A Comparison of the SteriTEQ™ Total Inoculation Method (STIM) with the USP <71> Membrane Sterility Test (MST).

The following information is presented to both define the appropriate operating standard for the sterility testing of compounded sterile preparations (CSP's), and present a qualitative comparison of the SteriTEQ Total Inoculation Method (STIM) with the USP <71> Membrane Sterility Test (MST).

1. **Applicable Standard.** While USP Standard <71> pertains to the sterility testing of "pharmacopoeial articles," the applicable operating standard for the conduct of sterility testing of CSP's is USP Standard <797>.

2. **Alternative Methods.** USP <797> prescribes the use of the MST in the sterility testing of CSP's as the "method of choice" where feasible, but also provides for the use of "methods not described in USP ... if verification results demonstrate that the alternative is at least as effective and reliable ... "[1] as the MST.

3. **STIM Superiority to the MST.** The STIM has been demonstrated in a proprietary verification exercise to be at least the equivalent of the MST in its sensitivity in detecting susceptible microorganisms in non-inhibitory CSP solutions, thus meeting the requirements of USP <797>. As a 'Best Practice,' the STIM is superior to the MST in both its ability to test the total solution content, its container and fluid pathway, and its ease and simplicity of execution for the following reasons:

a. The STIM evaluates more sample material than MST. The assumption with direct injection, or USP 'aliquot' testing methods is that only a portion of the product volume is actually tested, thus preventing evaluation of a substantial portion of the remaining sample and a resulting lowered confidence in the sample. However; the STIM actually evaluates more of the sample than the MST in the following manner: In the conduct of the MST, <100% of the CSP is drained through a test membrane via extraneous tubing into the membrane canister or housing. Following transfer of its contents, the original container and upstream tubing retain a minute portion of the CSP, thus preventing evaluation of 100% of the CSP content. Because the STIM is a non-invasive inoculation of growth medium directly into the CSP container, requiring no transfer of its contents, 100% of the CSP is effectively evaluated.

b. The STIM evaluation is more comprehensive. In the conduct of the MST, the CSP container and upstream tubing interior surfaces, in some cases constituting up to 0.5 $ft.^2$ of surface area, remain inaccessible to the test, thus preventing the MST from evaluating the sterility of these critical product-contact surfaces. Minute latent microbial contamination may continue to reside on the walls, creases, or ports of the CSP container interior following drainage of <100% of its contents through the MST testing pathway. The STIM provides for the testing of 100% of the CSP, as well as 100% of its container interior surface area, thus omitting no product or container interior surface area from evaluation.

c. The STIM is more efficient. Certain characteristics of MST testing may reduce its efficiency of CFU development and detection. Because the MST membrane mean porosity is 0.45µ, the smallest microorganisms (i.e., Brevundimonas diminuta @ 0.2µm) may pass through the membrane undetected. In addition, the transfer and filtration process, in and of itself, may stress microorganisms, rendering them incapable of replication and detection. Both of these potential conditions are ruled out in the stationary, quiescent STIM testing method.

d. The MST is comparatively difficult, expensive, and time-consuming. The MST is a laboratory exercise requiring up to 14 complex spiking, transfer, washing, inoculation, and disconnection manipulations and techniques to execute reproducibly and with precision, thus increasing the

probability of false results. Few pharmacies, clinics, and home healthcare institutions are equipped or funded to reliably perform this test accurately, and often must send out sterility testing samples to outside
laboratories, at a cost many times that of the STIM. The STIM involves only the use of a common multi-dose vial and syringe/needle assembly, and is identical to normal, simple compounding additive techniques. COST: The comparative cost of the STIM is $1.21 per sample, as compared to MST laboratory samples, ranging from $75.00 to more than $200.00 each.

e. The MST may introduce indeterminate false-positive results. False-positive and -negative results may have a pronounced adverse effect on CSP process control, allowing either the continuation of a process compromise in the case of *false negative* results, or, in the case of *false-positive* results, causing the expenditure of time, money, and resources needlessly to correct a compromise that does not actually exist. In addition, the MST is normally conducted by a second, often non-pharmacy operative who, because of the MST's comparative difficulty and complexity, may inadvertently contaminate the sample. Any such false-positive result unjustly reflects adversely on the technique of the compounding operative.

In comparison, the STIM is very simply and routinely carried out by the actual compounding operative within the scope of his or her routine compounding aseptic technique, and presents no opportunity for false-positive contamination. Because the STIM exercise occurs as a standardized aseptic manipulation within the continuum of the operative's normal aseptic compounding techniques, any failure, whether introduced during compounding or testing, is considered a lapse in that individual's aseptic technique, and may be justifiably investigated as such.

[1] Standard No. <797>, USP, Inc. Bethesda, MD December, 2008.