Shape ^a	Result (% of parts > 115% of ideal mass)
Matuschka and Graves 2001	Volunteers. LGS Health Products pill cutter	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		

^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.

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

Author	Panel and Splitting device	Products	Tablet Shape ^a	Result (% of parts > 115% of ideal mass)
Teng et al. 2002	Trained pharmacy student Razor blade	Hydrodiuril 50 mg	Round	15
		Glyburide 5 mg	Rectangle	15
		Oretic 25 mg	Round	45
		Oretic 50 mg	Round	20
		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.

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)
M a - tuschka 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 Coumadin 5 mg—orientation 2 Furosemide 40 mg—orientation 1 Furosemide 40 mg—orientation 2 Glipizide 10 mg Metoprolol 50 mg Zolof 100 mg	0.0 (NR to 0.18) 0.5 (NR to 1.4) 0.8 (NR to 1.7) 1.3 (NR to 7.3) 0.08 (NR to 0.95) 0.1 (NR to 0.4) 0.1 (NR to 0.3)
Teng et al. 2002	Trained individual in laboratory conditions	Razor blade	Zolof (sertraline) 100 mg Glyburide 5 mg Hydrodiuril (hydrochlorothiazide) 50 mg Oretic (hydrochlorothiazide) 50 mg	0.4 (NR to 1.2) 2.6 (NR to 6.7) 0.8 (NR to 3.0) 0.8 (NR to 2.0)
	Trained individual in laboratory conditions	Manual	Glyburide 5 mg Hydrodiuril (hydrochlorothiazide) 50 mg Oretic (hydrochlorothiazide) 50 mg	0.4 (NR to 1.2) 0.3 (NR to 0.7) 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.

Table 4. History of EP Standards Proposed and Enforced for the Subdivision Characteristics of Scored Tablets

Date Published	Period Enforced	Action	Test and Standard(s)	Reference
October 2001	April 1, 2002 – June 30, 2002	First implementation of tablet subdivision accuracy standards.	<p>For tablets for which subdivision is authorized, it is demonstrated to the satisfaction of the competent authority that the subdivided parts comply with either Test A for <i>Uniformity of content of single-dose preparations (2.9.6)</i> or with the test for <i>Uniformity of mass (2.9.5)</i>, as appropriate.</p> <p>Uniformity of Content: Subdivide 10 tablets and randomly select 10 parts from 10 subdivided tablets and, using a suitable analytical method, determine the content of active substance(s) in each individual part. The preparation complies with the test if each individual content is between 85% and 115% of the average content. The preparation fails to comply with the test if more than one individual content is outside these limits or if one individual content is outside the limits of 75% to 125% of the average content.</p> <p>If one individual content is outside the limits of 85% to 115% but within the limits of 75% to 125%, determine the individual contents of another 20 units (subdivided tablet parts) taken at random. The preparation complies with the test if not more than one of the individual contents of the 30 units is outside 85% to 115% of the average content and none is outside the limits of 75% to 125% of the average content.</p> <p>Uniformity of Mass: Subdivide 20 tablets and weigh individually 20 parts selected randomly and determine the average mass. The preparation complies with the test if not more than 2 of the individual masses deviate from the average mass by more than the following percentage deviations <i>and</i> no individual mass deviates by more than twice that percentage: 10% for tablets < 80 mg; 7.5% for tablets between 81 and 249 mg; 5% for tablets > 250 mg.</p>	Monograph 0478. <i>Ph. Eur. Suppl. 4.1</i> ; 2002:2433–2436.

^a No change in *Ph. Eur. Supplements 5.6, 5.7, 5.8, 6.0, 6.1, and 6.2 5* to current *Ph. Eur. 6.4*.

Table 4. History of EP Standards Proposed and Enforced for the Subdivision Characteristics of Scored Tablets (continued)

Date Published	Period Enforced	Action	Test and Standard(s)	Reference
April 2002	NA	Proposed Revision to Monograph 0478 (<i>Ph. Eur. 4.1</i>): Clarify breaking method.	Tablet should be “broken by hand.”	<i>Pharmeuropa</i> 2002 Apr; 14(2):302–304.
October 2002	NA	Proposed revision to Monograph 0478 (<i>Ph. Eur. 4.1</i>): Clarify prevailing test method.	Content of Uniformity test can be replaced by Uniformity of Mass test for tablets containing 25 mg or greater of an active substance that comprises 25% or more (by weight) of one tablet.	<i>Pharmeuropa</i> 2002 Oct; 14(4):725–728.
April 2003	NA	Proposed revision to Monograph 0478 (<i>Ph. Eur. 4.1</i>): Clarify prevailing test method and sampling procedure.	If the subdivided parts of the tablet contain < 2 mg of active substance or the content of the active ingredient in the subdivided parts is < 2 % of the total mass of the subdivided tablet, the test of Uniformity of Content prevails. Two halves of the same tablet should be included in the test.	<i>Pharmeuropa</i> 2003 Apr; 15(2):322–324.
January 2004	NA	Proposed revision to Monograph 0478 (<i>Ph. Eur. 4.1</i>): Clarify prevailing test method and sampling procedure.	Two halves of the same tablet should be included in the test. Subdivided tablets should comply with test 2.9.6A (Uniformity of Content) irrespective of their content of active ingredient.	<i>Pharmeuropa</i> 2004 Jan; 16(1):51–55.
April 2004	NA	Proposed revision to Monograph 0478 (<i>Ph. Eur. 4.1</i>): Elimination of Uniformity of Content requirement and propose new Uniformity of Mass test.	Take 30 tablets at random. Take 10 tablets from among these and break them in parts by hand, mix the parts. Take 10 parts at random and determine the average mass. Weigh each part individually. The tablets comply with the test if the mass of each part is between 85% and 115% of the average mass. The tablets fail to comply with the test if more than one individual mass is outside these limits, or if one individual mass is outside the limits of 75% to 125% of the average mass. If one individual mass is outside the limits of 85% to 115% of the average mass but within the limits of 75% to 125%, determine the individual mass of another 20 parts taken at random from the remaining 20 tablets. The tablets comply with the test if not more than one of the individual masses of the 30 parts is outside 85% to 115% of the average mass and none is outside the limits of 75% to 125%.	<i>Pharmeuropa</i> 2004 Apr; 16(2):250–252.

^a No change in *Ph. Eur. Supplements 5.6, 5.7, 5.8, 6.0, 6.1, and 6.2* 5 to current *Ph. Eur. 6.4*.

Table 4. History of EP Standards Proposed and Enforced for the Subdivision Characteristics of Scored Tablets (continued)

Date Published	Period Enforced	Action	Test and Standard(s)	Reference
June 2004	January 1, 2005 to March 31, 2005	Revised Monograph 0478: Revised guidance on prevailing test method and revision to the test and standards for Uniformity of Content .	<p>Uniformity of Content test prevails if tablets with a content of active substance of tablet less than 2 mg or less than 2% of the total mass. If the preparation has more than one active substance, the requirement applies only to those substances that correspond to the conditions above. <i>Pharmeuropa</i> 16(2) proposed testing method and standard adopted for assessing Uniformity of Content for subdivided tablets.</p> <p>Uniformity of Mass test prevails in all other instances. Original <i>Ph. Eur.</i> 4.1 test method and standard remains in place.</p>	Monograph 0478. <i>Ph. Eur. 5.0.</i> ; 2005: 626–628.
October 2005	NA	Proposed revision to Monograph 0478 (<i>Ph. Eur. 5.0</i>): Clarification on timing of testing efficacy of break mark(s) and proposal to eliminate Uniformity of Content standards.	<p>In order to ensure that the patient will receive the intended dose, the efficacy of break-mark(s) must be assessed during the development of the product, in respect to uniformity of mass of the subdivided parts. Each authorized dose must be tested using the following test:</p> <p>Uniformity of Mass: Take 30 tablets at random, break them by hand and, from all the parts obtained from one tablet, take one part for the test and reject the other part(s). Weigh each of the 30 parts individually and calculate the average mass.</p> <p>The tablets comply with the test if not more than one individual mass is between 85% and 115% of the average mass. The tablets fail to comply with the test if more than one individual mass is outside these limits, or if one individual mass is outside the limits of 75% to 125% of the average mass.</p>	<i>Pharmeuropa</i> 2005 Oct; 17(4):512–514.
December 2005	July 1, 2006 to December 31, 2006	Revised Monograph 0478 (<i>Ph. Eur. 5.0</i>): Clarification of which tablets are subject to the subdivision standards' elimination of Uniformity of Content tests and standards, and revision to Uniformity of Mass test.	<p>Only tablets for which the break mark is needed to comply with the posology should be tested.</p> <p>Uniformity of Mass: Testing and standards proposed in <i>Pharmeuropa</i> 17(4) are adopted and enforced.</p> <p>Uniformity of Content requirement is eliminated.</p>	Monograph 0478. <i>Ph. Eur. Suppl. 5.5</i> ; 2006: 4166–4168.

^a No change in *Ph. Eur. Supplements 5.6, 5.7, 5.8, 6.0, 6.1, and 6.2 5* to current *Ph. Eur. 6.4*.

Table 4. History of EP Standards Proposed and Enforced for the Subdivision Characteristics of Scored Tablets (continued)

Date Published	Period Enforced	Action	Test and Standard(s)	Reference
December 2006	NA	Proposed revision to Monograph 0478 (<i>Ph. Eur. 5.5</i>): Clarification of which tablets are subject to subdivision standards and tests, instructions for handling broken/crumbled tablets, and proposal of additional standards.	<p>Remove restriction of <i>Ph. Eur. 5.5</i>, which states that only tablets for which break marks needed to comply with posology should be tested for Uniformity of Mass.</p> <p>Uniformity of Mass: instructions should be given about how to handle tablets that cannot be broken or that crumble upon subdivision for their inclusion in the calculation of Uniformity of Mass.</p> <p>Proposed additional testing and standards for efficacy of score marks including Ease of Subdivision and Loss of Mass upon subdivision.</p>	<i>Pharmeuropa Scientific Notes</i> , 2006(2): 1–7.
June 2008 ^a	January 1, 2009 to March 31, 2009 ^a	Monograph 0478 unchanged from previous published standards (<i>Ph. Eur. 5.5</i>).	<p>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 authorized 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 authorized dose must be tested using the following test.</p> <p>Take 30 tablets at random 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% to 115% 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% to 125% of the average mass.</p>	Monograph 0478. <i>Ph. Eur. Suppl. 6.4</i> ; 2008.

^a No change in *Ph. Eur. Supplements 5.6, 5.7, 5.8, 6.0, 6.1, and 6.2 5* to current *Ph. Eur. 6.4*.

Table 5. Standards Proposed to USP for the Subdivision Characteristics of Scored Tablets

Loss of Mass	<p>Take 30 tablets at random. Weigh each tablet. Break each tablet by hand, and weigh each of the subdivided parts. Calculate the loss of mass for that tablet. Repeat the procedure for the other 29 tablets, and calculate the mean loss of mass.</p> <p>Criterion for Loss of Mass: The tablets comply with the test if the mean loss of mass is not more than 3.0%.</p>
Accuracy of Subdivision	<p>Take 30 tablets at random and break them by hand. From all the parts obtained from one tablet, select one part and reject the other part(s). Weigh each of the 30 parts individually and calculate the average mass.</p> <p>Criterion for Accuracy of Subdivision: The tablets comply with the test if not more than 1 individual mass is outside the limits of 85% to 115% 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% to 125% of the average mass.</p>

Table 6. Test and Criteria for Ease of Subdivision of Scored Tablets

Ease of subdivision
<p><i>Panel:</i> Select a panel of 10 healthy elderly volunteers with mean age ≥ 75 y and none < 65 y. There are no restrictions on male/female ratio, and previous membership on a breaking panel is not an exclusion criterion, but impaired use of hand and/or fingers is an exclusion criterion.</p>
<p><i>Procedure:</i> Each panelist is instructed to break by hand one tablet in a way he/she would do if he/she were a patient, without having a "tryout" of the tablet to be tested.</p>
<p>The investigator scores every tablet given to the panelist either "breakable" or "not breakable."</p>
<p>Criterion for Ease of Subdivision: Each of the 10 panelists should be able to subdivide the tablet. If the tablets do not comply with this test, the elderly panel is expanded from 10 to 30 using the same inclusion criteria and procedure. When a total of 30 tablets have been tested, at least 27 tablets (78%) must be deemed "breakable" by hand.</p>
<p>Notes:</p> <ul style="list-style-type: none"> • Each panelist should not break more than 10 tablets during one session. • During the test, panelists must not know the results from other panelists. • Care should be taken that the panelist does not swallow the tablet before or after breaking. • Care should be taken that the panelist washes his/her hands after the session is completed.