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Cleaning Validation for Packaging Equipment: Part 1

Sometimes I am asked about cleaning validation for packaging equipment, and the thought behind the question appears to be that this is not a critical cleaning process and therefore doesn't require cleaning validation. While it is true that effective cleaning of some packaging equipment may be much easier to achieve, it is not necessarily true that the effectiveness of such cleaning is non-critical.

Before I discuss the topic, let's make sure of some definitions. By packaging equipment I am referring to primary packaging equipment, usually of a finished drug product. That includes such examples as liquids being filled into vials and then capped, and tablets being filled into bottles and then capped. Once the finished drug product is in its primary packaging container, any secondary packaging (bottle or vials into cartons, for example) is generally not critical, and cleaning validation is not required (although cleaning may be needed for the equipment to continue to function appropriately, it is usually not necessary for the quality and safety of the packaged drug product).

Why is cleaning for the primary packaging equipment critical? For the same reason that cleaning of the mixing or blending equipment is critical – it is possible that residues from one product to be packaged may contaminate (affect the safety or quality of) the next manufactured product on the same packaging line. In one sense primary packaging may be viewed as even more critical in that residues on some surfaces (such as hoppers, slats, and filling needles) may be more likely to *non-uniformly* transfer to the next manufactured product. What may happen is that residues on certain surfaces may preferentially transfer to a given portion (usually the first portion) of the next packaged product. In PDA Technical Report #29, these equipment locations are referred to as "critical sites".

For example, in a liquid filling operation, where 10,000 L is being filled 50 mL per bottle, residue in the cleaned filling needle is not likely to be evenly distributed into all 200,000 bottles of filled product. Rather, that residue may preferentially be removed and only contaminate the first 10 (for example) bottles. In this sense, cleaning validation is even more critical for packaging equipment.
Some may question whether cleaning validation is required for packaging of such items as coated tablets and gelatin capsules. After all, coated tablet residues left on surfaces are most likely to be residues of the coating left on surfaces due to such effects as abrasion. However, if those coated tablets can be crushed during the packaging process, then drug active may be released. The same is true for capsules, where active material may be released and be present on equipment surfaces before cleaning. If not adequately cleaned, those residues of actives may contaminate the next packaged product. And, because of non-uniform transfer, this concern becomes even more critical. In the case of capsules and coated tablets, if one can clearly establish that the capsules or coated tablet are never crushed or otherwise damaged so as to release product, then it may be possible to write a justification as to why cleaning is not critical and thus cleaning validation may not be required. However, even in that situation, it would be prudent to prepare a plan of action if (in the future) capsules or coated tablets are crushed to release active.

If packaging equipment cleaning is critical and cleaning validation is required, the next steps are to consider the how/when/where of cleaning validation. We'll cover these next month, with a focus on surfaces to consider in measuring residues, on setting limits, and on protocol challenges.