

the machine was fitted with a plastic liner that reduced the clinging and enabled quantitative discharges. The installation qualification (IQ)/operation qualification (OQ)/and performance qualification (PQ) were performed to qualify the filling machine for cGMP manufacturing. The Model LM-14 is a compact, portable bench top unit complete with carrying handle. It is an ideal machine for small fill weight, low volume applications. Other filling machines exist which are suitable for large operations.

**[0040]** Pre-cleaned and sterilized 20-mL vials, sterilized gray butyl rubber stoppers and flip-off aluminum seals were purchased. In a class 100 room, under laminar flow, the vials were filled in a glove box with EtO-treated AS. Scheduled weight checks were performed to ensure the filled weights met specifications. The filled vials were stoppered, sealed, and tested for release. After meeting requirements for sterility, identity, purity, content uniformity, and after constitution in sodium phosphate buffer, for solution pH, osmolality, and particulate counts, 5,500 of the filled vials were labeled SRI Batch 14462-16, assigned WR256283:BR29487, and designated as Component One of our AS dosage form.

Analytical Methods of Specifications for Sterile Intravenous Artesunate (110 mg/vial)		
Tests	Analytical Methods	Specifications
Appearance	Visual	Fine crystalline powder
Color Identity	Visual	White to almost white
IR	Conforms to Reference Spectrum	Must comply
HPLC	HPLC SRI TM 1900.200	Must comply
Assay (HPLC) calculated on water-free basis	HPLC	98.0 to 102.0%
pH	SOP SRI 004.009	7.2-7.7
Particulate Matter in Injections	USP 788>, small volume injections	No More Than (NMT) 6000 particles of size 10 µm/vial. NMT 600 particles of size 25 µm/vial.
Uniformity of Dosage Units	USP 905>, Solids in Single Unit Containers	None outside 88-132 mg/vial, RSD of 10 vials ≤6.0% in Level 1; if fail, go to Level 2.
Sterility	USP 71>	Sterile
Bacterial Endotoxins, LAL, Kinetic	USP 27 through Sup 85>	35 EU/mL

#### Placebo

**[0041]** The selection of a material for the AS placebo was based on a likeness in appearance and physical characteristics to that of the AS dosage form, in addition to being biologically inert. The placebo for the AS Dosage Form was Mannitol, 200 mg/vial.

**[0042]** A large number of possible placebos were investigated. The two final candidates were mannitol and glucose, with the former having a slight edge. Because the particle size of the commercially available USP mannitol was larger than that of the AS bulk drug, the mannitol was milled and sieved to match the size and appearance of the AS powder prior to sterilization. Sterilization by irradiation initially looked promising, but after two weeks on the shelf the irradiated mannitol became discolored. Ultimately, treatment with EtO proved successful, and the sterilized mannitol was dry-filled into the same type of glass vials as the active material and processed identically. Because the density of our mannitol

was nearly twice that of the AS bulk drug, the filled placebo mass was nearly twice that of the active, to maintain comparable filled volumes. After having met requirements on content uniformity, identity, and purity, and after constitution with phosphate, for solution pH, osmolality, and particulate counts, 2,500 vials of the placebo were labeled SRI Batch 14462-28 and designated WR016506:BR29487. To maintain anonymity, a common label, identifying both the AS and Placebo, was used for vials of the active as well as vials of its placebo.

**[0043]** In Phase I clinical trials the placebo was ethylene oxide treated mannitol, exhibiting the same appearance and dissolution characteristics as the Active Pharmaceutical Ingredient (API). The placebo was manufactured by SRI International. All clinical materials are stored, maintained, and shipped by the repository contractor (monitored and managed by The Department of Chemical Information). The repository contractor also prepares the double-blinded samples of artesunic acid or placebo for clinical use under guidance from the Department of Chemical Information. The placebo has provided an acceptable control for the recently completed phase I clinical trials.

Analytical Methods and Specifications for Sterile Placebo for Injection (200 mg/vial)		
Test	Analytical Methods	Specifications
Appearance	Visual	Fine crystalline powder
Color	Visual	White to almost white
Absence of Artesunic Acid	I.R.	None detected
Mannitol Content	USP (Identity)	Passes
Ethylene Oxide Residual	USP 71>	200 ppm
Ethylene Chlorohydrin Residual	NV SOP 12C-25 (ECH) USP 71>	120 ppm
Sterility		Microbial growth is not observed
Uniformity of Dosage Units	USP <905>, solids in Single Unit Containers	None outside 88-132 mg/vial, RSD of 10 vials ≤6.0% in Level 1; if fail, go to Level 2.
Particulate Matter in Injections	USP <788>	No More Than (NMT) 6000 particles of size 10 µm/vial. NMT 600 particles of size 25 µm/vial.

#### Dosage

**[0044]** A typical dosage of  $\alpha$ -artesunic acid for parenteral administration is 10 mg/mL for a 10 mL injection. 110 mg is the unit dose for manufacture. Typically, using a sterile syringe, 11 mL of sterile Phosphate buffer for injection will be added to the 110 mg artesunate vial and the vial swirled for about 4-6 minutes for full dissolution. Dosing is 1-4 mg/Kg body weight for intravenous administration with the possibility of up to 8 mg/Kg in some cases. Preferred dosing is 2-3 mg/Kg body weight for intravenous administration for three days. A drip bag is also suitable for administration of the dose. A dosage of 50 mg/mL is suitable for IM injection. IM treatment will be in the range of 1-5 mg/Kg body weight. Give dosage one to two times per day for 3 days for IM. Because the present inventors use a phosphate buffer solution, they are able to obtain a higher concentration of AS for injection than that which can be obtained with the 5% glucose dilution medium required by the Guilin formulation.