BLEND ANALYSIS DRUG DEVELOPMENT & SAMPLING EFFECTS

'...Sample thieves can make a difference...

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BUA - Impacting Sampling

BLEND UNIFORMITY AND STANDARD BUA SAMPLING TECHNIQUES

Fda's draft blend uniformity analysis (BUA) originated from US state judge Wolin's decision in the US vs. Barr Laboratories case (NJ USA 1993) which prompted the FDA to re-examine and modify its policies and scientific understanding on blend uniformity analysis and sampling techniques.

The FDA draft guideline and future amendments to cGMP regulations proposes to rule that the commercial batch final blended granulate (for solid dosage forms) be routinely tested for active ingredient homogeneity (Content Uniformity USP).

Wolin's seven-year-old ruling (1993) stated simply that the sample size of the **final blend** should be set at no more than three times (3X) the dosage unit weight of the tablet or capsule. Sampling could be ***either*** from the **drum** or preferable the **mixing unit**.

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3 X Sampling of the final blend may not always give good uniformity result

Both Judge Wolin's and the FDA's assumption that the current technology using modern sampling devises provides a means to consistently collect minute, representative unit dose samples from a much larger (10^6) static powder blend without a sampling bias does **not** always hold true - thus the FDA's current guideline introduces an important tool allowing for a scientifically justified **10X** sampling of the dosage unit weight of the tablet, capsule etc.

A comprehensive review and evaluation of the scientific literature highlights that current sampling technology is beset by a predominance of varying sampling techniques with resulting sampling bias.

Different Sampling thieves or dies give different results with the same final blend

ISSN 0793 694X US/Canada ISSN 0793 7784 Euro ISSN 0793 7822 Pacific Rim

Sampling error can be introduced by three key factors namely:

- **Sample thief design**
- **Sampling technique**
- **Final blend formulation properties**

The physical design of the sample thief and even the most recently developed side-sampling[1] or end-sampling[2,3] "slug thief" can produce unacceptable large sampling errors. [1]Globe-Pharma NJ; [2]Du-Pont-Merck; [3]Rutgers University - "best unit".

Sampling technique should always be the same from development to commercial batch lots. Different sampling techniques with the same thief can profoundly impact on sampling error, producing non representative results, with respect to the true blend uniformity value.

Factors that can bias the sample in four different ways are:

- Sampling motion (smooth, twisting jerking, or oscillating actions etc.)
- Sampling angle (vertical, acute, downwards).
- Sampling thief orientation in the bed (Side-sampling probe rotation of chamber is up (360°), down (180°), or on the side (either 45°; 90° or 135°).
- Depth of powder bed (top, middle or bottom sampling).

In general, where development studies show the need for more than **3X** sampling (4X to 10X unit weight) as a prerequisite, then do so and amend your SOPs (see model) as sampling error **increases** as the sample size and / or formulation potency **decreases**.

Process Qualification

Final blending process, like Tablet Hardness Qualification, is one of the series of unit processes that require process qualification validation.

This validation should be performed at the Process Qualification and / or Pivotal batch manufacturing stage. The GMP rules require that the process is validated and consistently produces the desired end product.

Testing final blend content uniformity as a suitable in-process control may well evaluate and highlight the incoming ingredient batch-to-batch differences as well as the physical variations in different lots of active material thus producing granule variation.

Bulk and tapped density and particle size of the active raw material should be checked with each new lot received and comply within the range specification limit. However routine BUA testing may eventually be a cGMP requirement even though blending is not the final unit process. Tablet compression or capsule filling is the actual end process!

Thus the necessity to establish both lower (LCL) and upper control limits (UCL) for the BUA content uniformity of the final blend is self-evident.

The final blended granulate assay should conform to within the mean ±2 or ±3 SD representing the *lower* **&** *upper* control limits (See SOP of the Month).

References:
1. Guidance to Industry Blend Uniformity Analysis FDA CDER US Oct 1999.
2. Int. Journal of Generic Drugs Vol. 02; Issue 02.1998
3. Current Good manufacturing Practice of Certain Requirements for the Finished Pharmaceuticals;1999.
4. United States of America vs. Barr Laboratories Inc., civil action for the district of N.J., Feb 1993.
5. J.T. Carstensen and M.V. Dali "Blending Validation and Content Uniformity of low content …powder blends " Drug development and Industrial Pharmacy Vol. 22 Issue 4 pp. 285-290 (1996).
6.J Berman, A Schoeneman and JT Shelton, Unit Dose Sampling - a tale of two thieves" Drug development and Industrial Pharmacy Vol. 22 Issue 11 pp.1211-1132 (1996).
7. J Berman, and J.A. Planchard "Blend Uniformity and Unit Dose Sampling" Drug development and Industrial Pharmacy Vol. 21 Issue 11 pp.1257-1283 (1995).
8.J.T. Carstensen and C.T. Rhodes " Sampling in Blending Validations" Drug development and Industrial Pharmacy Vol. 19 Issue 20 pp.2699-2708 (1993).

Tips & Traps on drug BUA Development

Do keep particle size distribution of granulate material as narrow as possible - fines percolating through coarser material may well result in non-representative final blend assay values.

Do remember that - changing the mesh size of the mill screen (0.6 1.2mm range) after FB Drying will impact on granule particle size and affect bulk density and the resulting hardness range

Do use the same sampling thief for all development, scale-up, and validation sampling operations.

Do formulate with appropriate glidants to keep the flow attribute of **all** the ingredients *similar,* thus preventing differential flow properties, resulting in non-representative BUA samples & assays.

SOPs

Do prepare a sampling and testing SOP for Pivotal batches - (as shown).

Do use this SOP for sampling and testing all *key* development (qualification lot), pivotal, and three commercial validation batches.

Do Develop a Standardised Sampling SOP to replicate routine sampling procedures with Sampling Record Forms (Ref.: this issue and Vol.01 No.6 - 1997).

BUA Samplers

Do take into account that all samplers sample dissimilarly, due to different construction geometry.

Do remember that the latest "end-sampling slug thieves" also produce significant sampling errors.

Do sample at least **3X** unit dose size, to avoid statistical sampling bias, depending on the detailed development report recommendations.

Do Remember that development data supporting **10X** sampling, when essential *is* acceptable especially where unit dose weights or tablet potencies are low.

In-process controls

Do remember that the variation in the final blend is generally greater, than in the finished drug product.

Do compare the mean of the final blend with the mean of the compressed cores/tablets or filled capsules.

Do sample 30 unit dose samples - 10 for analysis and 20 for reserve testing, if needed later.

Sampling

Do Remember that the draft guideline's **10X** sampling rule does take into account *all* inherent problems in current sampling technology and equipment.

Do use the same sampling style, thief orientation, and hand operations when sampling - retrain operators bi-annually and record the training.

Do take into account that bed pressures at the bottom of powder beds give different samples (and thus assays) to those results from the top and middle container positions.

Do sample at the same level and at the same entrance angle - every time.

Do keep the side-chambered sample thief *orifice* pointing in the same direction every time you sample, i.e. (either at 360^{o} ↑ ; 45^{o} ↗ ; 90^{o} → ; 135^{o} ↘ or 180^{o} ↓).

Don't use different sample thief types from operator to operator - choose the 'best' available and use it consistently, in a standardized manner.

Don't rely solely on the final blend assay as an in-process test; above a well specified, process controlled and validated manufacturing procedure (due to inherent sampling error of the final blended material).

Don't forget that uniformity changes can occur during compression or filling

Don't forget that the assay of the final granulate blend is as good as the sampling technique - and no final blend sampling procedure is free of error.

ISSN 0793 694X US/Canada ISSN 0793 7784 Euro ISSN 0793 7822 Pacific Rim