Contains Nonbinding Recommendations

Draft Guidance on Perflutren

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the Office of Generic Drugs.

Active Ingredient: Perflutren

Dosage Form; Route: Injectable; intravenous

Recommended Studies: In vitro

Additional Comments: Comparative testing should be performed on the test and reference product under the same conditions and activated as per the label instructions. In brief this should include shaking the product vial for 45 seconds using a VIALMIX.

In Vitro Option:

To qualify for the in vitro option for this drug product all the following criteria should be met:

i. The test and Reference Listed Drug (RLD) formulations are qualitatively (Q1)[1] and quantitatively (Q2)[2] the same (Q1/Q2).

ii. Acceptable comparative physicochemical characterization of the activated test and Reference Standard (RS) products. The comparative study should be performed on at least three exhibit batches of both the test and RS products and should include:[3]

- Appearance, pH, and osmolality of the activated suspension product
- Number based particle size and size distribution of microspheres greater than and equal to 1 µm in size. The particle size distribution should be compared using population bioequivalence (PBE) (95% upper confidence bound) based on D_{50} and SPAN [i.e. $(D_{90}-D_{10})/D_{50}$)]. The applicant should provide no fewer than ten data sets from three different batches of both the test and RS products for PBE analysis. Full profiles of the particle distribution should also be submitted for all samples tested. Please refer to the Guidance on Budesonide inhalation suspension for additional information regarding PBE.
- Number concentration (number of microspheres per mL) and volume concentration (volume of microspheres per mL)

[1] Q1 (Qualitative sameness) means that the test product uses the same inactive ingredient(s) as the reference product.
[2] Q2 (Quantitative sameness) means that concentrations of the inactive ingredient(s) used in the test product are within ±5% of those used in the reference product.
[3] The manufacturing process for the exhibit batches should be reflective of the manufacturing process to be utilized for commercial batches.

- Ultrasound backscatter coefficient. The applicant should develop an appropriate method to characterize and compare the backscatter coefficient over clinically relevant ultrasound frequencies (i.e. 1-8 MHz).[4,5,6] Representative profiles of the backscatter coefficient over this ultrasound frequency range and a statistical comparison of backscatter coefficients of the test and RS products at no less than three frequencies within this range (i.e. low, medium, and high ultrasound frequencies within the clinically relevant range) should be provided.

[4] Gorce, J.M., Arditi, M. and Schneider, M., 2000. Influence of bubble size distribution on the echogenicity of ultrasound contrast agents: A study of SonoVue™. Investigative radiology, 35(11), pp.661-671.
[5] Insana, M.F. and Hall, T.J., 1990. Parametric ultrasound imaging from backscatter coefficient measurements: Image formation and interpretation. Ultrasonic imaging, 12(4), pp.245-267.
[6] de Jong, N. and Hoff, L., 1993. Ultrasound scattering properties of Albunex microspheres. Ultrasonics, 31(3), pp.175-181.