Excerpts taken from the PDA 2005 Annual Conference Paper presented by Julius Z. Knapp and Gerald W. Budd

Part IV: New Developments in Visual Inspection

Implementation of Standard Procedures for Visual Inspection: NIST Traceable Automated Contaminating Particle Measurements, using the NIST^2-ParticleVision™ System

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New Directions

There are three possible batch quality evaluation measures now in view.

1. The most accurate and economically effective measure of visible particle contamination in a parenteral batch is the batch reject rate. For accuracy, the raw inspection data must be evaluated with a calibration curve relating particle rejection probability to particle size. The use of the calibration curve transforms the variable raw accept/reject decision into a sharply delineated action. The visible inspection data must be determined in a fully validated inspection procedure using the defined light intensity and operating conditions.
2. A quick evaluation of the composition of contaminating particle provides a starting point for corrective action. When process improvement is a major focus, continuous analysis of the particles in the rejected containers provides production staff with corrective action information.
3. The Attribute Sampling Inspection can provide a rough, independent check procedure when the raw visible inspection data is transformed with a calibration curve relating particle size to it's rejection probability and the Knapp Accept/Reject boundary conditions are used. The results of the Attribute Sampling Inspection Tables must still be statistically interpreted to provide useful results.

Process Improvement Perspectives

The minimum average batch rejection probability cannot be evaluated with the present individual component piece-wise testing procedure now in use. This approach to the determination of system capability in automotive engine terms is the equivalent of testing the dimensions of individual components of an engine and using those tests to evaluate the dynamic performance of the engine. The failure to implement performance testing before production begins means that dynamic testing is performed with the loss of pharmaceutical product. The minimum average batch rejection probability can be evaluated by testing a fully processed and assembled container group; such as the quantity of containers used for the media fill test. This can be performed with a test group of containers filled with WFI, stoppered and capped in the normal procedure. The containers in the test group are inverted and shaken on a microbiological shaker for ½ hour and then inspected after storage long enough for all cavitation bubbles in the containers to have dissipated.

This test will show the cleanliness of the washed glassware and the effectiveness of the inverted container gravity draining system used in container washing. Another particle source is the rubber fragments generated in the shaker bowl and that have adhered to the surface of the stopper. These fragments can be dislodged in the normal agitation that occurs in product shipment and, in solution products, be detectable at the clinical injection site. Detection of the source of these visible particles in the production process and on-going process improvement is essential under PAT directives.

Meniscus Effects

Recent work has shown that the movement of the liquid in the container in response to the spin and stop particle movement pulse must be considered the response of a tuned non-linear system. The Figure 5 below shows the effect of using non-optimized spin excitation pulses on the shape of the meniscus during the inspection period.

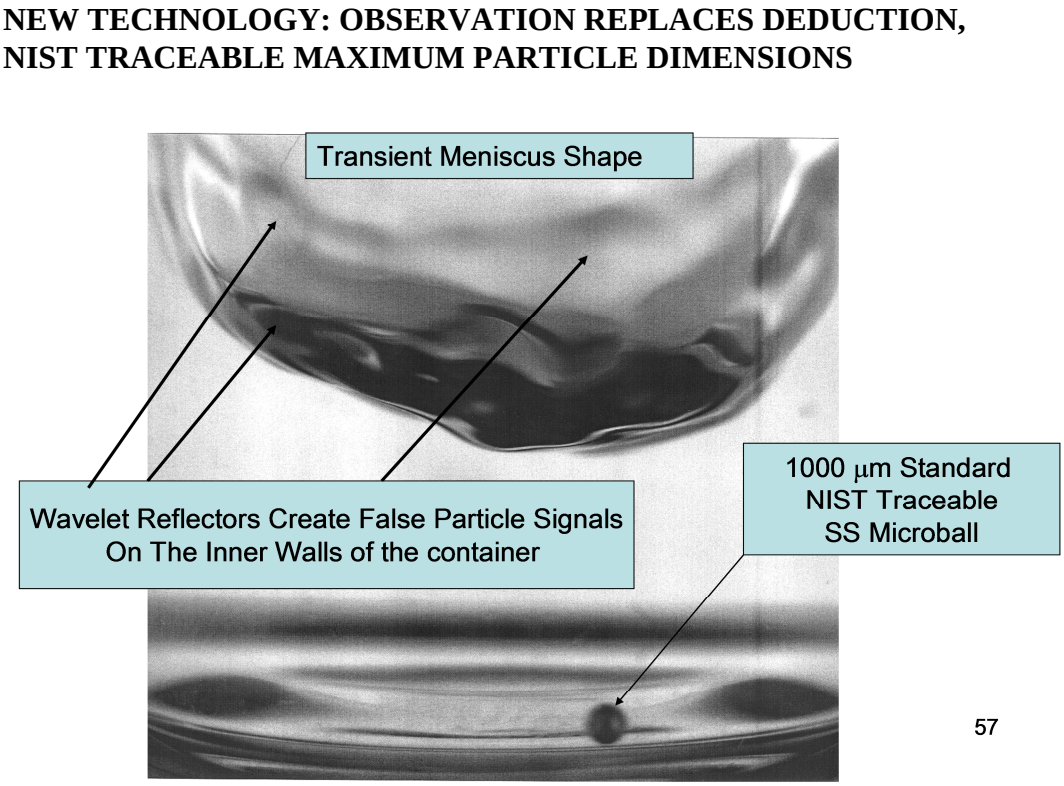

FIGURE 5 - Side Effects from the Dynamic Meniscus Contour

An non-optimized spin pulse can result in multiple deformations of the shape of the meniscus. The resulting cavelets can produce focused light spots on the walls of the container that cannot be separated from particle signals. A 1000 μm calibration ball is seen in the foreground.

An Optimized Motion Profile for repeatable Fluid Dynamics

The Phoenix Imaging NIST^2-ParticleVision™ System provides a unique platform for the study of fluid dynamics within small containers, specifically those used for small volume injectables (SVI). The system has the ability to pre-positioning particles in the container by rotation of the

container using a pre-determined “Velocity Motion Profile” (VMP). The characteristics of this VMP are unique to each container shape, size, fill volume, viscosity of fluid, and the surface tension of fluid.

A characteristic VMP is illustrated in FIGURE 6 below. It shows the start of the profile from the initial rest condition (S0). The ramp up to a initial spin velocity (R1), the spin velocity (V1) and the ramp down to zero velocity (R2). In general, only a single spin or angular velocity is required for most materials. However, the velocity during spin need not be a constant and may vary during the profile. The duration of the spin is critical and is very influential in the amount of energy imparted to particles in the solution. The ramp down from the spin velocity to zero velocity is also a major factor in the fluid dynamics and often is as rapid as possible. The image acquisition sequence can occur at a number of points within the profile but normally occur after zero velocity has be obtained, indicated by (T0) in Figure 6. Large heavy particles tend to settle very rapidly and the image acquisition sequence for detection of these particles must occur shortly after the rotation has stopped. Additional image acquisition sequences may be performed at other times to enhance the detection of other types of contaminating particles, represented by T1 and T2 in the figure.

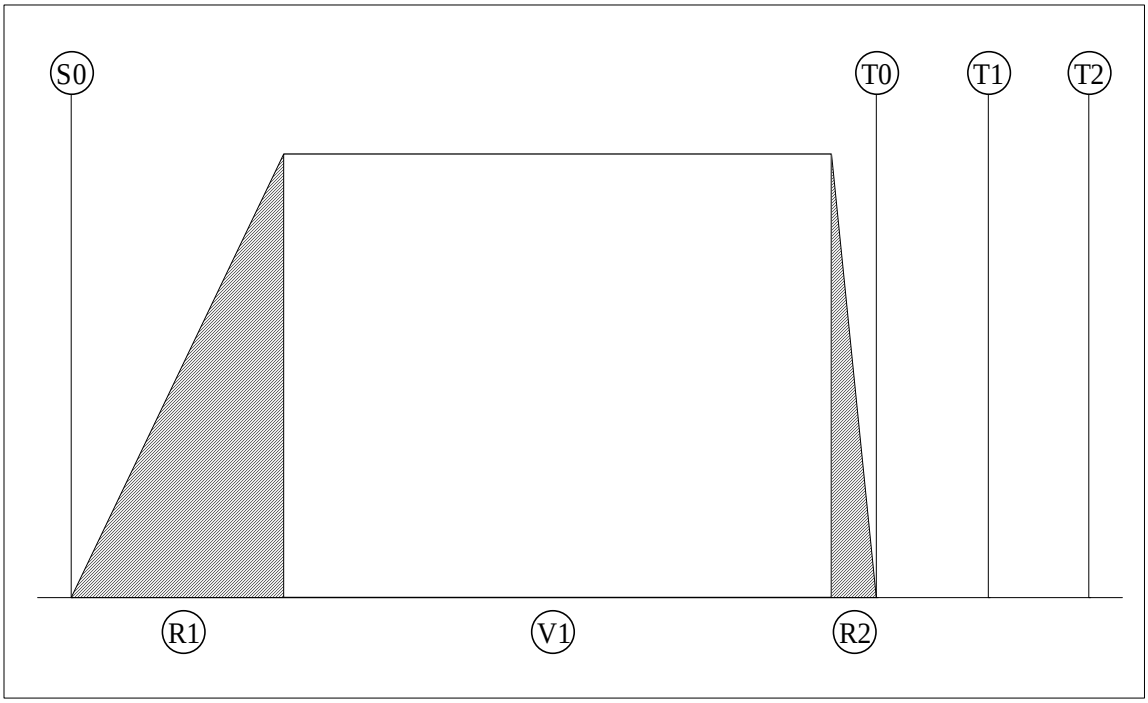

FIGURE 6 – Representative Velocity Motion Profile

The ideal VMP causes substantially all of the particles in the injectable solution in the container to rotate, with approximately equal initial velocity, in a shell volume adjacent the inner walls of the container. As more energy is imparted in the velocity motion profile the fluid will experience a toroidal motion in which fluid will move along the container bottom toward the center of axis of rotation, upward along the axis of rotation and then downward along the container walls. The proper velocity motion profile will cause the migration of particle from the inner wall of the container toward the center of the container.

The degree of migration of the particle is directly related to the mass of the particle, heavy particles will migrate only slightly away from the wall, and particles with less mass will migrate toward the bottom center of the container. Particles with the least mass will be moved to the

center of the container and may even be lifted from the floor of the container. It is desirable to use a velocity motion profile that will position particles in the mass range being studied in a small volume on the bottom of the container at the center of rotation, referred to as the optimized inspection volume (OPTIV).

Illuminating all the particles within the optimized inspection volume with a patented lighting allows for the imaging of particle as small as 40µm in diameter. The detection of particles by movement on the container bottom and in solution is achieved by orienting the sensor with a downward angle with respect to the axis of symmetry of the container. The optimized motion profile allows for the detection of all particles within the optimized inspection volume of the container.

Dynamic Flow Effects with an Optimized Meniscus Shape

The following six-image sequence commences 48 milliseconds after the end of the spin and stop velocity pulse and continues at 48 millisecond intervals. The images illustrate the result of toroidal flow on particle movement in a container following an optimized spin and stop velocity pulse. The particles are 100 µm diameter carbon balls in 3ml of WFI in 5 ml container. The particles begin near the perimeter of the container and migrate toward the center of rotation.

FIGURE 7.1 – T_0

FIGURE 7.2 – T_0 + 48 milliseconds

FIGURE 7.3 - T_0 + 96 milliseconds

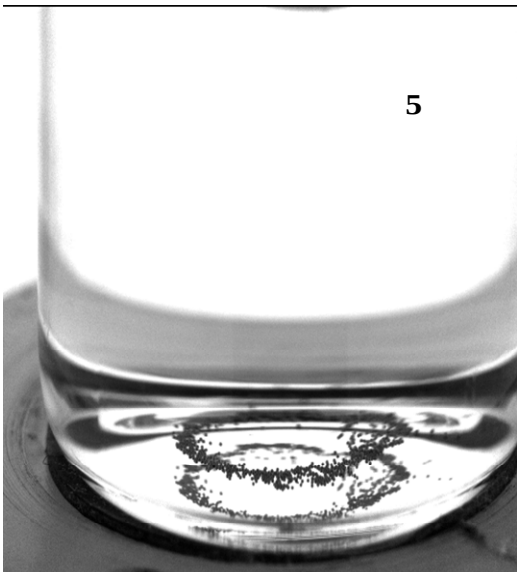

FIGURE 7.5 – T_0 + 192 milliseconds

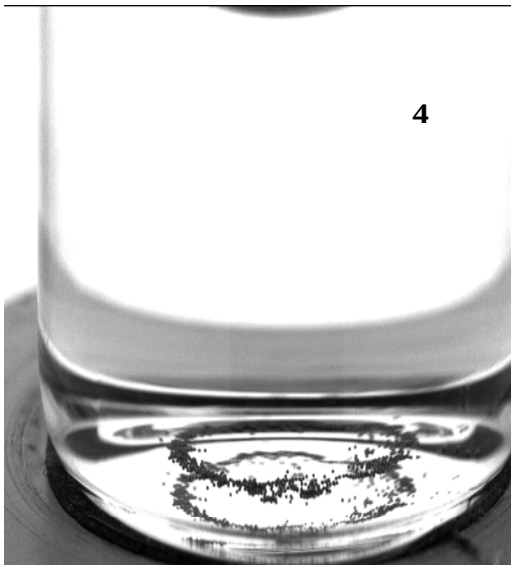

FIGURE 7.4 – T_0 + 144 milliseconds

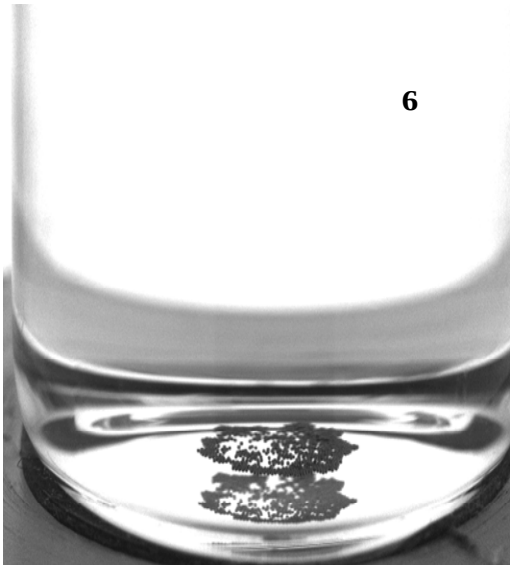

FIGURE 7.6 – T_0 + 240 milliseconds

The sequence of images in Figure 7 commences immediately after the end of the spin pulse in which the carbon particles have been centrifuged to the container walls. Fig. 7.1 records the collapse of the carbon particles from their position on the inner wall of the container into a ring formation at the bottom of the container. The image sequence shown in Figures 7.2 through 7.6 show particle movement toward the center of the container, concentrating near the axis of rotation. The final image shows a mound centered in the vial pulled in the direction of the imposed toroidal flow.

This data indicates that the pattern of fluid flow under the test conditions can be defined as:

1. down at the container walls
2. across the container bottom toward the central axis of rotation
3. up on the axis of rotation
4. across the meniscus toward the outer wall and repeat

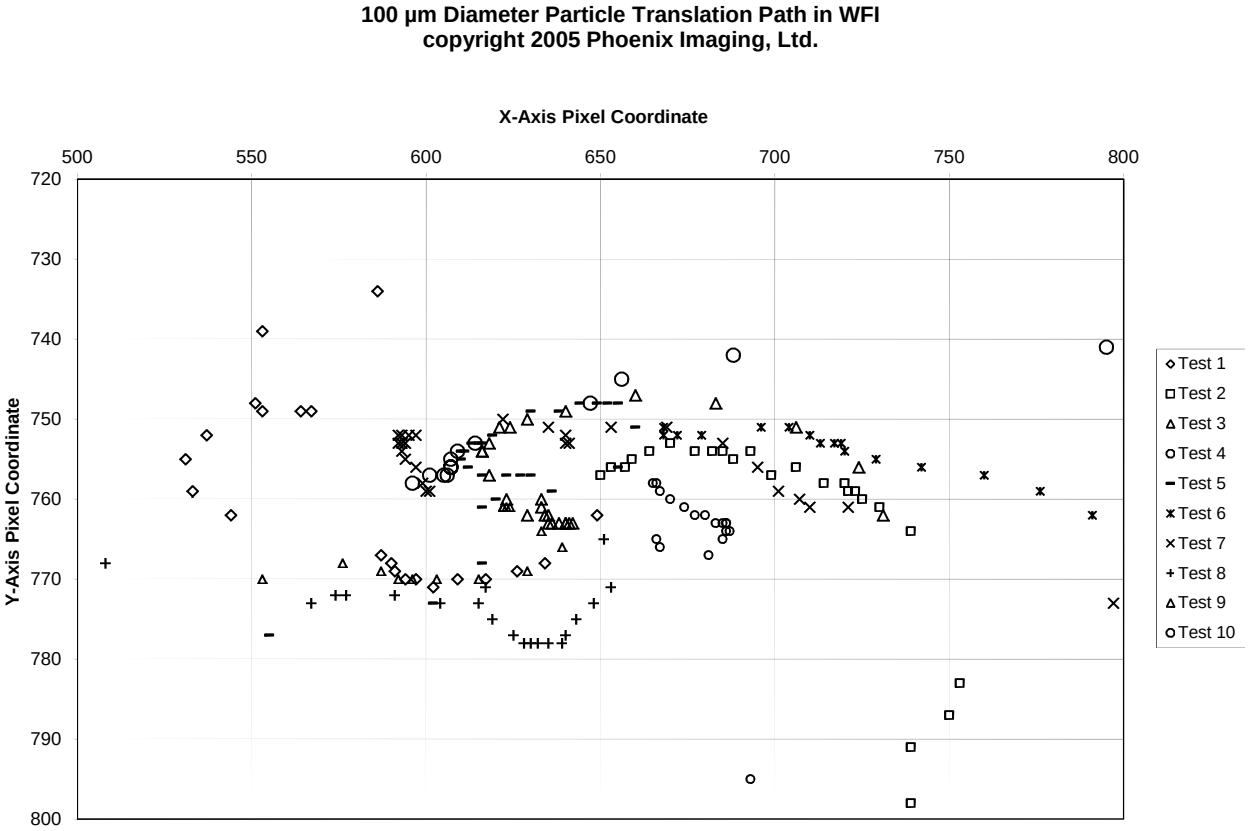

FIGURE 8 – Movement of Particle toward Axis of Rotation for 10 independent runs

Study of the Particle Movement in Transient Sequence

Figure 8 above illustrates the results of 10 tests using the same experimental conditions. The sample was removed from the instrument between each test and the particle, a 100µm stainless steel sphere, was allowed to randomly position itself in the container prior to the start of the next test sequence. The instrument used a consistent motion profile, a sequence of acceleration, duration at velocity, and deceleration. The particle paths illustrate that the general tendency is to migrate toward the center. This area of concentration is fairly well defined and allows the instrument to measure particles in this volume

accurately. The basic concepts implemented in the instrument are protected by U.S. and International Patents with additional improvements patent pending[33].

Insights from the Study of the Liquid Transient Sequence

The experimental data reported here was recorded on a single station hand positioning device. The accuracy achieved uses switching of the size evaluation algorithm during the measurement, a concept that cannot be realized with presently available automated particle detection systems. The commercially available non-destructive automated visible particle inspection systems use invariant pulse height particle signal analysis.

The system can be easily expanded using a parallel design to incorporate multiple inspection heads. The inspection head incorporates the mechanical rotation device, illumination module, sensor module and image processing unit. The Sensor and Illumination Module are designed for the inspection of a specific size, shape and fill volume container. The modules are designed to be interchangeable and are self-locating on hardened steel pins, that is the Sensor Module is a sealed unit designed for a specific field of view. The housing seals the CCD sensor and optics inside the package and does not require opening to make the interconnections. This allows a Certified Calibration Curve to be generated in advance for each Sensor Module shipped to a customer. The Sensor Module Calibration Curves can be entered into the ParticleVision™ system to provide accurate measurements. The latest iteration of instrument has renamed the product as ParticleScope™.

Achieving the sizing accuracy of the single container bench top system reported here in a high speed fully automatic inspection system that can accommodate current production line speeds can be accomplished with the addition of a container handling system. Closing the process improvement loop requires the addition of a fast, semi-automated, particle identification system that is now available.

Extrapolating the demonstrated toroidal flow pattern to the inspection of particle contamination in lyophilized products is now defined. Heavy particles will be trapped on the bottom surface of the cake/container interface. Floating debris will be trapped in the top surface of the cake. Particles embedded in the body of the cake must be of a size that will respond to low energy Brownian currents in the liquid phase of the product. These smaller particles are well below the visible particle range. A paper by Knapp and Colleagues will present a detailed experimental report on this aspect at the 2005 PDA Annual Meeting.

Calibration Curve Details

The particle sizes chosen for the containers range from those with low probability detection rates in the Accept and Gray Zones to the Reject Zone ‘must-reject’ particle sizes that are detected without significant error. To attain inspector performance comparable to that on a production line, it is important to limit the number of the ‘must-reject’ particle contaminated containers to 25 % of the total test group. To achieve correlatable visible particle inspection data, the quality and the quantity of the light at the inspection point, the physical capability and expertise of the inspector, the inspection background and the duration of the inspection must all be standardized.

A calibration curve relating particle detectability to particle size was made with a dimensioned range of NIST traceable stainless steel microspheres using the laboratory version of the ParticleScope™ system. This calibration curve is the Rosetta Stone to achieving a practical process line measurement capability. Using the high speed image processors based on current PC technology and proprietary vision analysis

technology it is possible for the ParticleScope™ system to perform analysis of multiple inspection volumes within the container. The optimized motion velocity profile allows the system to "place" contaminating particles of a specific mass range within defined inspection volumes within the fluid. Unlike many systems that search for random contaminating particles, this technology anticipates the position the contaminating particles within defined inspection volumes where they can measured. Each inspection volume can use a unique image analysis algorithm to extract the data with particular characteristics. The capability of the system is illustrated in FIGURES 9 and 10. FIGURE 9 represents small particles with a diameter of <350 µm with a density less than 8.2 gm/cc. This is referred to as the Calibration Curve for small heavy particles. This inspection volume is centered around the center bottom of the container. The FIGURE 10 represents the large heavy particles that settle quickly and are found near the interior wall on the bottom of the container. It should be noted that the system will "detect" the presence of particles 100% of the time. However, the particle size is only measured when they are positioned within the inspection volumes. When position within the inspection volume(s) the system will determine the particle size measurements with 1% accuracy with 95% Confidence limits.

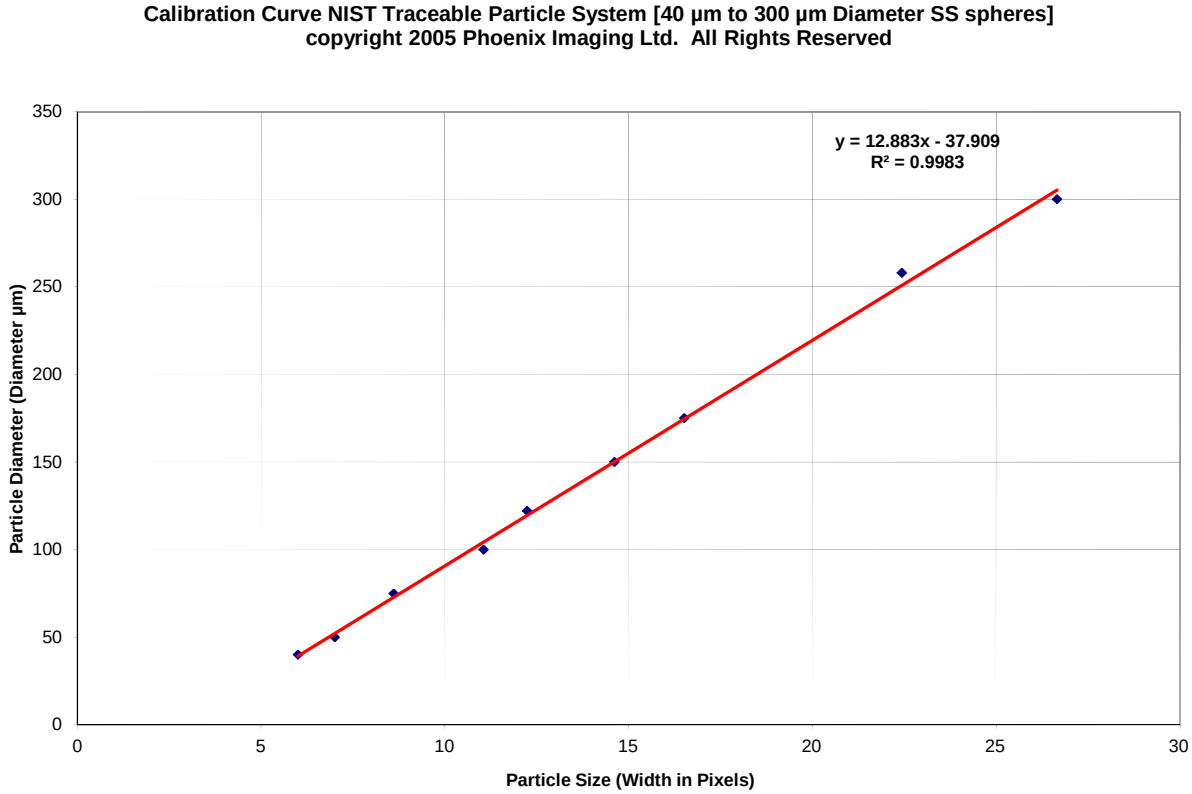

FIGURE 9 – CENTER FIELD ±1% LINEARITY CURVE WITHIN 95%CONFIDENCE LIIMITS FROM 50 TO 300µM

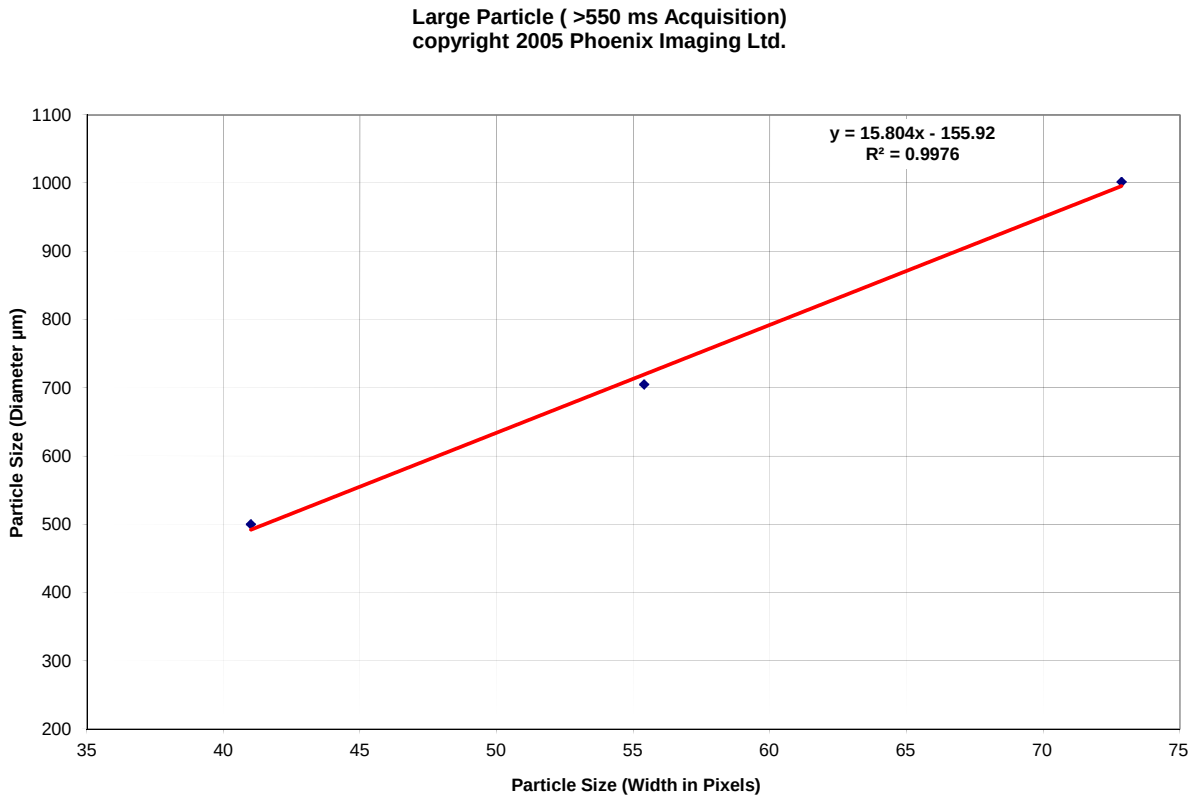

FIGURE 10 - NEAR FIELD ±1% LINEARITY CURVE WITHIN 95%CONFIDENCE LIIMITS FROM 450 TO 1000µM

CONCLUSIONS

Accurate visible particle measurements and validations based on them can now be achieved with new NIST traceable maximum particle sizing technology.

The final selection of new particle contamination acceptance limits must wait the accumulation of correlatable data. There is widespread belief that the quality of present production has outstripped the measurement capability now in use.

The impact of the advances in Science and Technology since the 1% Level II Quality Standard was first publicized in 1968 must be considered in the selection of new quality limits. The fully developed methodology in digital circuit manufacturing that marked the latest advance to 0.6 micron geometry marks a sea change in the perception of the quality limits for parenteral manufacturing. Economically effective methodology to limit particle contamination to a size that can traverse capillaries is now available. The question that must now be asked is what cost/quality goal should be set.

An immediate goal of moving to a 0.65% AQL is a conservative action. The final choice of new contaminating particle acceptance limits must wait the accumulation of correlatable data firmly supported by NIST traceable measurements.

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