Risk-Based Blend and Content Uniformity Assessment: A Case Study

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Purpose

For solid oral dosage forms, blend and content uniformity (BU/CU) are critical for ensuring minimal dose-to-dose variability. Per 21CFR211.110, current good manufacturing practice for finished dosage form requires adequate mixing to assure uniformity and homogeneity. In an effort to streamline regulatory assessment, Office of Pharmaceutical Manufacturing Assessment (OPMA) developed several review guides pertaining to BU/CU assessment of solid oral dosage forms between 2020 and 2022. However, when it comes to applying these general frameworks to actual cases, OPMA assessors frequently face the challenge of making an appropriate regulatory decision based on a complexity of impacting factors.

Aiming to disseminate these complex factors, we present a recent case study to demonstrate our regulatory approach in assuring BU/CU for an immediate release tablet drug product. Our assessment incorporated various relevant factors, such as the initial risk scenario, available data, sampling plan, statistical method, and commitment for validation and commercial batches. In addition, BU/CU issues for similar products discovered during recent facility inspection were also taken into consideration. This case study adds to a more detailed interpretation of the BU/CU assessment directives outlined in the review guides, which should enhance our regulatory decision-making when tackling future cases of similar nature.

Case Study Outline and Initial Risk Scenario

- Immediate-release tablet, 5mg and 15mg strengths
- Drug load at 6.2% (moderate drug load, though on the lower end)
- Direct compression into tablets
- Drug product facility has **documented BU/CU issues** (see right):
  - A recent inspection report revealed that facility used a **large sample size for blend uniformity testing**, which may mask variability in the blend. With this enlarged sample size, BU has no failure. However, **CU failed in 3 batches**. 2 of the 3 failed batches **did not have root cause identified**.

Since multiple OOS's were observed for assay and blend uniformity, we reviewed the test method for sample preparation and also analytical method validation. Per test method ***(Exhibit LM-36, Page 7)*** for blend assay, sample size equivalent to 40mg of [redacted] needs to be weighed into a 100mL volumetric flask. This would translate to weighing about 400mg blend sample size (to obtain 40mg of [redacted]) in 100mL volumetric flask for testing. Due to repeated OOS, through an interoffice communication the sample size for blend assay was increased to 4gm for all strengths and for blend uniformity increased sample size to 4x - 8x times for 5mg strength ***(Exhibit LM-37)***. The analytical method was revalidated in January of 2018 and the method was modified to weigh about 4gm of blend sample ***(Exhibit LM-38, Page 25)*** to obtain [redacted] content equivalent to 400mg and the size of the volumetric flask was increased to 1000mL from 100mL ***(Exhibit LM-38, Page 6)***. It may be noted that the final concentration of the sample did not change however increase of sample size from 400mg to 4gm for testing would mask the variability due to segregation in dry blend for low dose [redacted] Tablets 5 mg) products. After the change in blend analysis method with ten times increased sample size, no failures in blend uniformity testing were observed. However, 3 additional batches failed for finished product Content Uniformity (CU) in 2018 (i.e. 1 batch for the 5 mg strength and 2 batches for the 10 mg strength).

Note: Drug name was redacted.

OOS No.	Strength	Date Initiated	Batch No.	Test parameter	Batch Disposition	Root Cause for Failure	Exhibit
OOS18095	10 mg	5/14/2018	RSC18225	CU by HPLC & Dissolution	Rejected	Batch specific Product issue	**Exhibit JG-12**
OOS18122	10 mg	7/13/2018	RSC18461	CU by HPLC	Rejected	No exact root cause identified	**Exhibit JG-13**
OOS18074	5 mg	4/17/2018	RSC18130	CU by HPLC	Rejected	No root cause identified & batch specific	**Exhibit JG-14**

These documented BU/CU issues discovered during inspection, automatically upgrades BU/CU risk scenario to **High**.

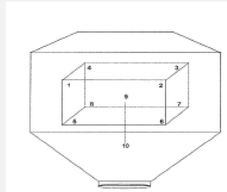
OPMA's Recommendation for High Risk Scenario

- For Exhibit and Validation batches: OPMA recommends comprehensive stratified CU (sCU).
- For Commercial batches: OPMA recommends to continue comprehensive sCU at appropriate interval for a significant number of batches.

BU Data Assessment

Blend Uniformity	Min: 95.6 Max:100.3 % RSD: 1.5	Min: 96.2 Max: 99.8 % RSD: 1.1	Min: 94.3 Max: 101.6 % RSD: 2.9

We reviewed the BU sampling plan (see right), sample size (2X unit dose), specs, as well as BU data for the three exhibit batches (see above). **All are acceptable.**



However, exhibit batch sCU data was not provided. Therefore, we issued an **IR** for exhibit batch sCU data and also to request Applicant perform sCU in validation and commercial batches.

- We specifically recommended ASTM E2810 sampling plan 2, 90%CI/95%Cov.

IR Response Review

Applicant's IR response did not provide the requested exhibit batch sCU data.

They did commit to performing sCU for validation and commercial batches, using our recommended sampling plan and CI/Cov. This sounded good on paper, but **their commitment is in discrepancy with their master batch records**, which indicated that sCU will only be performed for the "first three validation batches" (see circle below).

Testing needed	Samples: Sample occasion	Samples: No. of samples to be taken/ Quantity per occasions	Samples: No. of samples to be tested	Acceptance Criteria
Uniformity of dosage units (Content uniformity, By HPLC) (Content uniformity on 3 tablets from each interval marked C1 - C40 **)	A minimum of 40 intervals, distributed throughout the compression run, shall be sampled. (40 intervals shall be inclusive of hopper depletion study samples) **SET-1:** Samples marked (odd number samples) i.e. C1, C3, C5, C7, C9, C11, C13, C15, C17, C19, C21, C23, C25, C27, C29, C31, & C33 for optimum speed and C35, C37 & C39 for hopper depletion study* at optimum speed. **SET-2:** Samples marked (even number samples) i.e. C2, C4, C6, C8, C10, C12, C14, C16, C18, C20, C22, C24, C26, C28, C30, C32 & C34 for optimum speed and C36, C38 & C40 for hopper depletion study* at optimum speed. Sample quantity shall be 3 tablets at each interval for each set. And shall be collect in duplicate (Total 6 tablets). @ Note: These 40 intervals shall include significant events. ¢	6 tablets at each time interval	Uniformity of dosage units (Content uniformity, By HPLC) (Content uniformity on 3 tablets from each interval marked. (Set- II samples shall be analyzed if set- I sample fails)	All individual results within the range of 75.0% to 125.0% of target strength and shall comply with ASTM 2810-11 sampling plan-2 (addressing both within location and between location variation) at goalpost of 85 - 115% LC for a target of 100% LC with 90% level of confidence and 95% of coverage.

Note: These stratified sampling instructions shall be applicable for first three validation batches.

IR Response Review (Continued)

Now, when it comes to commercial batches, Applicant propose using sampling plan 1 (testing 1 tablet per location), which is **less stringent** than our recommendation of sampling plan 2. Furthermore, their **acceptance criteria are not in line with ASTM E2810**, indicating a lack of understanding for ASTM E2810 methodology.

Testing needed	Samples: Sample occasion	Samples: No. of samples to be taken / Quantity per occasions	Samples: No. of samples to be tested	Acceptance Criteria
Uniformity of dosage units (Content uniformity, By HPLC) (Content uniformity on 1 tablets from each interval marked C1 – C10 **)	A minimum of 10 intervals, distributed throughout the compression run, shall be sampled. (10 intervals shall be inclusive of hopper depletion study samples) **SET-1:** Test one tablet from each location samples collected from different locations at optimum speed. **SET-2:** Test remaining two tablets from each location samples collected from different locations at optimum speed.	3 tablets at each time interval	Uniformity of dosage units (Content uniformity, By HPLC) (Content uniformity on 1 tablets from each interval marked. (Set- II Remaining two tablets samples shall be analyzed if set- I sample fails)	**Stage 1:** Mean is within 90.0% to 110.0%of target and RSD is ≤ 5.0% **Stage 2:** Mean is within 90.0% to 110.0% of target and RSD is ≤ 6.0%

Note: These stratified sampling instructions shall be applicable for commercial batches.

When the mean is between 90-110%, upper limit on SE should be 1.267%, not 5.0 or 6.0%.

We also looked into recent OPMA assessment of ANDAs with the same Applicant and with the same drug product facility. We found a recent ANDA assessment where OPMA reviewer similarly flagged the facility's BU/CU issues and requested sCU for commercial batches. Applicant's response was not adequate. This provides supporting evidence that Applicant has significant issues with sCU.

Final Outcome: CR Deficiency

Your current sampling plan for commercial batches has insufficient statistical stringency and is therefore not acceptable. Continue the same comprehensive stratified CU sampling plan (as you have proposed for validation batches) in a statistically significant number of commercial batches.

Conclusion

This case study demonstrated the importance of connecting BU/CU issues discovered during recent facility inspection to Applicant's submission data. Together they provide powerful insight into Applicant's manufacturing process control. As observed from this case study, a lack of understanding of ASTM E2709/E2810 methodology can lead to critical deficiencies. Assessors should also examine master batch records for any discrepancy from their written commitment.

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Disclaimer

Identifying information (such as ANDA number, drug/Applicant/facility name) was removed/redacted. The authors have nothing to disclose in terms of conflict of interest. This poster presentation reflects the views of the authors and should not be construed to represent FDA's views or policies.