Richard Kelly:

The FDA is aware of this limitation of LD. The FDA conducted research into the extent of comparability of various common particle size analysis techniques. The sample chosen was nitrofurantoin. It was chosen because of its acicular morphology and because it contained significant fines.

In the poster they presented in Feb 2001 they concluded that

FDA SCIENCE POSTER FEB 2001

COMPARATIVE ANALYSIS OF COMMON PARTICLE SIZING TECHNIQUES FOI PHARMACEUTICAL POWDERS

H.R. Prasanna, E.H. Jefferson, J.S. Taylor, A.S. Hussain, R.F. Karuhn, R.C. Lyon

- Nitrofurantoin Drug Substance
  - Low Solubility (0.2-0.4 mg/ml at pH 7.4)
  - Dissolution is dependent on particle size
  - Large Particle Size Range (d_{10}=18u; d_{90}=300u)
- Particle Size Techniques
  - Sieving (ATM Sonic Sifter)
  - Laser Diffraction (Malvern Mastersizer)
  - Light Obscuration (AccuSizer)
  - Image analysis (Nikon Image-Pro Microscopy)
  - B.E.T. Surface Area Analysis (Micromeritics Flowsorb)

Richard Kelly:

"The large population of fine particles was only detected by the particle counting techniques (image analysis and light obscuration) and not by the ensemble technique (laser diffraction).

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Summary

- The laser diffraction data verified that the sieving reproducibly yielded fractions consistent with the size of the sieves. In general, the sizes measured by the three techniques were larger than expected from sieving. This was attributed primarily to needle shape particles passing lengthwise through the sieves.
- Comparing the three particle size techniques by mean size of distribution:

  Image Analysis > Light Obscuration > Laser Diffraction
- Comparing the three particle size techniques by resolution of distribution:

  Image Analysis > Light Obscuration > Laser Diffraction
- The large population of fine particles was only detected by the particle counting techniques (Image Analysis and Light Obscuration) and not by the ensemble technique (Laser Diffraction).
- The B.E.T. Surface Area Analysis could not distinguish between the five fractions.

Richard Kelly:

Therefore, in the case presented of acicular particles in the presence of fines we might conclude that LD would not be the particle size analysis technique of choice. In this case we would recall Dr. Brian Scarlett's words that for product quality control and manufacturability that "The more vital requirement is that the instrument should be sensitive to those changes in the particle size distribution which causes a change in the product properties. There is no virtue in an instrument being very reproducible if it is so insensitive so that it does not detect the relevant changes".

It is also to be noted that Dr. Scarlett directly rebutted the popular false mantra "Accuracy does not matter."

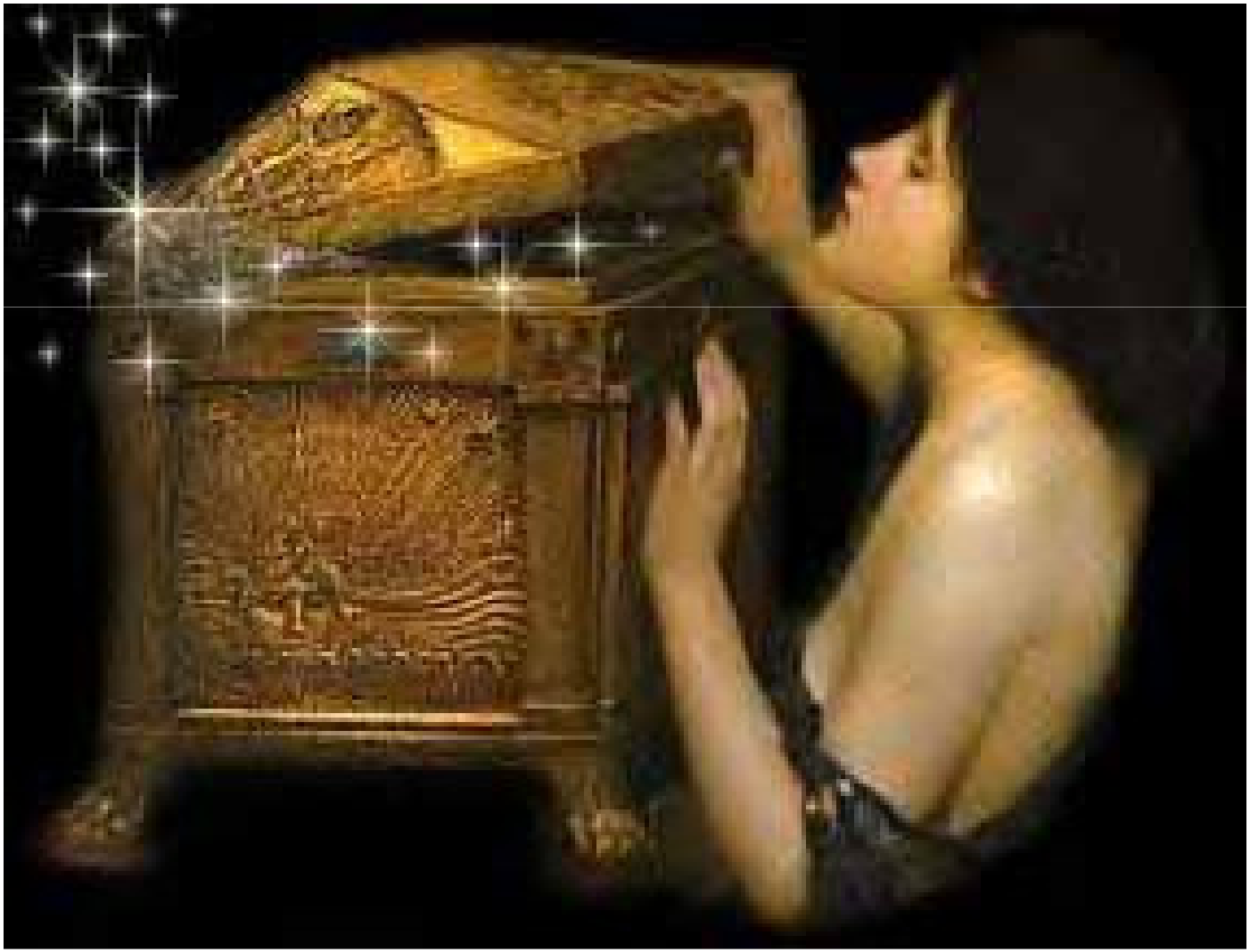
EXERPT FROM MAY 2003 AAPS PSWS SPEECH GIVEN BY BRIAN SCARLETT

The control of an existing product or process requires less stringency than the design of a new product or process. For control, the minimum requirement is that the instrument should be reproducible. Practically, this means that the instrument variance is much less than the sample variance. The more vital requirement is that the instrument should be sensitive to those changes in the particle size distribution which cause a change in the product properties. There is no virtue in an instrument being very reproducible if it is so insensitive so that it does not detect the relevant changes. The accuracy of the measurement is more difficult to achieve since it concerns the actual size of the particles and there arises the question of definition. Nevertheless, in product design, and consequently also process design, the actual size of the particles may be crucial. If the particles must actually match the size of a capillary or pore in the body, then an arbitrary scale of measurement is insufficient and the question of what is to be measured must be addressed.

Richard Kelly:

Findings such as these might be considered by the true analytical scientist as photons of the light of reason and gladly accepted as further aid in finding ones way to truth. However, those that love the dark hate the light. So, many LD devotees see these findings as possibly being part of the content of a Pandora's box . As we know fear is one of the primary forces in a dark age and LD devotees fear that these findings might disrupt their unchecked use of their favorite particle size analysis technique.

DARK AGE: PRIMARY MOTIVATIONAL FORCE



Richard Kelly:

This fear reinforces no see, no hear, no speak evil behavior making the drafting of truly useful guidance documents difficult if not impossible.

POPULAR CROSS VALIDATION STRATEGY WITHIN THE PHARMACEUTICAL INDUSTRY

Richard Kelly:

From personal experience I can tell you that well intentioned individuals have attempted to have findings such as those discussed today included in some useful fashion into guidance documents. For instance, David Driscoll of the Beth Israel, Deaconess hospital of the Harvard Medical School found that the LD limit of detection weakness could actually put patients at risk of death if LD were used in a QA environment for the monitoring of IV lipid emulsions. Therefore, an attempt was made to have such information included in a guidance document. Shortly before the document ws to be presented for approval, the LD forces rose up and scrubbed the document clean of any statement that might cause the unchecked use of LD to be questioned.

A good guidance document, recognizing the widespread use of LD, should make it very clear what the “actual” versus “advertised” operating principles of this technique are and present some form of prescription for a rational procedure by which the decision as to whether LD is a suitable technique for the problem at hand is to be made. The mistakes of the European position paper on LD method development should not be repeated.

As mature scientists we should be willing to admit what is fact and what is but the lingering remnant of the LD fairy tale.

LD: LIMIT OF DETECTION