Perspective on testing for particulate matter in injections.

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The initiation of standards. There have been twenty years, that is to say a generation, of testing for particulate matter in injections. Initial concern was raised by an experience in Australia in the early 1960s. The USP approach to selecting injections that would have standards was first enunciated in late 1983. At that time, 55,000 particles (10 and 25 micron cuts) were allowed for a liter of large-volume injection. See USP XXI, p. 1257 ff and Pharmacopeial Forum, vol. 9, Nov.-Dec, 1983, p. 3729. These were patient-oriented, not based on process capability. Limits were 11,000 per container on small-volume injections based on five additives. There were no reports of medical incidents while that initial standard was in force. Lower limits were subsequently put into force for both types of injections.

The initial establishment of any limit for large-volume injections was heatedly disputed between the Food and Drug Administration and Pharmaceutical Manufacturers Association, and it dragged on for years. Later, industrial organizational concern for injections passed to the Health Industry Manufacturers Association. Few individuals involved in the development of that first standard by USP on the part of either the Food and Drug Administration or PMA are still intimately involved. The head of the Office of Compliance at the time was Theodore Byers. He and Bud Loftus wrote the first drafts of current Good Manufacturing Practices based on their observations of the injections industry. I mention this only to indicate that there has always been a great deal of emotion around this now relatively manageable topic.

Conceptual framework. The elected experts of the Pharmacopeia stated the basis of their concern on which limits were selected: **cumulative particulate insult** to the patient. See also Pharmacopeial Forum, vol. 12, Jan.-Feb., 1986, p. 1089. It is important to note that in establishing a limit for particles contributed by multiple intravenous additives, the experts accepted *double the number of particles* that are specified in the standard for large-volume parenterals as being an acceptable insult. See USP 26, p.2189, ff. for present limits. Note that the experts considered the fact that more than one LVP bag is hung daily. The adult requirement is about 2750-ml. water from all sources daily so 3-4 bags are needed. As a worst case, one may calculate that the elected experts now allowed for as much as 110,000 particles counted microscopically from four bags each with four additives, and every container at the limit. This is consistent with USP24 Third Suppl. for counting bicarbonate preparations. Using averages for the two particle cuts, spherical shape and unit density, and one can view that as about 0.4 milligram of particles or as <0.1 ppm, consistent with the high variance in count data (Horwitz-Alpert Curve).

Selection of a limit on particulate matter is a difficult challenge. 1. There is no toxicological equivalent of a dose-response curve that has been documented for particulate matter in injections. 2. There is no equivalent of a “no observable effect level”, N.O.E.L. 3. There is no known threshold above which unacceptable effects are observed. 4. There is no known lethal dose, i.e., LD-50. 5. Particle significance varies with morphology. 6. There is no risk/benefit

ratio for particles. Therefore, unlike limits established for impurities in pharmaceuticals, there is no way to select a *safety factor* to include in the calculation of a limit. The result is selection of a *comprehensive and prudential standard*. It is based on the patient's interest under realistic conditions of intravenous therapy. At the low-level of particulate matter that a patient would be exposed to, there is no known acute or chronic toxicity. Rather, the limits were based on particles of sufficient size to occlude capillaries, with primary emphasis on the heart-lung preparation. The presumption was that the particles are neither metabolized nor redissolved.

Nevertheless, the experts opted to limit the cumulative insult to any patient that would be the result of multiple instances of intravenous therapy, or prolonged intravenous therapy. Due consideration was given to process capabilities, but these were not determinative.

Assisted by their concept of cumulative particulate insult, the experts exempted a number of medical use situations and non-vascular routes of administration. These exemptions applied as a matter of revision policy for many years, until they were actually incorporated within the Chapter <788> in the Pharmacopeia. The Food and Drug Administration at that point opposed forcefully the continuation of exemptions. Since the technology for all injections had improved, and more laboratories were proficient in performing the tests, USP experts removed the exemptions effective March 2001. International Harmonization was another outcome.

The precipitate. At this point we must discuss the actual particles precipitated, treated here as calcium carbonate alone. Precipitated calcium carbonate does not have a fibrous structure, forming instead rhombohedric crystals from water. Please note that the particles in the Australian experience 40 years ago were fibrous. USP experts were informed that fibrous particles were the more threatening to the patient. Furthermore, just as calcium carbonate is easy to precipitate it is rapid to redissolve, and these small particles would present a large surface area for that event. The Henderson–Hasselbalch equation, based on pKa and the pH of blood, calculates a proportion of 800: 1 of bicarbonate to carbonate, favoring dissolution of carbonate. Episodic administration of a bicarbonate solution therefore should not be seen as an irreversible deposition of particles. It should not be seen as a chronic hazard, i.e., extending beyond 30 days. The acute problems of carbonate precipitates in intravenous therapy are recognized generally, and are not part of my expertise.

The potential product in question as I understand it has two chambers. One may consider the larger chamber as a large-volume parenteral and the smaller as the equivalent of the *sum* of four small-volume additives. Thus the small compartment at USP limits of 12,000 plus 1200(10 and 25 micron cuts) and the larger at 12,000 plus 1200 per liter, as packaged. At 40 liters per day, this yields 530,000 particles for the large-volume portion alone. This could correspond to about 5 milligrams of calcium carbonate at a density of 2.72 from the smaller chamber and about 2 milligrams (d=1.0) of unspecified particles from the larger, when at the limits and treating the second chamber(s) as additives.

This exceeds the present USP conceptual framework tenfold so that a separate standard using different limits will be necessary. The product described is infused as a rate 10 times that envisaged by the present standard. But the establishment of a tenfold lower concentration, or a total particle limit, is within the range of present day technology for the large-volume

component, depending on needed shelf life. My only question is on the initial bicarbonate component, in terms of manufacturability. A daily limit of 53,000 particles would be needed to stay within the present USP conceptual framework. More if there can be a reallocation between the two compartments as mentioned next.

Where it is known that the particulate matter content of the large compartment does not increase substantially in storage and handling, I ask the following question--- cannot the limit on particulate matter for the product taken as a whole be allocated between the two compartments? That presumes the above 1:1 ratio of additive content to large-volume content. That is to say, the limit on the larger compartment would be substantially tighter, with a concomitant increase in the limit on the smaller compartment. Thus, there would be more tolerance for carbonate precipitate, especially if the "additive chamber" is proportionately less than the above.

Normal manufacturability taken with *nondisruptive* distribution of this product, and the dose regimen and patient prognosis as described to me leads me to conclude, in the light of the foregoing considerations that this product should not be seen as having a significant particulate matter problem. I see no ethical problem, but I see an uphill battle to convince regulators.

ASTM Test. In terms of cumulative insult to the patient after *disruptive* distribution and handling, for the sake of argument, at 4 percent rate of nonconformance than the probability is 2 per thousand of a patient receiving a second non-conforming container, depending upon whether the failure is associated with individual containers in the shipping package or is a characteristic of the shipping package in its entirety.

That 4% failure rate is reported to occur after subjecting the product to a common ASTM Test. Is this test a grossly exaggerated test in view of actual shipping and handling selected for this product? Would it accompany a large order of various LVPs?
If so, then the tail is wagging the dog in product realization. Perhaps UPS has information relevant to this issue. I do not. The ASTM office in Philadelphia has background on its standards that may illuminate the applicability to your product.

HACCP. It is a real stretch to discuss particulate matter of modern pharmaceuticals in terms of hazard. For the sake of argument let us pursue the application of this risk management approach to product quality. A key concept is the *critical control point*. The current guidelines come out of the food industry, and are based on microbiological considerations. FDA is already primed enough to work with HACCP. What I suggest is the establishment of the critical control point downstream at the point of use of this new article. That is to say the hospital pharmacist is the last professional in the chain of quality control. In essence this is what happens when expiration dates are observed. One may refer to Appendix F of the 1997 guidelines, available on the FDA web site for a decision tree that allows for the establishment of a critical control point after a change, flexing in this case, that would adversely affect the article. A quality control step is called for at this point, capable of verification.

Imagine determination by the pharmacist by physical observation of either the outer package or the inner container that allows an immediate determination of go/no go. Sorry, but that infers

returns. For example, a glass fiber in a semi-rigid plastic, colored as necessary for contrast, would allow determination of unacceptable flexing of the product. It would also serve as a minder to the pharmacist to avoid doing just that thing. There are, I am sure other inexpensive means to this end. The point is that due diligence would have been shown provided that there are data that show a correlation between the flex-indicator and non-conforming contents of particulate matter. I envisage fewer confirmatory shipping studies.

My understanding is that your company is searching for certainty of protective packaging, which is the other alternative, although extensive shipping studies are entailed.

Conclusion. The question comes, in view of the indefinable insult to patients, is there any likelihood that a new conceptual framework is possible? Yes. The key is the status and prognosis of the patient. This is a risk-benefit decision best made by medical experts. FDA medical people are more likely to see the value of such a product. My experience with the review chemists is that there is general resistance to interpretations such as above. As described to me, I would see no ethical problem in this if reasonable limits on the bicarbonate compartment are possible, allowing for higher limits than the present USP daily equivalents, consistent with the extreme medical situation.

As an opening suggestion, since **no medical incidents** were reported pointing to the original limits in force for several years, I suggest an approach to the USP Expert Panel and FDA medical experts based on some allocation between the two compartments to match that total. Realistically, that was 220,000 daily for the large-volume and 176,000 for the small-volume contributions, reasoning as above, and for the worst case. This allows room for downward negotiation. The sum is four times the present level of limits.

Establishment of a *critical control point* downstream in the hospital pharmacy would be innovative, may attract some support within FDA, and may neutralize concern for the upside of the damaged units.

Research of the developmental record for the present ASTM test may present a basis for impeachment with substitution of a less exaggerated, aggressive test based on the actual conditions during shipping and handling of this product.