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Excipient variability: Mostly a fuss

Excipients can, and do, cause batch failures in pharmaceuticals, which raises two questions for formulators: 1) How often are they the culprit and 2) can we elucidate what role excipient variability plays in this manufacturing fact of life?

The industry has had some successes in capturing excipient variability using principal component analysis (PCA) to study the data in certificates of analysis [1]. The approach works well with common excipients that have a long manufacturing history and robust data set. It's also a powerful way to capture actual variability and can, with appropriate care, determine which vendors produce "low-variability" materials. It can also capture the real variability in manufactured systems rather than some elusive "edge-of-specification" material that may be unrepresentative in other ways.

You can then choose to use a high-capability vendor (i.e., one whose products have shown low variability). You can also make decisions about vendors who will not or cannot make such data available.

Reported data can be satisfyingly tight and reproducible for many reasons. Assuming that we can trust the numbers—which you can check using some basic data analysis techniques—we are left with what author and chemist Primo Levi captured in his eloquent story, "Chromium," i.e., that analytical incompetence masks real variability [2]. A careful purchaser can test this possibility.

Of course, "specifications" don't capture everything about a material and what they miss may be important to you. However, you could ask, "If everything we know about a material suggests that it isn't variable, what are the chances that what we don't know about it is variable?" We can test that hypothesis. In many cases, vendors whose products have a good record of "low variability" in the parameters that are generally reported (or required by the pharmacopeia) also show low variability in infrequently measured parameters [3]. Thus, you could at least narrow the number that you decide to test for the unknown parameter.

Plus, some methods are more variable than others, and their results may not reflect the material tested. For example, particle size tests on excipients can be difficult to interpret [4]. Of course, particle size can affect excipient performance, but it's a relatively subtle effect in many cases. So if PCA of an excipient reveals "site differences" in materials that relate specifically to particle size, should we assume that those materials will perform differently in our formulations? Indeed, are they different at all? Before assuming material variability, maybe you should test whether the analytical methods from each site produce the same outcomes.

Large pharmaceutical companies have the resources to implement the approaches discussed above, but you can also use a statistical approach, which would be much less costly than failed batches.

My position: If you're using a pharmacopeial-grade excipient from a trustworthy vendor in a process that you understand, and you've done the due diligence to show that the vendor's process has a high capability, then the chances of "excipient variability" causing a batch failure are acceptably low, and you can take steps to reduce them further.

We work in an innovative industry, stuffed with talented people, and we've served patients well. However:

1. If you have a completely novel (at least to your company) process that you've never studied (let alone seen implemented by your manufacturing partners), why blame the excipients for a failure?

2. If you use a vendor with whom you don't have a strong and trusting relationship, should you blame the variability of the vendor's excipients for failures?

3. If you choose an excipient and go "off trail" in how you use it, is the variability of the excipient to blame if your process suffers a failure? *T&C*

References

1. Kushner, J. Utilizing quantitative certificate of analysis data to assess the amount of excipient lot-to-lot variability sampled during drug product development. Pharm. Dev. Technol., 2013 18(2): 333-342.

2. Levi, P. The Periodic Table, "Chromium." 1975.

3. Gamble, J.F. et al. Investigation into the degree of variability in the solid-state properties of common pharmaceutical excipients—anhydrous lactose. AAPS PharmSciTech. 2010 Dec; 11(4): 1552–1557.

4. Gamble, J.F. et al. Investigation into the impact of sub-populations of agglomerates on the particle size distribution and flow properties of conventional microcrystalline cellulose grades. Pharm. Dev. Technol., 2011 16(5): 542-548.

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