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

Part I: Background Information on Current Methodology

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

Julius Z. Knapp
Research & Development Associates, Inc.
Somerset, New Jersey

&

Gerald W. Budd
Phoenix Imaging Ltd.
Livonia, MI 48152
gbudd@phoeniximaging.com

An essential feature of the non-destructive inspection for contaminating particles in injectable products is that these contaminants are randomly sourced and are randomly located within the containers of an injectable product batch. The USP has defined the capability of the skilled human inspector to detect and remove particle contaminated containers as the quality level benchmark for injectable products. Following GMP, any new inspection procedure must be shown to be at least as effective as its predecessor. The preceding methodology was the single container inspection for visible contaminating particles performed at the injection site by clinical personnel. Fortunately, the methodology for comparing and evaluating human inspection performance is now well established.

New data on the control of the non-linear resonance of liquid movement in the container makes possible the transformation of the randomly positioned contaminants into a well-defined inspection volume. This new liquid excitation capability makes possible the capture of a sequence of particle size determinations whose mean value contributes to improved data sizing accuracy.

Knapp's publications have established that particle detection is described by the probability of detection. Without a reference standard however, his work has been difficult to standardize. A set of NIST traceable sized spheres in stainless steel and glass is now available. The spheres range in sizes from poorly to uniformly detected in each inspection. This provides an opportunity to establish a standard detection probability to contaminating particle size calibration curve. The USP adoption of such a calibration curve will provide the basis for an international standard of visible contaminating particle quality levels. Use of the calibration curve transforms the probabilistic variability of visible inspection data described by Knapp into the "simply repeatable form" required for the correct use of the Attribute Sampling Inspection Tables. The present use of these tables with raw inspection data results in the acceptance of inferior quality batches and the rejection of good batches.

The standard calibration curve should be augmented with production rejected material using either the Phoenix Imaging NIST^2 -Particle Vision™ System or a low power stereo microscope. The technology presented here uses cutting edge technology and has demonstrated sizing accuracy within 10 µm from 40 to 300 µm particles and ±3% accuracy from 500 to 1,000 µm diameter particles.

INTRODUCTION

Evaluation that the visible particle incidence rate is within USP[(1)] acceptance limits for human or veterinary use is an essential part of the injectable batch release procedure[(2-4)]. It is also an essential prerequisite to the continuous improvement of the quality of an injectable product batch and to the reduction of product cost. These ends have been achieved by incorporating advances in behavioral science, physics and biophysics, illumination and mechanical engineering, pharmaceutics and statistics into a single analytical structure.

Any proposed inspection for visible contaminating particle size in an injectable product, manual semi-automated or fully automated must be validated before it can be used on a USP listed product. Validation in this GMP sense means that it must be demonstrated to be at least as effective as the preceding method or mechanism. The preceding method of inspecting injectable products for contaminating particles was the inspection of single containers by clinical staff at the injection site.

Visible contaminating particles, as shown in Knapp's papers[(5-18)], are randomly distributed throughout the batch. As such, a validated 100% inspection is essential to achieve accurate, sensitive contaminating particle incidence rate results. The use of the Attribute Sampling Inspection Tables with raw visible particle inspection data results in the incorrect rejection of good batches and incorrect acceptance of undesirable batches. The use of the Knapp-Abramson analysis framework provides the methodology which transforms raw visible particle inspection data into a form acceptable to the Sampling Tables. For general use, the sensitivity and accuracy of the batch reject rate makes its use more desirable than decisions reached with the model based Sampling Inspection. Although the use of Attribute Sampling Assay Tables can be made compatible with raw visible inspection data, its limited sensitivity and the need to interpret the probability of the results obtained may very well shrink its future use to that of an investigatory tool.

UNIFORM VS RANDOM BATCH CONTAMINATION

The introduction of a visible particle standard set in which the dimensions of the progressively sized single particles are traceable to the primary dimensional standards maintained by NIST[(19)] makes possible the generation of a calibration curve. This calibration curve relates particle size to particle detectability providing a stable, transportable, national and international reference standard of particle visibility. The conversion of the prime particle visibility parameter from detection probability to the measurement of particle size results in a measure better suited to continuous monitoring and quality adjustments in a production environment.

Investigation of the incidence rate of visible contaminating particles must begin with a choice of the type of contamination that is to be investigated. For uniform contaminants, that is, identical contaminants found in all containers in a batch, small sample destructive testing using particle counters have been shown to produce accurate and reproducible results. To be precise, the accuracy of particle counter results is available only at low concentration values [(20-25)]. These contaminants are traceable to the washing and preparation of the container and/or stopper, the product formulation or interaction of the pharmaceutical product with the container or the stopper.

For random contaminants in a parenteral batch there is no information prior to a 100% inspection as to which containers in the batch are contaminated. Accurate determination of the incidence rate of randomly sourced and randomly introduced contaminating particles can only be determined with a validated 100% inspection. A validation demonstration, in the GMP sense, is a demonstration that any intended use on a USP listed product must result in equal or better quality to that achieved with the preceding method or

mechanism. For parenteral products, the benchmark for inspection results are the results obtained by the agitation and inspection performed by clinical personnel at the injection site.

This determination, based on the use of human capability, can now be accurately evaluated using an accretion of advances in behavioral studies, biophysics, pharmaceutics, statistics and technology which became available in the period from 1940 to the present.

The final step from the present anarchy of visible contaminating particle measurements in injectable products to a measurement whose accuracy is traceable to NIST maintained dimensional standards has been demonstrated with the NIST^2-ParticleVision™ System[(26)], a NIST traceable particle measurement system. The combination of current imaging technology supported by the growth in PC power has brought into being a cost effective link between the determination of visible particle contaminated containers in injectable products to the introduction of corrective measures on the production line.

Combining NIST traceable sizing of stable microspheres with statistically accurate determinations of their rejection probability has made possible realization of a calibration curve relating the probability of manually detecting a contaminating particle to its NIST traceable maximum physical size. With USP acceptance and use of this calibration curve, inspection sensitivity and discrimination can both be defined and securely evaluated. This means that the basic manual inspection at all producing sites, and therefore the validated capability of any contaminating particle inspection method or mechanism, can now be evaluated on a level playing field. The availability of secure statistically reproducible contaminating particle data makes possible the on-going cycle of parenteral production line process improvements envisioned in PAT[(27)] publications.

CURRENT PERSPECTIVES

This development comes at a time in which the repercussions of the 1995-1996 tsunami level quality control disaster in parenteral products in Japan are still reverberating around the world[(28)]. The quality failure in Japan initiated a worldwide chain reaction. In the United States there was recognition that the USP standard for injectable products, that they be “essentially free” of visible contaminating particles could not provide a basis for harmonized quality standards. A USP request for technical assistance from the PDA[(29)] was met by the assembly of a group of industry experts to chart a path from the present anarchy to a scientifically literate measurement method.

Based on cGMP philosophy, the benchmark capability of any particle inspection for contaminating particles in an injectable product container must be at least as effective as the single container inspection by clinical personnel at the injection site. This benchmark capability must be equaled or exceeded by any proposed alternative method or mechanism. This includes any deviation from the single container clinical inspection and any semi- or fully automated inspection system.

Since human capability provides the reference standard for particle contamination assays, the conditions required for secure manual inspections have been scrutinized. A list of these conditions commences with the quantity and quality of the light at the inspection point, the inspection background employed, recognition that particle movement is essential for efficient detection, the duration of the inspection and recognition that the decrease of efficiency with inspector fatigue must be considered. An extension from the concepts developed from inspection system validation to batch quality determination is described. With new vision technology non-destructive measurements of visible particles within 10μm with an experimental worst cast linearity of 3% from 50 to 1,000 μm is described.

The final step to a scientifically defined procedure whose accuracy is traceable to NIST maintained dimensional standards has been made for visible contaminating particles. This step has been made possible through the realization of new concepts with advances in vision technology and advanced PC hardware and software. The advances in PC hardware and software have been driven by their need in non-contacting measurement applications. With this powerful new capability the next step forward from a research-level validation of new visible particle inspection methods or devices based on the probability with which particles can be detected to a method suited for the parenteral production floor can now be made.

The central concept that makes NIST traceable maximum particle size measurements possible is the generation of a calibration curve relating the probability of detecting a particle to its physical size. When this calibration curve is determined with microspheres that have been inspected under standard conditions (light quality and intensity, manipulation of the container, duration of the inspection, the background employed) and sized with NIST traceability, the basis for an accurate international standard of particle contamination quality has been established.

The standard (particle size)/(particle rejection probability) calibration curve can be considered an equivalent to the use of the set of standard microspheres used to calibrate particle counters. The probability that similar microspheres will be found in a biological or chemical suspension is small. The microspheres in the calibration sample are used to determine that the functionality of the visible particle inspection method or system has the sizing accuracy desired.

This new capability provides the means with which visible contaminating particle measurements can be as securely harmonized as measurements of temperature, length or time. The result of this new measurement accuracy, based on previously achieved measurement improvements, will be optimized production processes in which quality improvement and cost reduction are simultaneously achieved. This joint improvement cannot result from “inspecting quality into a product”, a phrase in the PAT presentations, it is made possible by the capability to make and accurately evaluate incremental process improvements. The stimulus for the new advances is directly traceable to a tsunami level failure of injectable product quality in Japan.

1995-1996 Tsumami Level Failure of Injectable Product Quality in Japan

The catastrophic failure of Japanese Quality Control in injectable products in 1995-1996 allowed insect body parts, hair, rubber and aluminum fragments in injectable product containers accepted for patient use. This failure originated in the belief in Japan that the repeatability of the small-scale destructive particle counter assays controlled batch quality to a higher degree than possible with a manual visible inspection. This conclusion is indeed correct when analyzing uniform batch-wide problems such as those traceable to failures in container or stopper product interactions or in the preparation of any component in the final packaged product. Small scale destructive testing cannot evaluate or control the incidence of the random low incidence rate visible contaminating particles. In the United States this after-shock review clarified the role of the benchmark performance of skilled manual inspection for randomly introduced visible contaminating particles.

The manual inspection of injectable products provides quality control for the incidence of random particle contamination up to the final clinical use-point. The security with which the sequence of skilled manual agitation and inspection removes visible contaminating particles from single containers in a batch of parenteral products was therefore re-affirmed as the USP and thus the GMP inspection performance benchmark. An analysis model using current measurement units and standard scientific methodology was required to transform the present craft level inspection procedure for contaminating particles to a

scientific process. The development of such an analysis model is the first prerequisite in science for secure quality in domestic production or for secure quality in international trade.

The second prerequisite for an assay that uses human capability is that the assay must be structured for performance within human capability limits. The assay must be designed to record the data that fully describes the variation in quality that is being investigated. Unless these two prerequisites are satisfied analysis of the inspection data cannot yield meaningful results.

Relevant Background

Statisticians at Bell Labs had developed relationships between the measured variation of a selected sample group of parts in a batch and the probability that the entire batch of parts or assemblies was of acceptable quality. Their analysis was restricted to the analysis of uniform errors whose deviation from the desired value could be measured in all units of the batch. MIL Spec 105 was an early tabulation of batch acceptance/rejection probability using the attribute sampling concept of quality control.

Sampling Inspections to control the quality of weapons and munitions was imported into the Armed Services from Bell Laboratories to help assure that mass produced components would fit together and that cartridge rounds would fire reliably. The use of the sampling inspection in mass production was never designed for tight control of production quality. It is used to save time and inspection labor and to signal major deviations from the quality target.

The capability to achieve control of quality with reduced delays and reduced inspection labor was imported by the FDA in WW II to evaluate pharmaceuticals produced for the Armed Services. The Navy's Bureau of Medicine, BUMED, headed by Capt. Solomon C. Pflug in WWII, controlled injectable product quality for the Armed Services.
He saw the potential of this new quality assurance technique and extended its use to parenteral products. When Pflug introduced the use of the Attribute Sampling Inspection to the Pharmaceutical Community in 1968, limitations in applying this type of quality control remained to be discovered.

The Attribute Sampling Inspection can still yield accurate results for the uniform errors of packaging components and fill quantity data that is 'simply repeatable'. Probabilistic data, such as raw visible inspection data must be converted into a form acceptable to the sampling Tables for accurate results. The defect categories that he established are listed in Table 1 below.

Critical:	A defect likely to result in hazardous or unsafe use of the product. Such as lack of product sterility and container leakage.
Major:	A defect likely to reduce usability or result in hazardous or unsafe use of the product. Particle contamination of an injectable product has been considered a major defect from Pflug's 1968 paper to the present.
Minor:	A defect not likely to reduce usability of the product, such as esthetic defects**.**

TABLE 1 – Pflug Defect Categories

The injectable product defect categories used and described by Pflug in 1968 are still employed. The Critical, Major and Minor injectable product quality categories were introduced to pharmaceutical use at

the 1968 FDA convoked National Symposium "Safety of Large Volume Parenteral Solutions" in July 28 and 29_{th} in Washington, DC and are still in use today.

The degree of control in a sampling inspection is selected by specifying one of the following control levels:

Normal Inspection: AQL = 2X the required quality level. This inspection is intended to detect a breakdown in process control signaling the need to shift to a tightened inspection. It is intended to protect against unusual quality deterioration by direct rejection of batches.

Tight Inspection: AQL = the required quality. The inspection itself is intended to give complete protection against unsatisfactory quality.

Reduced Inspection: AQL = 3X the required quality level. This inspection is intended to detect a breakdown in process control signaling the need to shift to a tightened inspection. It is intended to protect against unusual quality deterioration by direct rejection of batches.

The Normal Inspection as shown above is set equal to twice the required quality level. This quality level is selected to indicate major deviations from the quality level desired. It cannot provide the sensitivity required for sensitive monitoring of batch quality.

References

1. "Sampling Procedures and Tables for Inspection by Attributes," American Society for Quality, ANSI/ASQC Z1.4-1993.

2. "Sampling Procedures And Tables For Inspection by Attributes," International Standards Organization, Version ISO2859-1 (1999).

3. "Statistics - Vocabulary and Symbols - Statistical Quality Control," American Society for Quality, ANSI/ISO/ASQC A3534-2-1993 (Revision and Redesignation of ANSI/ASQC A1-1987 and ANSI/ASQC A2-1987).

4. USP 28, United States Pharmacopoeia, 2005, <788> Particulate Matter in Injections, United States Pharmacopeial Convention, Inc., Rockville, MD, (2005).

5. Knapp, J.Z. and Kushner, H.K., "Generalized Methodology for Evaluation of Parenteral Inspection Procedures," Bull. Parenteral Drug Assoc., 34, 14 (1980).

6. Knapp, J.Z. and Kushner, H.K., "Implementation and Automation of a Particulate Detection System for Parenteral Products," Bull. Parenteral Drug Assoc., 34, 369 (1980).

7. Knapp, J.Z., Kushner, H.K. and Abramson, L.R., "Automated Particulate Detection for Ampuls Using the Probabilistic Particulate Detection Model," J. Parenter. Sci. Technol., 35 (1981).

8. Knapp, J.Z., Kushner, H.K. and Abramson, L.R., "Particulate Inspection of Parenteral Products: An Assessment," J. Parenter. Sci. Technol., 35, 176 (1981).

9. Knapp, J.Z., and Kushner, H.K., "Particulate Inspection of Parenteral Products: From Biophysics to Automation," J. Parenter. Sci. Technol., 36, 121 (1983).

10. Knapp, J.Z., Zeiss, J.C., Thompson, B.J., Crane, J.S. and Dunn, P., "Inventory and Measurement of Particles in Sealed Sterile Containers," J. Parenter. Sci. Technol., 37, 170 (1983).

11. Knapp, J.Z., "Detection and Measurement of Particles in Sealed Containers," Chapter in "Filtration in the Pharmaceutical Industry," Ed. Theodore H. Meltzer, Marcel Dekker, Inc., N.Y. (1986).

12. Knapp, J.Z., "Process Control By Non-Destructive Testing," International Conference on Liquid Borne Particle Inspection and Metrology, May 11-13, Arlington, VA. (1987).

13. Knapp, J.Z. and Abramson, L.R., "Automated Particulate Inspection Systems: Strategies and Implications," J.Parenter.Sci. Technol., 44, (2) 74-107 (1990).

14. Liquid and Surface Borne Particle Measurement Handbook, Ed. Julius Z. Knapp, Thomas A. Barber, Alvin Lieberman, Chapter 9, Julius Z. Knapp, 295-450, Marcel Dekker, (1996).

15. Knapp, J.Z., "Absolute" Sterility and "Absolute" Freedom from Particle Contamination, PDA J. of Pharm. Sci. and Tech., 52, 173 (1998).

16. Knapp, J.Z., "The Scientific Basis for Visual Particle Detection," PDA International Conference, Feb. 22-26, 1999, Conference Proceedings p187-219 (1999).

17. Knapp, J.Z., "Origin, Result and Measurement of USP 'Essentially Free' Inspection for Visible Contaminating Particles," Presented at: Visible Inspection Round Table, PDA-FDA Meeting, September 28, Bethesda, MD, (1999).

18. Liquid and Surface Borne Particle Measurement Handbook, Ed. Julius Z. Knapp, Thomas A. Barber, Alvin Lieberman, 1996, Chapter 9, Julius Z. Knapp, 295-450, Marcel Dekker.

19. NIST, Gaithersburg, Maryland, National Institute of Standards & Technology, U.S. Department of Commerce, Washington D.C.

20. Knapp and L.R. Abramson, "A Systems Analysis of Light Extinction particle Detection Systems," p.283, Proceedings, International Conference on Particle Detection, Metrology and Control, Arlington, VA, (1990).

21. J.Z. Knapp, Ed., T.A. Barber, A. Lieberman Assoc. Editors, "Liquid and Surface Borne Particle Measurement Handbook" Marcel Dekker, N.Y., (1996).

22. J.Z. Knapp and L.R.Abramson, "A New Coincidence Model for Single Particle Counters, Part I: Theory and Experimental Verification" J.Pharm.Sci.& Tech., 48, 3, 110-134, May/June (1994).

23. J.Z. Knapp, A. Lieberman and L.R. Abramson, "A New Coincidence Model for Single Particle Counters, Part II: Advances and Applications" J.Pharm.Sci.& Tech., 48, 5, 255-292, September/October (1994).

24. J.Z. Knapp and L.R. Abramson, "A New Coincidence Model for Single Particle Counters, Part III: Realization of Single Particle Counting Accuracy" J.Pharm.Sci.& Tech., 50, 2, 99-122, March/April (1994).

25. Liquid and Surface Borne Particle Measurement Handbook, Ed. Julius Z. Knapp, Thomas A. Barber, Alvin Lieberman, 1996, Chapter 10, Julius Z. Knapp, 295-450, Marcel Dekker.

26. NIST^2-ParticleVision™ System, Phoenix Imaging, Ltd., Livonia, Michigan. (2005) gbudd@phoeniximaging.com.

27. FDA, Bethesda, Maryland, Center for Drug Evaluation Research, http://www.fda.gov/cder/guidance/4619fnl.htm.

28. Kuomara, Kunio, "Japan Quality Issues", Proccedings, PDA Annual Meeting, Philadelphia, PA, (1997).

29. PDA Task Force Report 37, in Press, PDA, Bethesda, Md., (2005).

30. Pflug, I.J., "Heat Sterilization," In "Industrial Sterilization," G.B. Phillips and W.S. Miller, editors. Duke University Press, Durham, N.C. (1973).

31. Pflug, I.J. and Smith, G.M., "The Use of Biological Indicators for Monitoring Wet-heat Sterilization Processes," Published in "Sterilization of Medical Products," E.R.L., Gaughran and K.Kereluk, editors. Johnson and Johnson, New Brunswick, NJ 193- 230 (1977).

32. Pflug, I.J., "Microbiology and Engineering of Sterilization Processes," Parenteral Drug Association, Philadelphia, PA 210-236 (1977).

33. U.S. Patents 5,365.343, 5,694,221, 6,498,645 and other Patent Pending. USPTO, Washington, DC.