In-vitro Population Bioequivalence (PBE) Parameters for Particle Size Distribution (PSD)

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Parameters required for Population BE (PBE)

- The conventional population bioequivalence (PBE) analysis were based on D10, D50, D90 & Span.
- D50 & Span as primary BE parameters, and D10 & D90 as supportive parameters.
- Currently, Z-average & PDI appear as surrogates of D50 and Span as primary parameters for some products, either as option or requirement.
- Additionally, the earth mover's distance (EMD) method was introduced when the particle size distribution may not be monomodal (more than 1 peak).

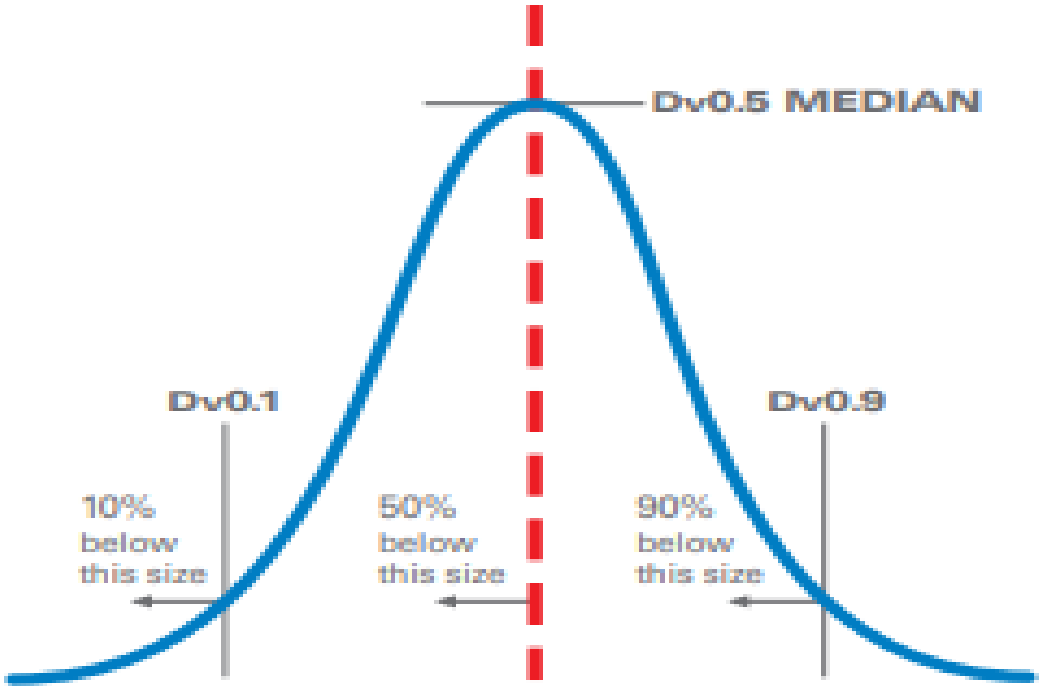
Examples on PSG Iron Injectable products

Product	Date	Guidance, in vitro criteria
Iron Sucrose	Nov,13	D50 and SPAN [i.e. (D90-D10)/D50] or PDI using PBE
Sodium Ferric Gluconate	Jun,13	D50 and SPAN [i.e. (D90-D10)/D50] or PDI using PBE
Ferumoxytol	Dec,12	D50 and SPAN [i.e. (D90-D10)/D50] or PDI using PBE
Ferric Carboxymaltose	Apr,16	Z-average size and polydispersity index using PBE
Iron Dextran	Oct,16	Harmonic intensity-weighted average particle diameter and PDI using PBE

Additional examples from PSG

Product	Dosage form	Date	Guidance, in vitro criteria
Paclitaxel	Suspension/Injectable	Sept, 12	D50 and SPAN or PDI
Azacitidine	Powder; IV (Infusion), Subcutaneous	Nov,19	D50 and SPAN
Fluticasone propionate	nasal	Feb,19	D50 and SPAN
Ciprofloxacin	injectable	Jul, 18	D50 and SPAN
Triamcinolone acetonide	injectable	Jul, 19	D50 and SPAN
Dantrolene sodium	IV	Oct,17	D50 and SPAN
Budesonide	Nasal	May,19	D50 and SPAN
Barium sulfate	Oral	Feb,18	EMD
Cyclosporine	Emulsion; ophthalmic	Oct,16	EMD

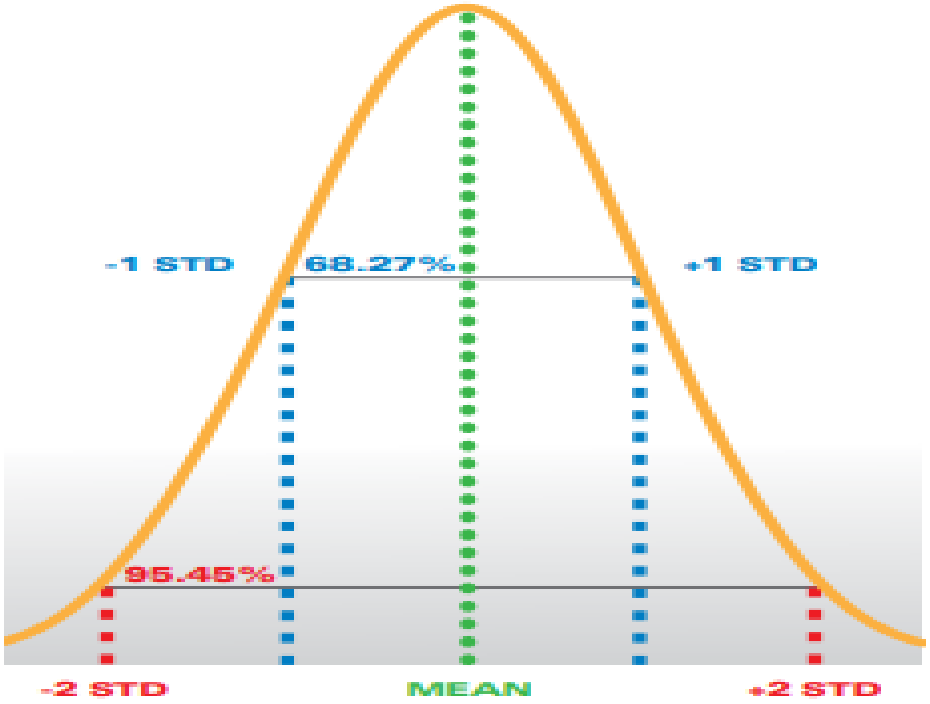
Definition of D10, D50, D90, and SPAN



- D90=Dv0.9
- D10=Dv0.1
- SPAN=$x = \frac{D90-D10}{D50}$

The span is a common calculation to quantify distribution width.

Definition of Z-average & PDI



- Z-average = MEAN

the intensity-weighted average

- $PDI = \frac{STD^2}{\text{MEAN}^2}$

the polydispersity index, which quantifies distribution width

Comparing SPAN & PDI

$$PDI = \frac{\sigma^2}{\mu^2} \quad \text{---------- Eq.1}$$

$$SPAN = \frac{D90 - D10}{D50} \quad \text{---------- Eq. 2}$$

The outcome of Equation 1 and Equation 2, both provide the distribution width relative to mean of a particle size distribution curve, based on dynamic light scattering techniques.

Relation between SPAN & PDI

- Assume X ~ Normal(μ, σ), here X is the diameter of a Particle.
  - Here, μ is population Mean and σ is population standard deviation
- D50 = μ
- D90 = μ + 1.282 σ and D10 = μ - 1.282 σ
- SPAN = $\frac{D90-D10}{D50}$ = 2* 1.282 σ/ μ and PDI = (σ/ μ)^2, by definitions

Rearranging these equations,

- SPAN = 2.564 * sqrt(PDI) and thus PDI = 0.152*SPAN^2

T/R Ratio between SPAN & PDI

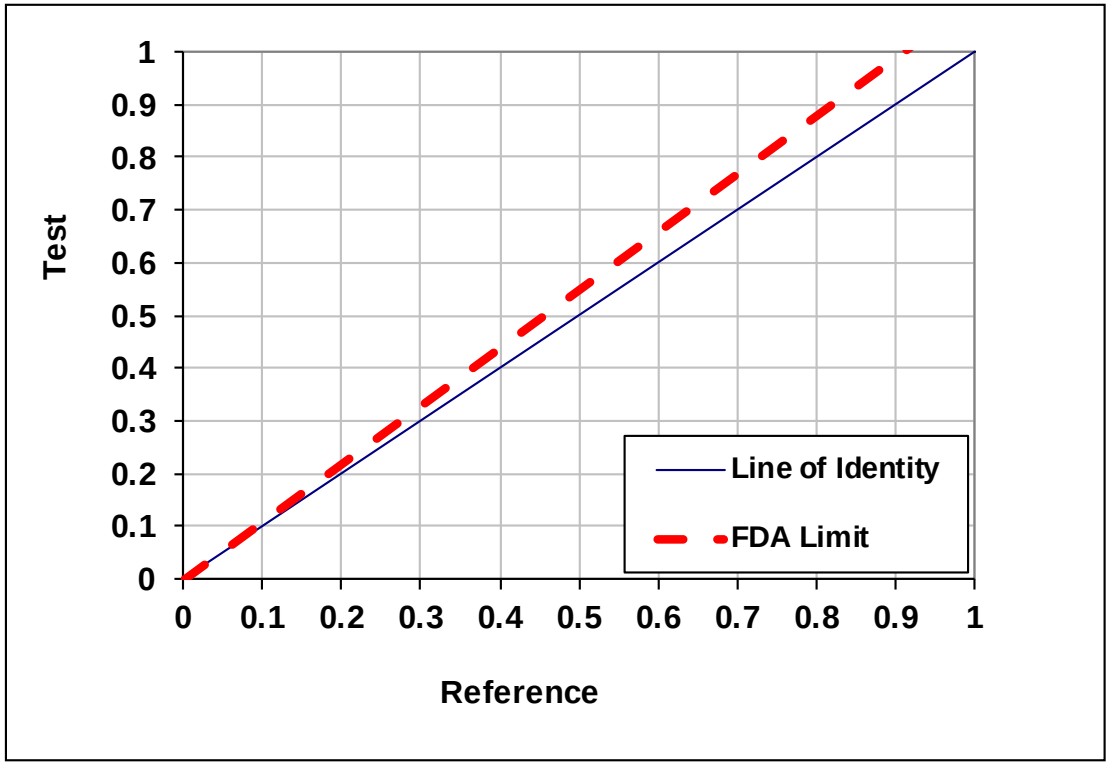
PDI_T/PDI_R=(SPAN_T/SPAN_R)^2

SPAN Ratio	PDI Ratio
0.80	0.64
0.85	0.72
0.90	0.81
0.95	0.90
1.00	1.00
1.05	1.10
1.10	1.21
1.15	1.32
1.20	1.44
1.25	1.56

PDI magnifies the T/R difference compared to SPAN.

Passing PBE for PDI can be more difficult compared to SPAN.

T/R Margin for PBE

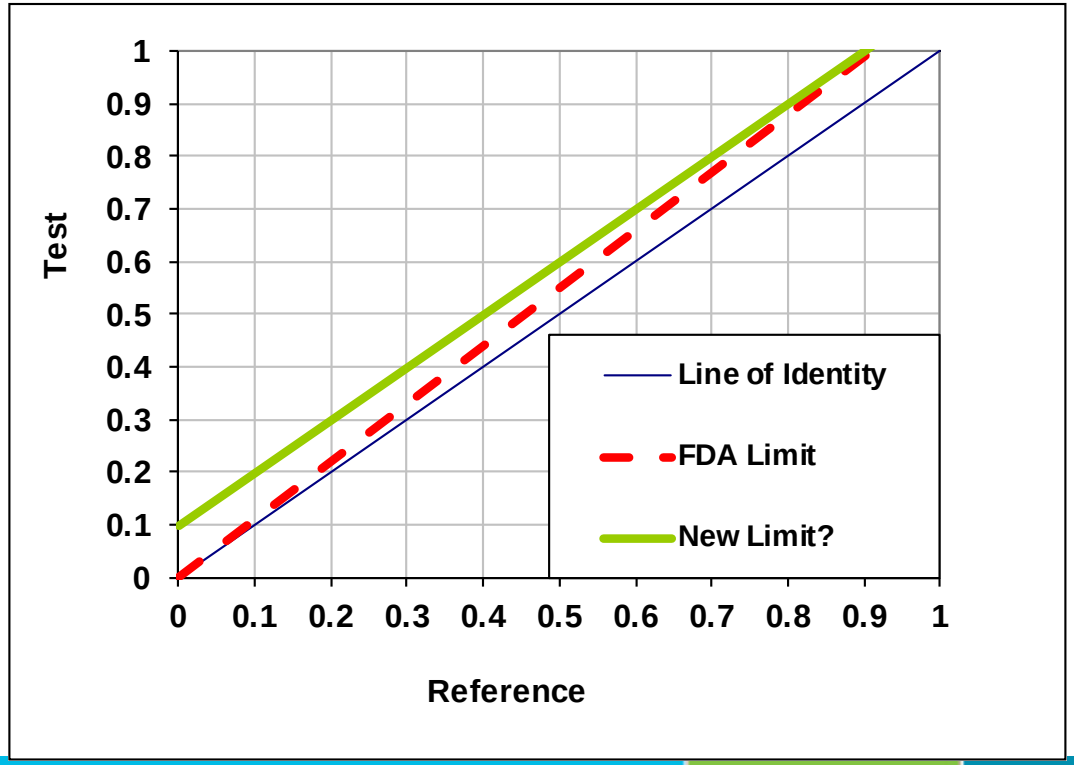


Because the values of PDI can be very small (~0.1), the margin for passing the PBE is very small (10% of 0.1), making it much harder to pass when even the difference is minuscule.

Conclusions

- The PDI is not the right parameter to replace SPAN.
- At a minimum, it is not the appropriate parameter when employing the current PBE method.

New Proposal Based on T-R for PBE



- |T-R| < 0.1 instead of 1.11 > T/R > 0.9 ratio when chosen to use PDI.

Questions

- Is employing Z-average and PDI (in place of D50 & SPAN) overly sensitive?
- Why the switch from D50/span to Zavg/PDI? What evidence is there that D50/ SPAN was problematic?
- If PDI or Span represent distribution width (variability), could it be a one-sided test? *Note: less variability for disparity should be beneficial.*
- Furthermore, do we need in-vitro PBE when in-vivo BE is required? Can it be supportive only?