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Passing USP 788 with Light Obscuration Puts You and Your Patients at Risk

Light Obscuration (LO) is a frequently used method for subvisible particle quantitation in biologics. However, it is well known to significantly undercount subvisible particles, particularly when the particles are proteinacious,[1-3] leading to questions about its accuracy and suitability for lot release.

In a famous example of over-reliance on LO, Omontys (Preginesatide, Affymax Inc.) was pulled from the shelves in 2013 due to the tragic death of seven patients and anaphylaxis in scores of others. At the time, the exact cause was unknown but a follow-on investigation by the FDA determined that subvisible particles were present even though Omontys passed USP 788 subvisible particle count thresholds using LO.[4] Unidentified subvisible particles and poor characterization of any drug could lead to deadly immunogenic responses.

The bad news did not stop in the clinic. Affymax's share price plunged over 85% on the news, costing the company $10 Billion. Affymax subsequently lost a distribution contract, had its stock delisted from the NASDAQ, and was forced to lay off 75% of its workforce. A year after Omontys was pulled from the market, Affaymax's Board of Directors and shareholders voted to completely dissolve the company and cease operations.

The lesson we can learn from Affymax is that passing USP 788 particle limits is too low of a bar for drug development programs. Simply checking a box that a product falls under a subvisible particle count limit is potentially catastrophic for both patients and manufacturers. Subvisible particles are a Critical Quality Attribute, and they need to be fully characterized throughout development. This includes obtaining accurate subvisible particle counts but also determining their source, how they are formed, and the impacts these particles have on patients. The most effective way to do this is with multiple orthogonal techniques, ideally using methods that can be used throughout the entire development process so baseline levels can be established early on. Had Affymax fully characterized their product during development as well as for lot release, they could have potentially reduced the fatal reaction rate to zero.

FAST DISSOLUTION OF AFFYMAX

- Failed to identify potentially deadly subvisible particles using light obscuration
- Share price drop from $14.10 to $2.34
- 75% workforce laid off
- Revenue projection of $700 M to $0
- Complete stoppage of business and operations

More recently, the FDA has stated that merely having particle counts below the USP limits does not mean that a drug product automatically passes the safety requirements because the USP limits established in USP 788 and 787 were not developed for proteinaceous particles and those historical limits are not supported by the safety data.[5] Quantifying the particle counts at the historic USP size bins (>10 µm, >25 µm) is required but so is characterizing particles <10 µm and knowing whether the particles present are intrinsic, inherent, or extrinsic. As is known from the previously cited literature, this something that cannot be obtained solely using LO.

One method that satisfies the FDA's characterization requirements and allows for analytical continuity from early to late-stage particle characterization is Aura™ from Halo Labs. Based on the original membrane microscopy method found in USP 788 and allowed under the newer digital imaging methods found in USP 1788, Aura is the only subvisible particle analysis instrument that is refractive index and sample volume independent. Therefore, it can be used at any development stage. Small (25 µL) volumes can be used early in development when sample is limited, and large (10 mL) volumes can be used in late-stage development and QC when samples are plentiful or there is a need to measure an entire container. In addition, the Aura provides a level of analytical robustness not seen with other methods. It measures 100% of the sample applied, easily allows for replicate measurements, provides images of both individual particles and the entire particle population, identifies the particle type (protein, non-protein, inherent, intrinsic, and extrinsic), and retains the measured particles if repeated analysis is required.

Ultimately, the burden of ensuring drug safety and saving patient lives is on everyone. As innovations and new technologies drive new drug discoveries, reliance on antiquated technologies or complying to outdated regulations will certainly lead to disastrous consequences to the patients we care for and the organizations we work for. Thus, it is incumbent on all to ensure that methods being used to assess product safety are robust, reproducible, and deliver the information needed to make the best decision about a product. With proper due diligence in characterizing drugs from development through lot release, we all can achieve the higher goal of saving lives.

References

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