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**PHARMACE Replete**

Essential Nutrients for Drug-Induced Depletion
Quality control is a vital component for compounding pharmacies and should be present in all aspects of the practice. In the compounding industry, it is essential to perform regular and standardized tests to ensure that the pharmacy is ahead of the curve and consistently striving to improve the quality of all compounded preparations. United States Pharmacopeia (USP) Chapter <795> states that appropriate control procedures shall be established to monitor the output and to verify the performance of compounding processes.¹

Qualitative and Quantitative Physical Verification

Both qualitative and quantitative physical testing techniques must be performed by all compounding facilities. Qualitative physical verification can be completed in-

¹United States Pharmacopeia <795> states that to ensure accuracy and completeness, the compounder shall observe the finished preparation. One such verification method described in United States Pharmacopeia <1163> is weight assessment of final nonsterile compounded preparations. This article will focus on this weight-assessment technique and discuss common pitfalls and tools which can be used to better comply with current industry quality-control guidelines.
house at the pharmacy by visually inspecting the final compounded preparation for organoleptic properties. Such observational properties can include, but are not limited to, color, texture, continuity, odor, and overall appearance. Due to the descriptive nature of qualitative verification, this lends itself to being subjective—will your visual inspection for the color pink be the same as your colleagues? Likely not, and this is why quantitative verification is essential. Quantitative verification deals with numbers and can be measured and statistically studied; examples include pH values and weight assessment. We will briefly cover a weight-assessment technique described in USP Chapter 1163 that can be performed on your individualized dosage units.

**WEIGHT ASSESSMENT**

USP 1163 defines dosage units as dosage forms containing a single dose or a part of a dose in each unit. Common examples of such dosage units include troches, capsules, gummies, tablets, and suppositories. Additionally, as per USP 1163, to ensure the consistency of dosage units, each unit in a batch should have a uniform weight within a narrow range. Keeping this in mind, weight-assessment calculations can be performed on nonsterile compounded individualized dosage units.

The first step is to determine the theoretical weight of the dosage unit. This is calculated by adding the weights of each component (e.g., active pharmaceutical ingredients [APIs], excipients, base) in the final compounded preparation and dividing this weight by the number of units. Once completed, each individual dosage unit from a representative sample must be accurately weighed. USP 1163 classifies this representative sample as a minimum of 5% of the total dosage units or 10 individual units, whichever is less. Once the actual individual weights have been documented, these must be compared statistically to the theoretical weight to determine if they fall within the defined, narrow range. This range has been set by USP 1163 as plus or minus 10% of the theoretical weight. If the actual weight of each unit in the representative sample falls within this specified range, the final compounded preparation/batch has passed the weight assessment. However, if any of the actual weights deviate outside the plus or minus 10% range, a review of every step in the compounding process must take place to ensure that all steps were performed correctly and nothing was overlooked or omitted. Additionally, USP 1163 states that weight assessment would then be repeated with a larger representative sample of the finished batch. For this second sample batch, USP 1163 establishes a minimum of 10% of the total dosage units or 20 individual units, whichever is less, while keeping this sample batch separate from the previous one. At this stage, if even one dosage unit from the second representative sample falls outside the plus or minus 10% range, the entire compounded batch must be destroyed. This weight-assessment technique can be used to verify troches, tablets, and suppositories, to name a few. When performing this weight assessment on capsules, it is key that the weight range of plus or minus 10% relates to the contents in the capsules and does not include the capsule shell. The contents in the capsule can be weighed by first taring the balance with an empty capsule shell and then weighing each individual capsule in the representative sample. The resultant actual individual weights will be representative of only the capsule contents.

Not only can weight assessment be executed for solid-dosage forms as just described, semi-solid preparations (such as creams and gels) can be put through a similar test. Once again, the first step is determining the theoretical weight of the final compounded preparation. The weight of an empty container is then recorded. This container is in turn filled with the compounded preparation and re-weighed. Next, the weight of the empty container is deducted from that of the filled container. This filled weight is compared to the theoretical weight to determine if it falls within the plus or minus 10% range. As with the other dosage forms, if a deviation is found, the compounding records must be reviewed. If no errors in the compounding records are found and the deviation cannot be explained, the entire compounded batch must be discarded.

**SAMPLE CALCULATIONS**

**EXAMPLE FORMULATION**

**Diazepam 5-mg Rectal Suppositories**

*Rx*

For 24 suppositories × 1.35 mL molds

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diazepam, USP</td>
<td>0.120 g</td>
</tr>
<tr>
<td>Propylene Glycol, USP</td>
<td>0.24 mL</td>
</tr>
<tr>
<td>Silica gel (micronized)</td>
<td>0.60 g</td>
</tr>
<tr>
<td>MEDISCA SPG Supposi-Base</td>
<td>28.77 g</td>
</tr>
</tbody>
</table>

Theoretical weight:

\[
\text{Theoretical weight} = \frac{\text{Weight of Diazepam} + \text{Weight of Propylene Glycol} + \text{Weight of Silica Gel} + \text{Weight of SPG Supposi-Base}}{\text{Number of Suppositories}}
\]

Theoretical weight = \(\frac{0.120 \text{ g} + (0.24 \text{ mL} \times 1.038 \text{ g/mL}) + 0.60 \text{ g} + 28.77 \text{ g}}{24}\)

Theoretical weight = 1.239 g
Acceptable weight range:

- Lower Acceptable Weight Limit = 0.90 \times \text{Theoretical Weight (1.239 g)}
- Lower Acceptable Weight Limit = 1.115 g
- Upper Acceptable Weight Limit = 1.10 \times \text{Theoretical Weight (1.239 g)}
- Upper Acceptable Weight Limit = 1.363 g
- Acceptable Range = 1.115 g - 1.363 g

First representative sample size (5% of total batch or 10 individual units, whichever is less):

Representative Sample Size = 0.05 \times \text{Total Batch Size (24 Suppositories)} OR 10 suppositories [whichever is least]

Representative Sample Size = 2 Suppositories

Collection of actual weights from representative sample and results:

<table>
<thead>
<tr>
<th>Weight</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suppository 1</td>
<td>1.211 g</td>
</tr>
<tr>
<td>Suppository 2</td>
<td>1.199 g</td>
</tr>
</tbody>
</table>

**COMMON PITFALLS**

A common misstep that occurs when performing these weight assessments is comparing the average weight of the representative sample to the calculated theoretical weight. It is imperative to use the actual individual weights, as opposed to the average weight of the sample, as this can be misleading. For instance, if half of the dosage units in the representative sample are over-filled and the other half under-filled, the average weight can still fall within the desired range. This can, in turn, lead to false-positive results. Moreover, not only is it crucial to use individual actual weights, it is just as important to set the plus or minus 10% weight range in relation to the theoretical weight and not the actual average weight. Setting the acceptable range based on actual weights is another common mistake, which can once again lead to false-positive results. If the individual actual weights fall within the range of the average actual weight, this suggests that the compounded dosage units were similarly filled amongst themselves. It does not indicate that the dosage units are adequately filled, as they were not compared to the theoretical weight.

The concept of using weight assessment as a quality-control tool at your compounding practice relies on assuming that the API concentration is uniform and the final compounded preparation is homogeneous. Although this technique is quick and inexpensive to implement, it will not replace the need to send final compounded preparations for external testing. Even if the weight of every single dosage unit falls within the plus or minus 10% range, these results cannot be extrapolated to the amount of API in each dosage unit. A positive result is indicative of a good filling technique, in that each dosage unit was evenly filled to an acceptable amount. For example, if the compounded mixture is not homogeneous and the API has settled before filling, the actual weights can be acceptable, but the amount of API would be concentrated in the second half of the units. Consequently, analytical testing of final compounded preparations with validated test methods is essential to ensure that the preparation is stable and accurately dosed.

**Factors Affecting Misdosing**

Many factors influence misdosing and commonplace examples include incorrect calculations, poor compounding techniques and facility-related issues. Erroneous calculations typically result from a failure to not account for conversions (e.g., salt to base), potency (e.g., water content and assay result), units (e.g., mg vs g), etc. These miscalculations can severely impact the overall patient outcome. Moreover, it’s no secret that training and practice result in improvement; hence, more experience typically implies a better technique. This highlights the importance of having all compounding per-
Quality Control

Minimizing Potential for Inaccuracy

One of the best approaches to avoid errors during the compounding process is by getting a second set of eyes to double-check all compounding records and calculations. The importance of relying on pharmacy colleagues (i.e., pharmacist-in-charge), and having access to a knowledgeable external technical support services team cannot be emphasized enough. This additional quality check significantly increases odds of discovering mathematical miscalculations and incorrect formulation steps. Moreover, every compounding practice should have accurate and complete standard operating procedures, master formulation records, and compounding records. These documents aid in ensuring that the right things are being done and that quality-control processes are built into them. For instance, all master formulation records for individualized dosage units should contain a physical-quantitative-weight assessment verification step similar to the one discussed earlier. Furthermore, as poor compounding techniques can lead to inadequate final compounded preparations, regularly attending training programs is another method to decrease potential for error. These training programs should be comprehensive and cover current industry guidelines, regulations, best practice standards, and trends to expand attendee knowledge on the subject matter. However, it is insufficient to simply send personnel to specialized compounding training programs, as without constant practice and learning, skills tend to be lost. Second to hands-on live trainings, on-site training modules come into play by continuously testing trained personnel on theoretical principles. All the aforementioned tools allow staff to be regularly tested on their knowledge and skill to ensure that all abilities are honed and that trained personnel remain current in their knowledge. Now, is it enough to just have all these tools on hand to simply comply with current regulations? No! These processes must be implemented and tailored to each individual compounding practice. Every process performed at the pharmacy must be documented because without such documentation the process was not completed in the eyes of an inspector. These extensive records will track trends and can help determine the underlying causes of errors.

Conclusion

The purpose of this article is to bring awareness to the importance of quality control in a compounding pharmacy. Although the covered weight-assessment calculation is not an all-encompassing quantitative verification technique, and is only one of many variables within a comprehensive quality-assurance program, it provides a quick and easy means of quality control. Such quality-control processes aid in achieving a final compounded preparation of the highest possible quality. With accurate quantitative weight-assessment verification techniques, the pharmaceutical compounding industry is another step closer to ensuring that patients receive the best possible pharmaceutical care.

References


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Perfect calculations and technique do not necessarily result in an acceptable, final compounded preparation if the compounding area, technology, and equipment are not up-to-date with current standards.