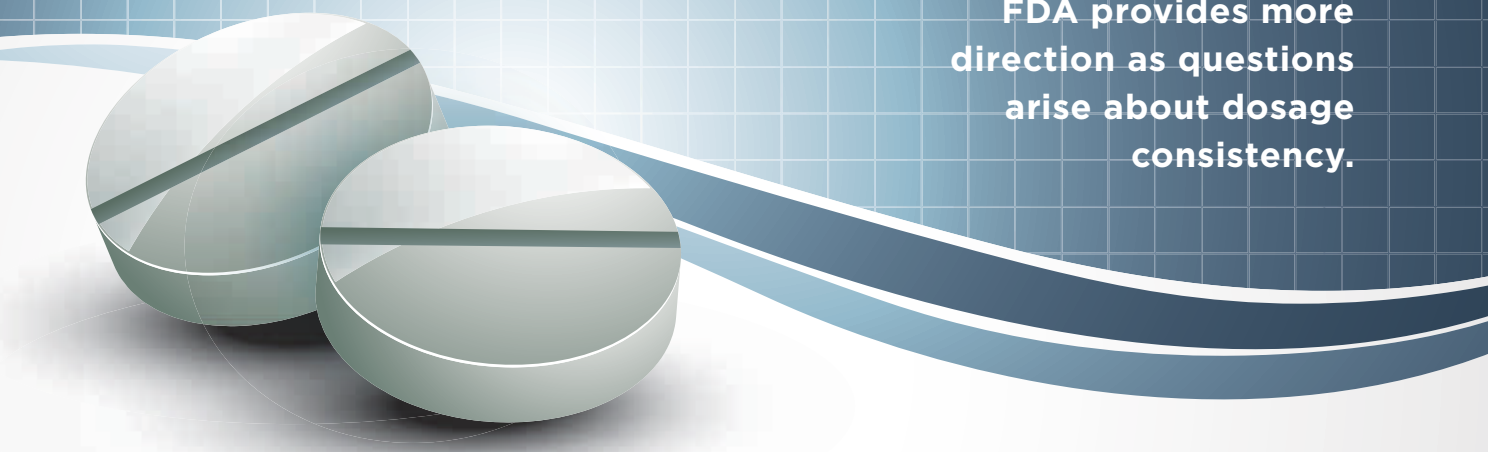
Split Decisions: Does Tablet Scoring Put Patients at Risk?

By Paul Thomas, Senior Editor

FDA provides more direction as questions arise about dosage consistency.



TABLET SCORING has long been used by oral solid dosage manufacturers—originally as a means to prevent tablet stress fractures, but recently as more of a cosmetic feature [1]. Bisects, of course, present manufacturing challenges. They "may be affected by the tablet cup depth, band thickness and the intended tablet hardness. As the tablet size increases or changes, so do the size and type of bisects that may be placed" [2,3].

A score is a useful feature for the patient who, for instance, wants to switch from a name-brand to generic product and may need to halve tablets to maintain a consistent dosage regimen. By some accounts, this is happening more often, as insurance companies and doctors are increasingly recommending that patients split tablets for proper dosing or even cost savings.

Scoring has also been an issue in determining whether a generic drug is equivalent to its reference product. Whether or not a tablet is scored (and scored properly) can play a role in the cat-and-mouse game that originating manufacturers play with would-be generic competition. A reference drug may have a well-defined score while a generic product may only have a cosmetic breakline—in such a case, is the generic truly equivalent?

As one consultant recently stated on a LinkedIn conversation, scoring is "a door to patient non-compliance." FDA has taken this to heart and has conducted its own research, finding that scoring can lead to discrepancies in tablet content, weight, disintegration, or dissolution. (If you've split tablets yourself at home, how often have you gotten a good, clean split?)

Last fall, the Agency established draft guidance for tablet scoring [4]. (See PharmaManufacturing.com for a link.) The guidance is intended to provide "consistent and meaningful criteria by which scored tablets can be evaluated and labeled by: (1) providing a harmonized approach to chemistry, manufacturing, and controls (CMC) reviews of scored tablets; (2) ensuring consistency in nomenclature (e.g., score versus bisect) and labeling; and (3) providing information through product labeling or other means to healthcare providers."

The draft guidance's fundamental guidelines and criteria are:

1. The dosage amount meant to be achieved after splitting the tablet should not be below the minimum therapeutic dose indicated on the approved labeling.
2. The scored dosage form should be safe to handle and not pose risk of unintended drug exposure.
3. Modified release products for which the control of drug release can be compromised by tablet splitting should not have a scoring feature.
4. The split tablet, when stored in standard high-density polyethylene pharmacy bottles and caps (no seal),

should meet established stability requirements for a period of 90 days at 25° C, plus or minus 2° C/60 percent Relative Humidity (RH), plus or minus 5 percent RH.
5. The split tablet portions should meet the same finished-product testing requirements as for a whole-tablet product with equivalent strength. A risk assessment should be provided to justify the tests and criteria for product with the proposed functional score.
6. The scored tablet should be tested using the indicated patient population to ensure patients can split the tablet correctly, as labeled.
7. The scoring configuration of generic drug products should be the same as the reference drug.
8. New study data on tablet splitability should be provided during postapproval for any product changes per FDA's SUPAC guidances.

For more clarity on this "divisive" topic, we sought out Dale Natoli, president of Natoli Engineering, who has 35 years of experience in tabletting and has written extensively on oral solid dosage forms.

PhM: From an equipment standpoint, what are the latest in improvements in tablet scoring or bisecting?

D.N.: There have been recent improvements to a bisect design commonly referred to as the "Pressure Sensitive" bisect to help reduce edge chipping and edge attrition. The new design requires a facet or radius eliminating the sharp edge on the tablet at the bisect and the beginning of the punch cup. The Pressure Sensitive bisect design is more common to the European pharmaceutical industry due to an earlier adoption of the European Pharmacopeia standards pertaining to uniform dose of a split tablet presented in 2002.

PhM: FDA wants to ensure good "splitability" for scored tablets. What are some of the keys or best practices for manufacturers in this regard?

D.N.: A key practice to adopt is establishing good communications regarding tablet requirements, powder and compression idiosyncrasies with your tooling supplier. When a tablet is required to be split providing equal dose, then careful consideration should be given to the tablet design. Proper tablet configuration, tablet thickness, hardness, bisect type, and placement play a tremendous role in achieving a uniform dose of a split tablet. Most tablet designers have the capability to create a digital model of a tablet with details of the bisect in relationship to the tablet thickness. Take advantage of these services when developing new products or when redesigning an existing tablet.

PhM: How about the monitoring and Quality Control of scored tablets? Have there been advances?

D.N.: I am not a tablet analytical expert but from my point of view there have not been advances related to equipment or testing protocol to assure that a bisected tablet will yield a uniform dose. On the other hand, from recent interviews with product development and QA professionals, achieving a uniform dose of a split tablet has recently gained more attention to assure compliance to the EU Pharmacopeia and the new proposed FDA Guidelines to comply with export regulations.

A recent development by Accu-Break Pharmaceuticals is a unique patented process and tablet design consisting of two layers. The first or bottom layer is a non-drug layer and is compressed flat and is used primarily as a base for the second layer consisting of the active powder. The top layer is compressed using an upper punch with a bisect or bisects engineered to precisely divide the active second layer and compress until the bisect slightly penetrates to the first non-drug layer, assuring a precise and uniform dose with each segment of the split tablet.

PhM: Finally, one consultant has said, "Scoring is just a door to patient non-compliance" and should be done away with. Your thoughts?

D.N.: There is no question that taking a whole tablet opposed to a split tablet provides the most accurate dose of a prescribed medicine. As a patient, I would feel more comfortable knowing that I am taking the proper dose of medication by only consuming a whole tablet. But unfortunately, I don't think we will see tablets designed to be split leaving us any time soon. It now becomes the responsibility of regulators to assure that if a tablet is to be split that it splits evenly and doses the proper amount of medication.

References

1. *Rowley, F. Minimize Tablet Bisect Risk: Part I. http://www.pharmamanufacturing.com/articles/2006/188.html*
2. *Rowley, F. Minimize Tablet Bisect Risk: Part II. http://www.pharmamanufacturing.com/articles/2006/234.html*
3. *Tableting Specifications Manual, 7th edition, APhA Tableting Specification Steering Committee, APhA Publishing, 2005.*
4. *FDA. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM269921.pdf*