Predictive Potential of Cmax Bioequivalence in Pilot Bioavailability/Bioequivalence Studies, Through the Alternative f2 Similarity Factor

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Supplementary Material
Descriptive Statistics of Simulated Pharmacokinetic Data

Contents

S.1. Simulations Where Test Product Presents a Lower Bioavailability than the Reference Product **3**

S.1.1. Simulated Volume of Distribution 3

S.1.2. Simulated Plasma Concentrations 7

S.1.3. Simulated Non-Compartmental Analysis Parameters 11

S.1.3.1. Maximum Observed Concentration 11

S.1.3.2. Time of Maximum Observed Concentration 14

S.1.3.3. Area Under the Concentration-Time Curve 16

S.2. Simulations Where Test Product Presents a Higher Bioavailability than the Reference Product **19**

S.2.1. Simulated Volume of Distribution 19

S.2.2. Simulated Plasma Concentrations 23

S.2.3. Simulated Non-Compartmental Analysis Parameters 27

S.2.3.1. Maximum Observed Concentration 27

S.2.3.2. Time of Maximum Observed Concentration 30

S.2.3.3. Area Under the Concentration-Time Curve 32

S.1. Simulations Where Test Product Presents a Lower Bioavailability than the Reference Product

S.1.1. Simulated Volume of Distribution

Table S1: Summary Statistics of Simulated Volume of Distribution, for Simulations where Test Product Presents a Lower Bioavailability than the Reference Product

	True Bioequivalent		True Bioinequivalent	
	Reference	Test	Reference	Test
30% IIV & 0% IOV	58.79 (30.7%) [58.72–58.87]	58.79 (30.7%) [58.72–58.87]	58.64 (30.5%) [58.57–58.72]	58.64 (30.5%) [58.57–58.72]
30% IIV & 10% IOV	58.95 (32.2%) [58.87–59.03]	58.95 (32.2%) [58.87–59.03]	58.93 (32.4%) [58.85–59.01]	58.93 (32.4%) [58.85–59.01]
30% IIV & 20% IOV	58.67 (37.1%) [58.58–58.76]	58.65 (37.2%) [58.56–58.74]	58.63 (37.6%) [58.53–58.72]	58.64 (37.6%) [58.55–58.74]
30% IIV & 30% IOV	58.71 (44.4%) [58.6–58.82]	58.76 (44.3%) [58.66–58.87]	58.85 (44.1%) [58.74–58.95]	58.88 (44%) [58.77–58.98]
30% IIV & 40% IOV	58.83 (53.4%) [58.71–58.96]	58.81 (53.2%) [58.68–58.93]	58.86 (53.1%) [58.73–58.98]	58.77 (52.9%) [58.65–58.9]
30% IIV & 50% IOV	58.93 (63.1%) [58.78–59.07]	59.11 (63.4%) [58.96–59.26]	58.77 (63.5%) [58.63–58.92]	58.73 (63.5%) [58.59–58.88]
30% IIV & 60% IOV	58.2 (75.3%) [58.04–58.37]	58.5 (75.8%) [58.34–58.67]	58.67 (75%) [58.5–58.84]	58.77 (74.8%) [58.6–58.93]

Values for Volume of Distribution (V) are in liters (L), and are presented as geometric mean (G_{mean}), with geometric coefficient of variation (GCV%) within parenthesis, and 95% confidence interval (CI) of the G_{mean} within square brackets.

$N = 210000$ for each group.

IIV – Inter-individual variability; IOV – Inter-occasion variability.

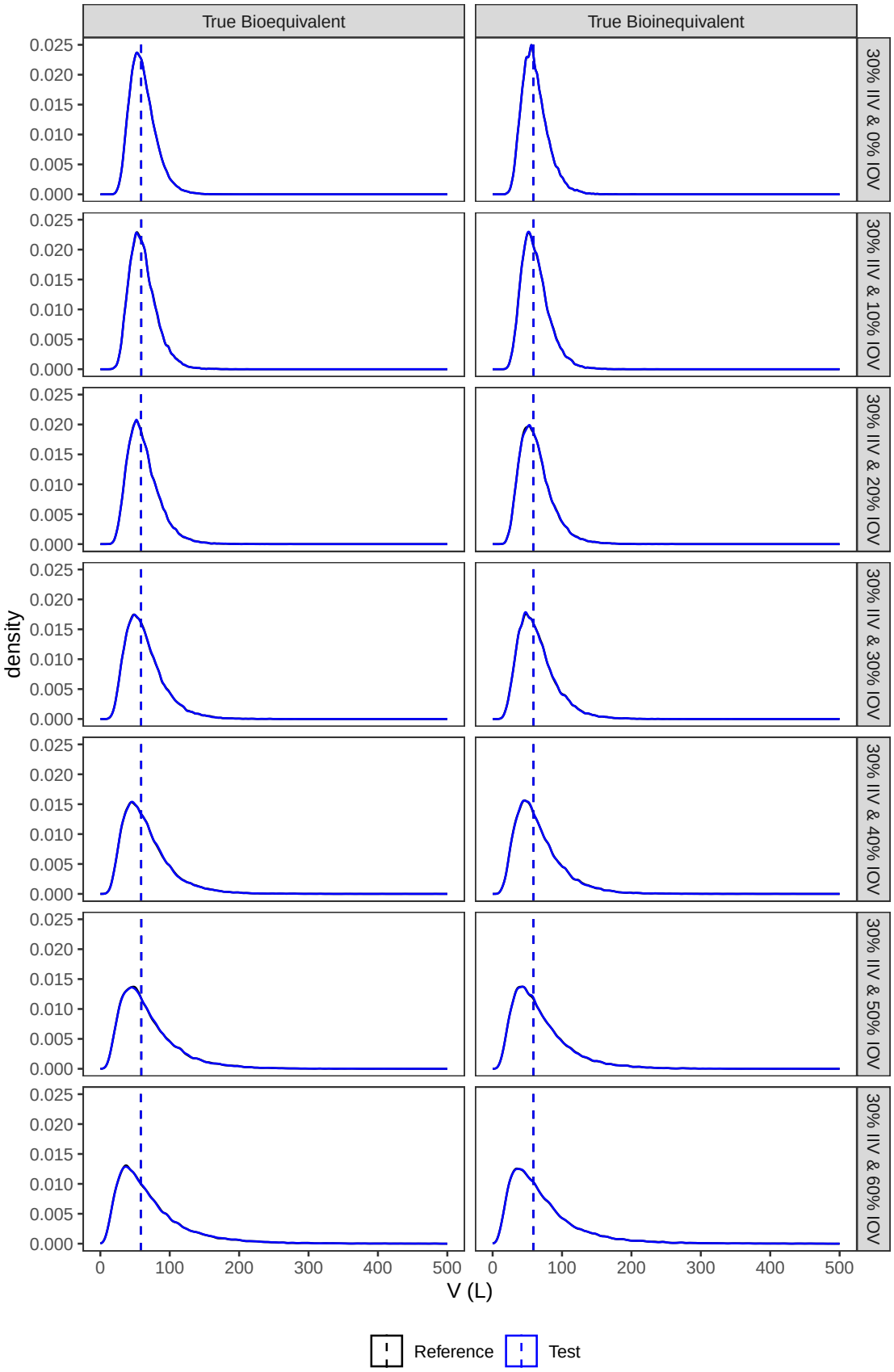

Figure S1: Distribution of Simulated Volume of Distribution, for Simulations where Test Product Presents a Lower Bioavailability than the Reference Product

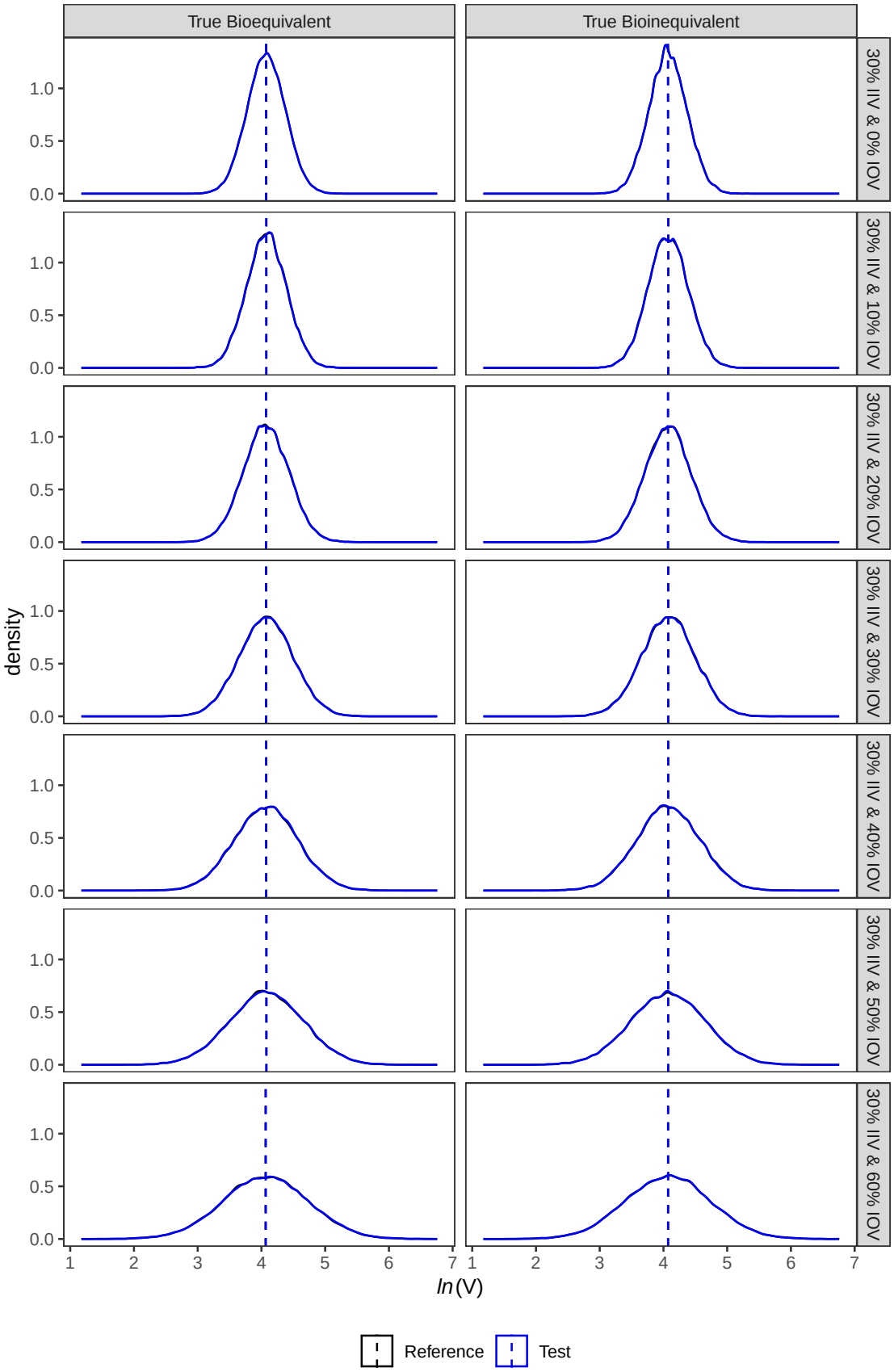

Figure S2: Distribution of *Ln*-Transformed Simulated Volume of Distribution, for Simulations where Test Product Presents a Lower Bioavailability than the Reference Product

S.1.2. Simulated Plasma Concentrations

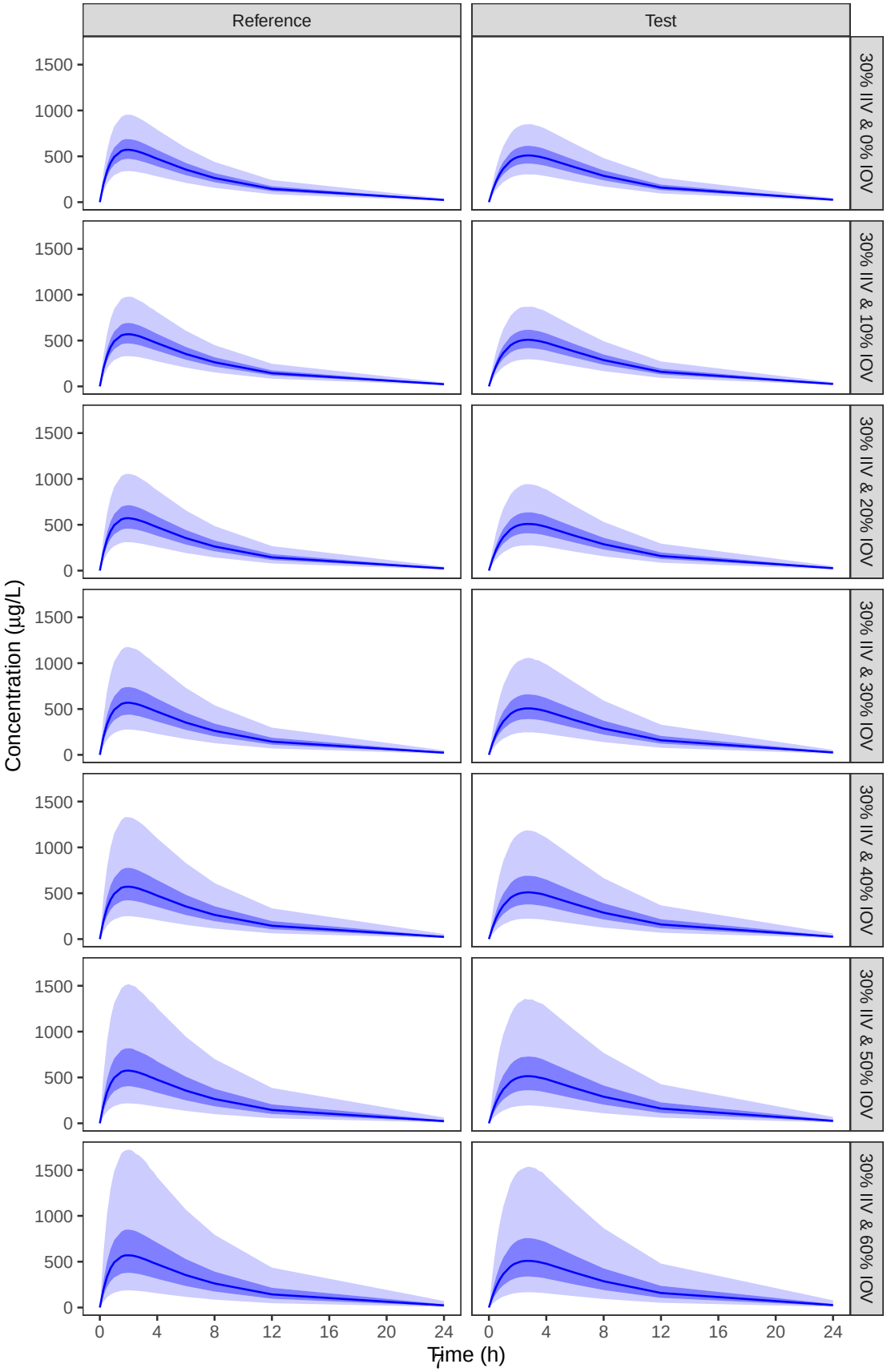

Figure S3: 90% Confidence Interval of Simulated Concentration-Time Data, for True Bioequivalent Simula-tions where Test Product Presents a Lower Bioavailability than the Reference Product – Linear Scale

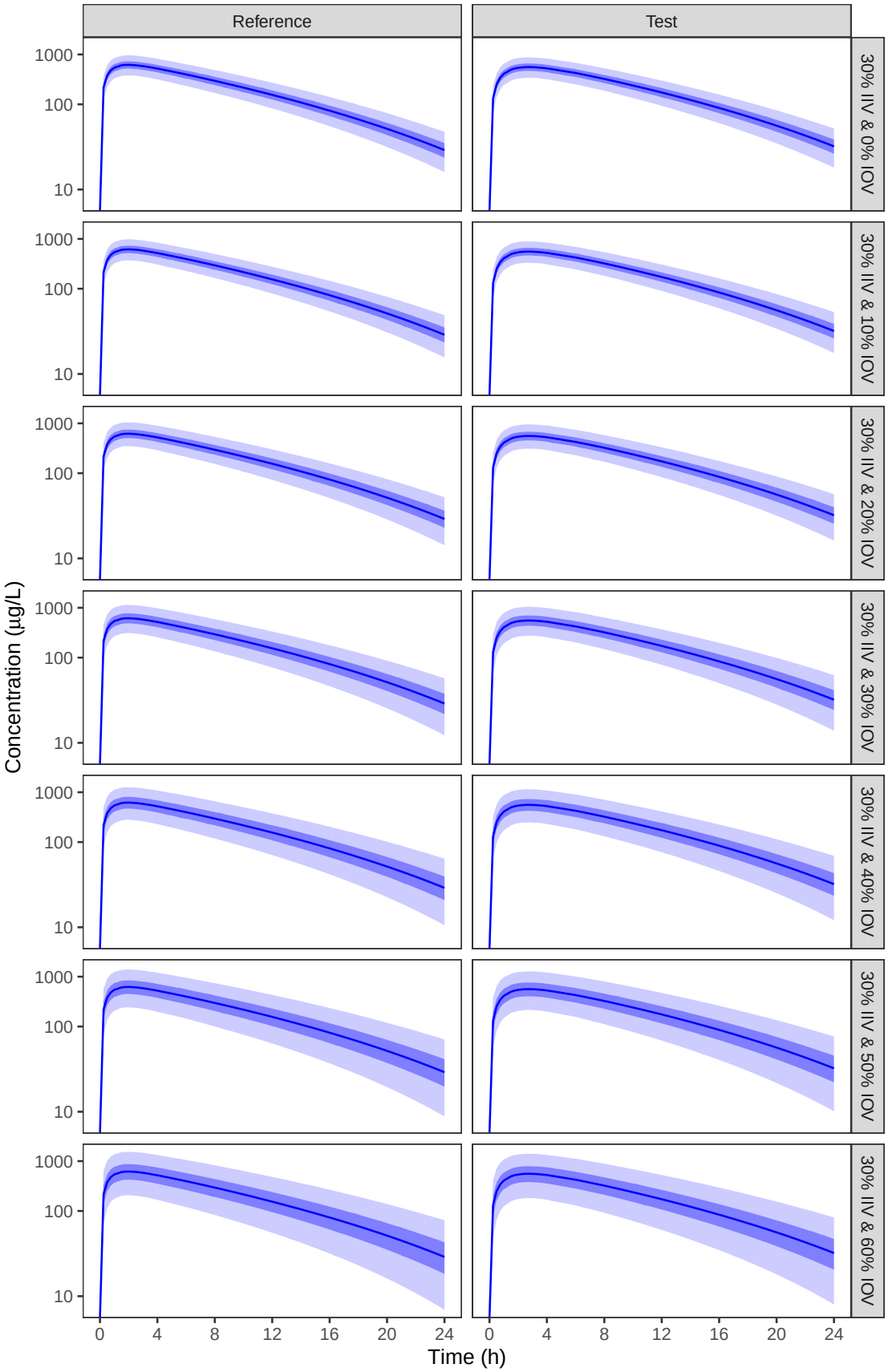

Figure S4: 90% Confidence Interval of Simulated Concentration-Time Data, for True Bioequivalent Simula-tions where Test Product Presents a Lower Bioavailability than the Reference Product – Semi-Logarithmic Scale

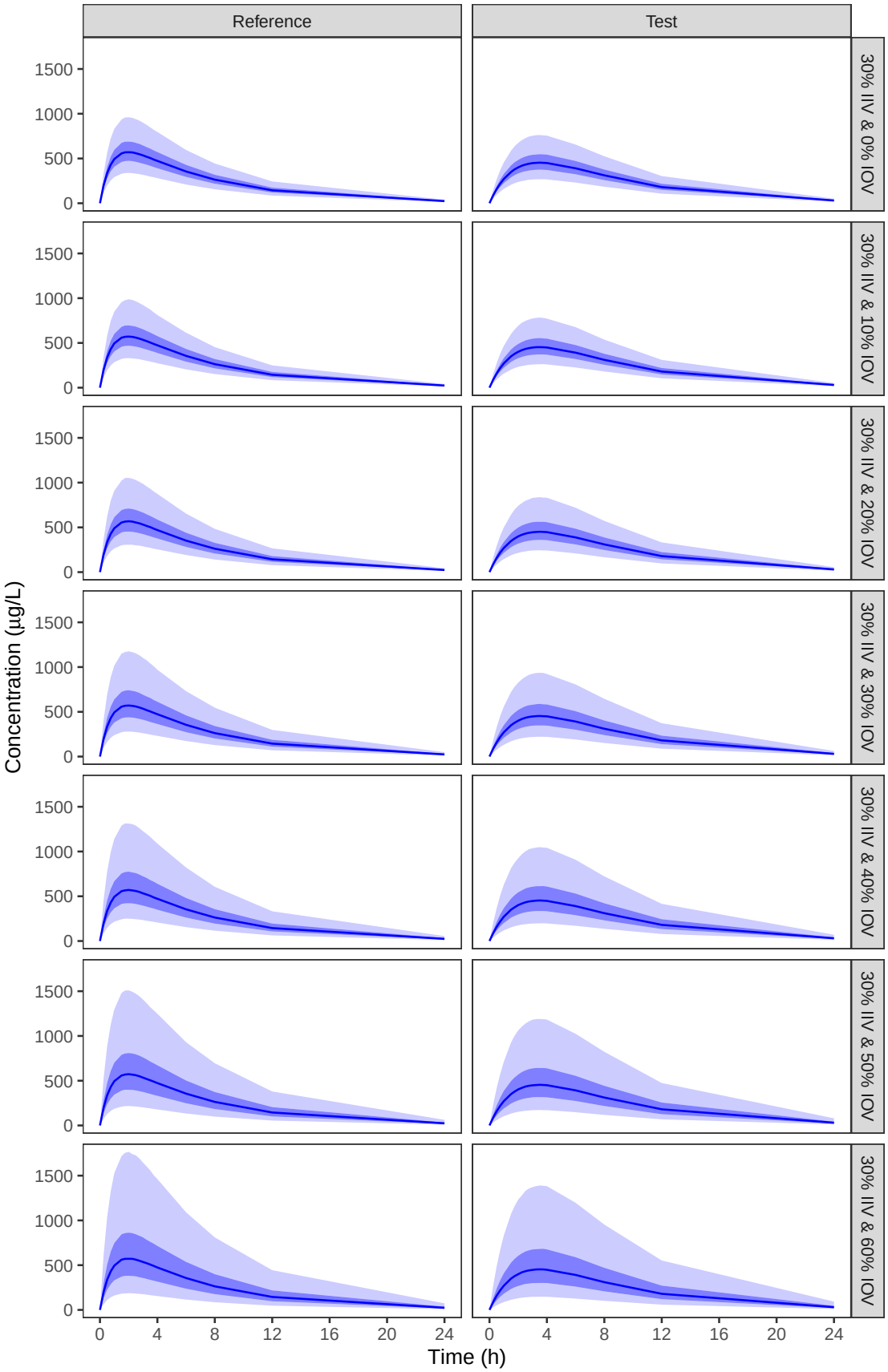

Figure S5: 90% Confidence Interval of Simulated Concentration-Time Data, for True Bioinequivalent Simulations where Test Product Presents a Lower Bioavailability than the Reference Product – Linear Scale

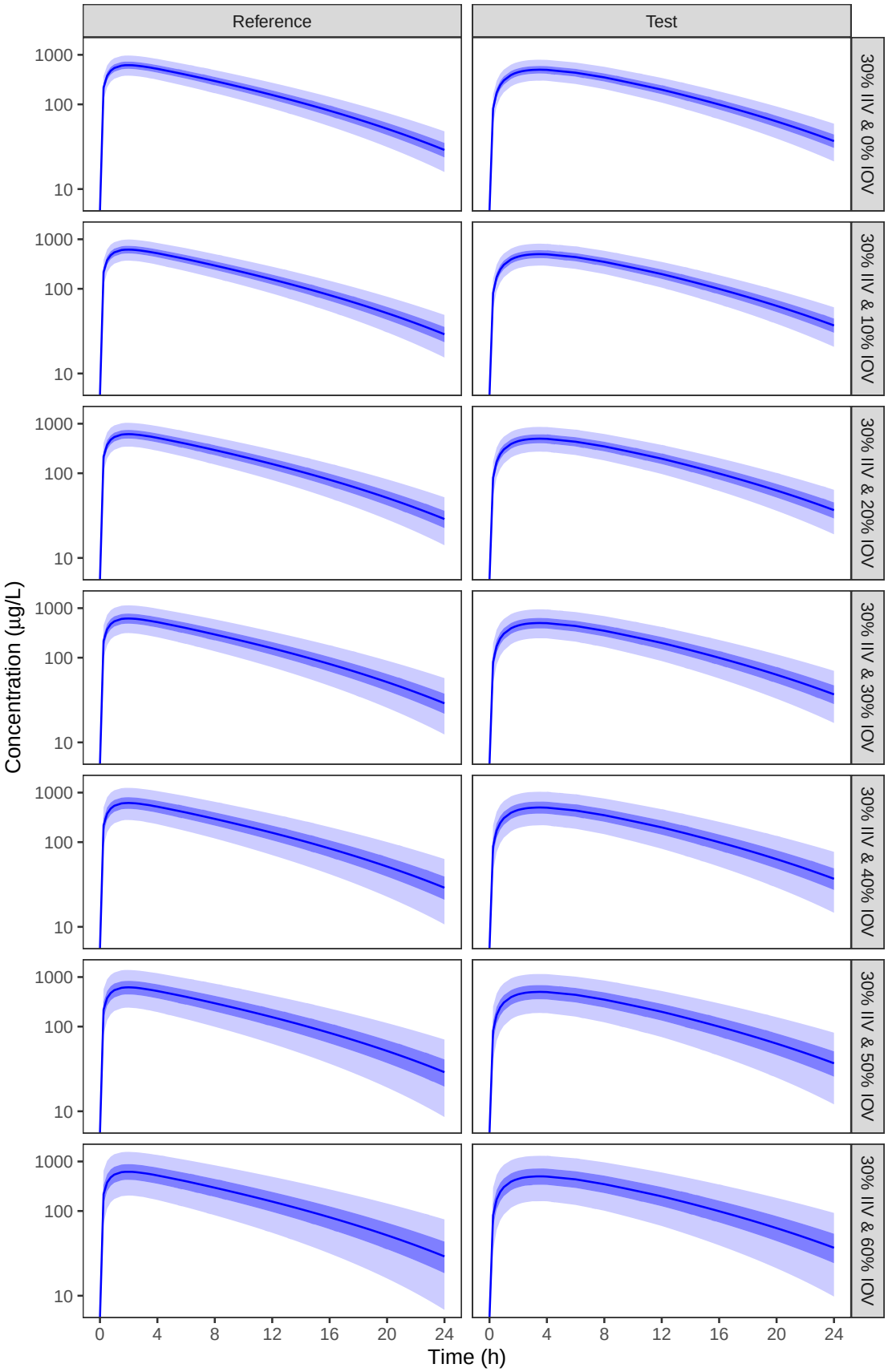

Figure S6: 90% Confidence Interval of Simulated Concentration-Time Data, for True Bioinequivalent Simula-tions where Test Product Presents a Lower Bioavailability than the Reference Product – Semi-Logarithmic Scale

S.1.3. Simulated Non-Compartmental Analysis Parameters

S.1.3.1. Maximum Observed Concentration

Table S2: Summary Statistics of Simulated Cmax, for Simulations where Test Product Presents a Lower Bioavailability than the Reference Product

	True Bioequivalent		True Bioinequivalent	
	Reference	Test	Reference	Test
30% IIV & 0% IOV	642.57 (31.4%) [641.73–643.41]	580.24 (31.3%) [579.48–581]	643.6 (31.1%) [642.76–644.44]	514.58 (31.2%) [513.91–515.25]
30% IIV & 10% IOV	640.65 (32.9%) [639.78–641.53]	578.51 (32.9%) [577.72–579.3]	640.92 (33%) [640.03–641.8]	512.06 (33%) [511.36–512.77]
30% IIV & 20% IOV	643.95 (37.7%) [642.94–644.95]	581.93 (37.7%) [581.03–582.84]	643.91 (38.2%) [642.9–644.93]	514.8 (38.1%) [513.99–515.61]
30% IIV & 30% IOV	643.26 (44.8%) [642.08–644.43]	580.42 (44.9%) [579.36–581.48]	642 (44.6%) [640.83–643.17]	512.7 (44.5%) [511.77–513.64]
30% IIV & 40% IOV	642.05 (53.8%) [640.67–643.44]	579.77 (53.6%) [578.53–581.02]	641.45 (53.6%) [640.07–642.83]	513.71 (53.5%) [512.6–514.81]
30% IIV & 50% IOV	640.86 (63.5%) [639.27–642.46]	576.84 (63.7%) [575.4–578.28]	642.08 (64%) [640.48–643.69]	513.91 (63.9%) [512.63–515.2]
30% IIV & 60% IOV	648.75 (75.8%) [646.88–650.62]	582.9 (76.1%) [581.22–584.59]	643.82 (75.5%) [641.98–645.67]	514.29 (75.2%) [512.82–515.76]

Values for Maximum Observed Concentration (C_{max}) are in μg/L, and are presented as G_{mean}, with GCV% within parenthesis, and 95% CI of the G_{mean} within square brackets.

$N = 210000$ for each group.

IIV – Inter-individual variability; IOV – Inter-occasion variability.

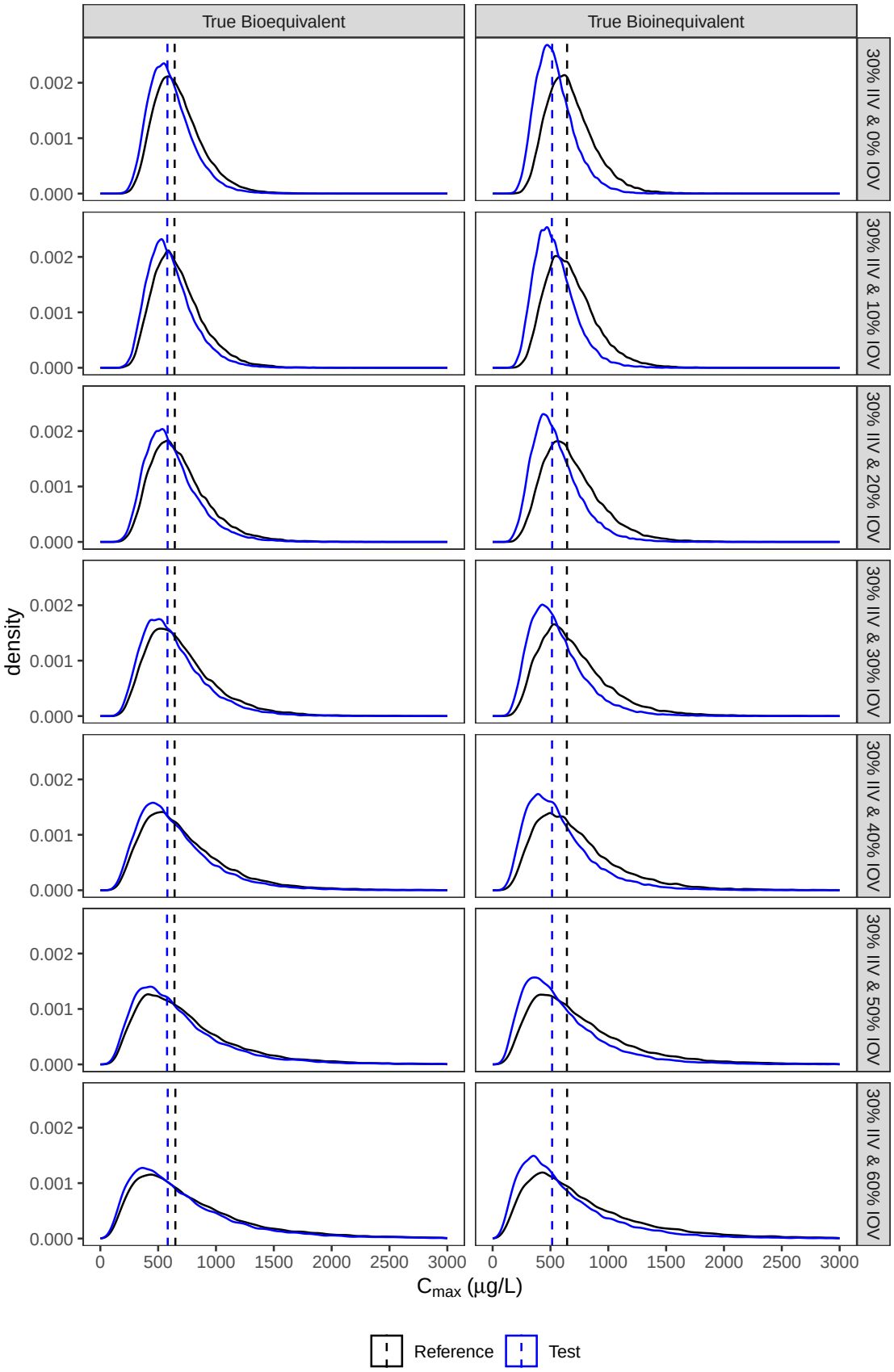

Figure S7: Distribution of Observed Cmax, for Simulations where Test Product Presents a Lower Bioavail-ability than the Reference Product

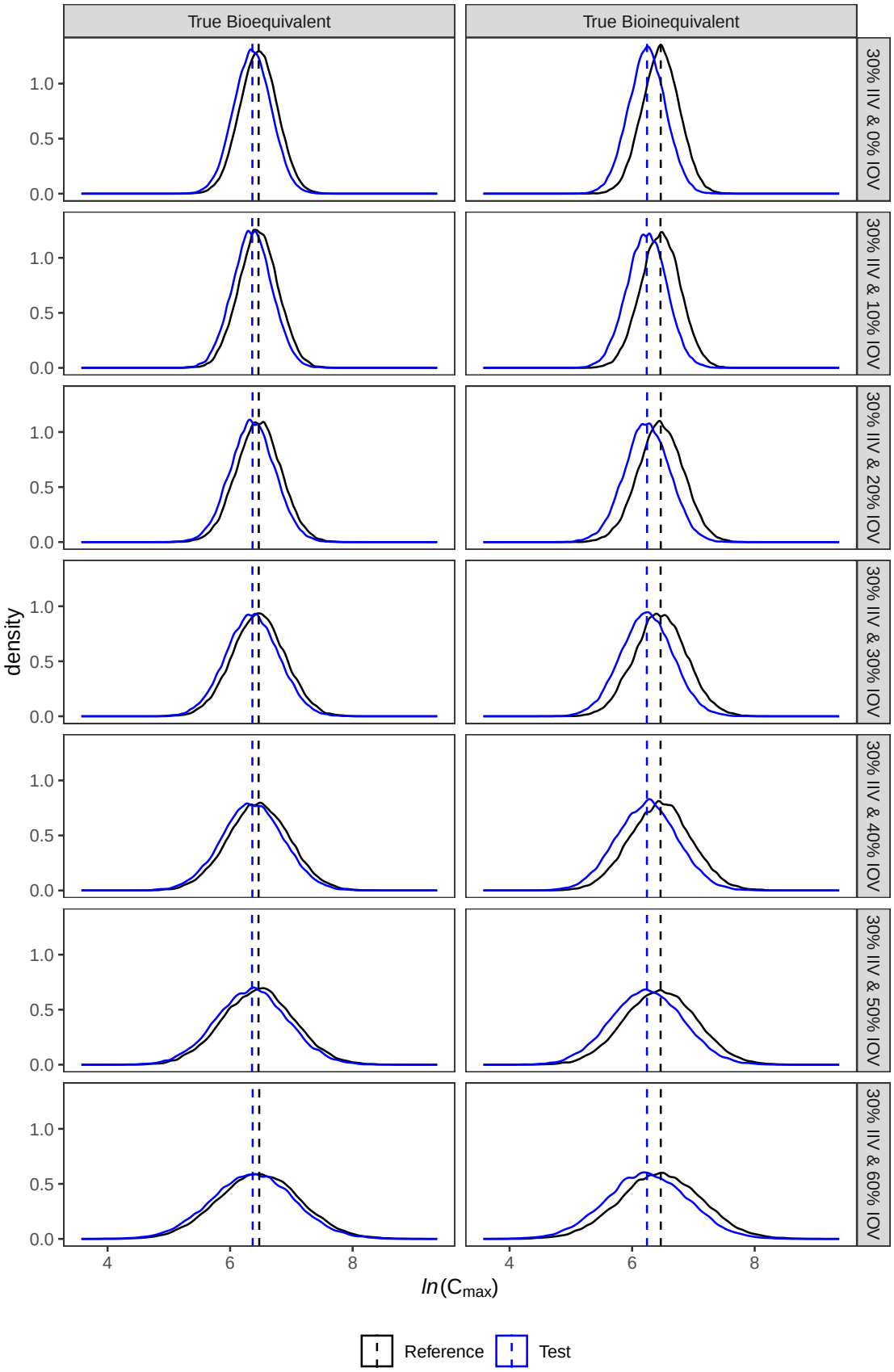

Figure S8: Distribution of *Ln*-Transformed Observed Cmax, for Simulations where Test Product Presents a Lower Bioavailability than the Reference Product

S.1.3.2. Time of Maximum Observed Concentration

Table S3: Summary Statistics of Simulated Cmax, for Simulations where Test Product Presents a Lower Bioavailability than the Reference Product

	True Bioequivalent		True Bioinequivalent	
	Reference	Test	Reference	Test
30% IIV & 0% IOV	2.25 (0.75–4)	2.75 (1–6)	2.25 (0.75–4)	3.25 (1.5–6)
30% IIV & 10% IOV	2.25 (0.75–4)	2.75 (1.5–6)	2.25 (0.75–4)	3.25 (1.5–8)
30% IIV & 20% IOV	2.25 (0.75–4)	2.75 (1–6)	2.25 (0.75–4)	3.25 (1.5–8)
30% IIV & 30% IOV	2.25 (0.75–4)	2.75 (1–6)	2.25 (0.75–4)	3.25 (1.5–6)
30% IIV & 40% IOV	2.25 (0.75–4)	2.75 (1–6)	2.25 (0.75–4)	3.25 (1.5–6)
30% IIV & 50% IOV	2.25 (0.75–4)	2.75 (1–6)	2.25 (0.75–4)	3.25 (1.5–8)
30% IIV & 60% IOV	2.25 (0.75–4)	2.75 (1.5–6)	2.25 (0.75–4)	3.25 (1.5–8)

Values for Time of Maximum Observed Concentration (t_{max}) are in hours (h), and are presented as median with range within parenthesis.

$N = 210000$ for each group.

IIV – Inter-individual variability; IOV – Inter-occasion variability.

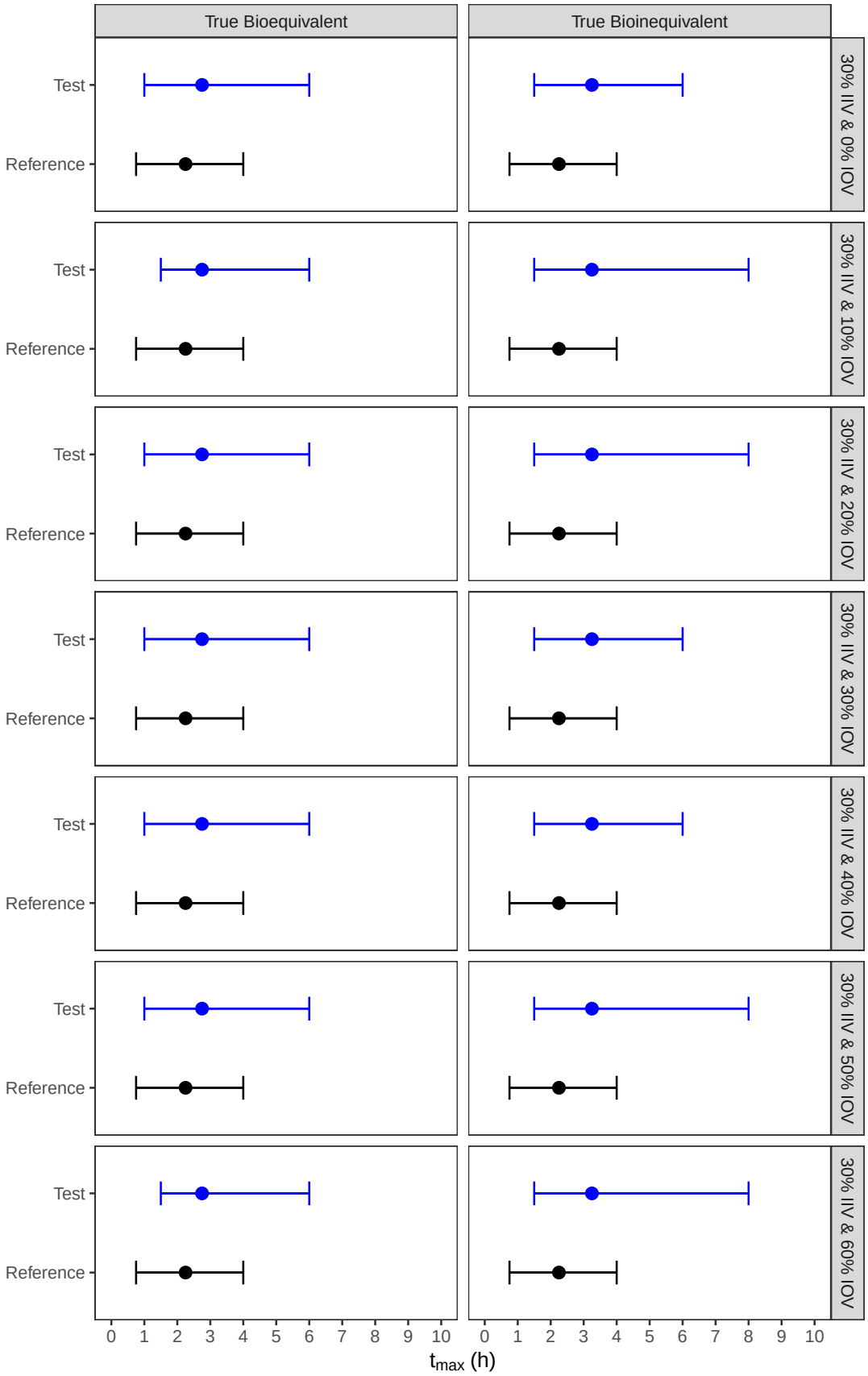

Figure S9: Distribution of Observed Tmax, for Simulations where Test Product Presents a Lower Bioavail-ability than the Reference Product

S.1.3.3. Area Under the Concentration-Time Curve

Table S4: Summary Statistics of Simulated AUC0-t, for Simulations where Test Product Presents a Lower Bioavailability than the Reference Product

	True Bioequivalent		True Bioinequivalent	
	Reference	Test	Reference	Test
30% IIV & 0% IOV	4951.25 (30.9%) [4944.86–4957.64]	4930.23 (30.9%) [4923.87–4936.6]	4961.11 (30.7%) [4954.75–4967.47]	4900.51 (30.7%) [4894.21–4906.81]
30% IIV & 10% IOV	4938.51 (32.3%) [4931.85–4945.18]	4917.09 (32.4%) [4910.46–4923.74]	4938.43 (32.6%) [4931.73–4945.14]	4877.68 (32.6%) [4871.06–4884.3]
30% IIV & 20% IOV	4961.11 (37.3%) [4953.46–4968.78]	4941.01 (37.4%) [4933.38–4948.66]	4965.32 (37.8%) [4957.56–4973.08]	4903.31 (37.8%) [4895.66–4910.98]
30% IIV & 30% IOV	4958.66 (44.5%) [4949.65–4967.69]	4932.36 (44.5%) [4923.41–4941.33]	4947.19 (44.3%) [4938.25–4956.15]	4883.78 (44.2%) [4874.96–4892.61]
30% IIV & 40% IOV	4947.1 (53.5%) [4936.5–4957.73]	4927.58 (53.3%) [4917.05–4938.13]	4946.54 (53.3%) [4935.98–4957.13]	4892.73 (53.1%) [4882.32–4903.17]
30% IIV & 50% IOV	4939.95 (63.2%) [4927.72–4952.21]	4903.76 (63.5%) [4891.57–4915.98]	4951.22 (63.6%) [4938.88–4963.58]	4893.86 (63.6%) [4881.67–4906.08]
30% IIV & 60% IOV	5001.7 (75.4%) [4987.36–5016.08]	4954.46 (75.9%) [4940.19–4968.78]	4963.79 (75.2%) [4949.6–4978.02]	4895.88 (74.9%) [4881.92–4909.87]

Values for Area Under the Concentration-Time Curve ($AUC_{0\text{-}t}$) are in μg·h/L, and are presented as G_{mean}, with GCV% within parenthesis, and 95% CI of the G_{mean} within square brackets.

$N = 210000$ for each group.

IIV – Inter-individual variability; IOV – Inter-occasion variability.

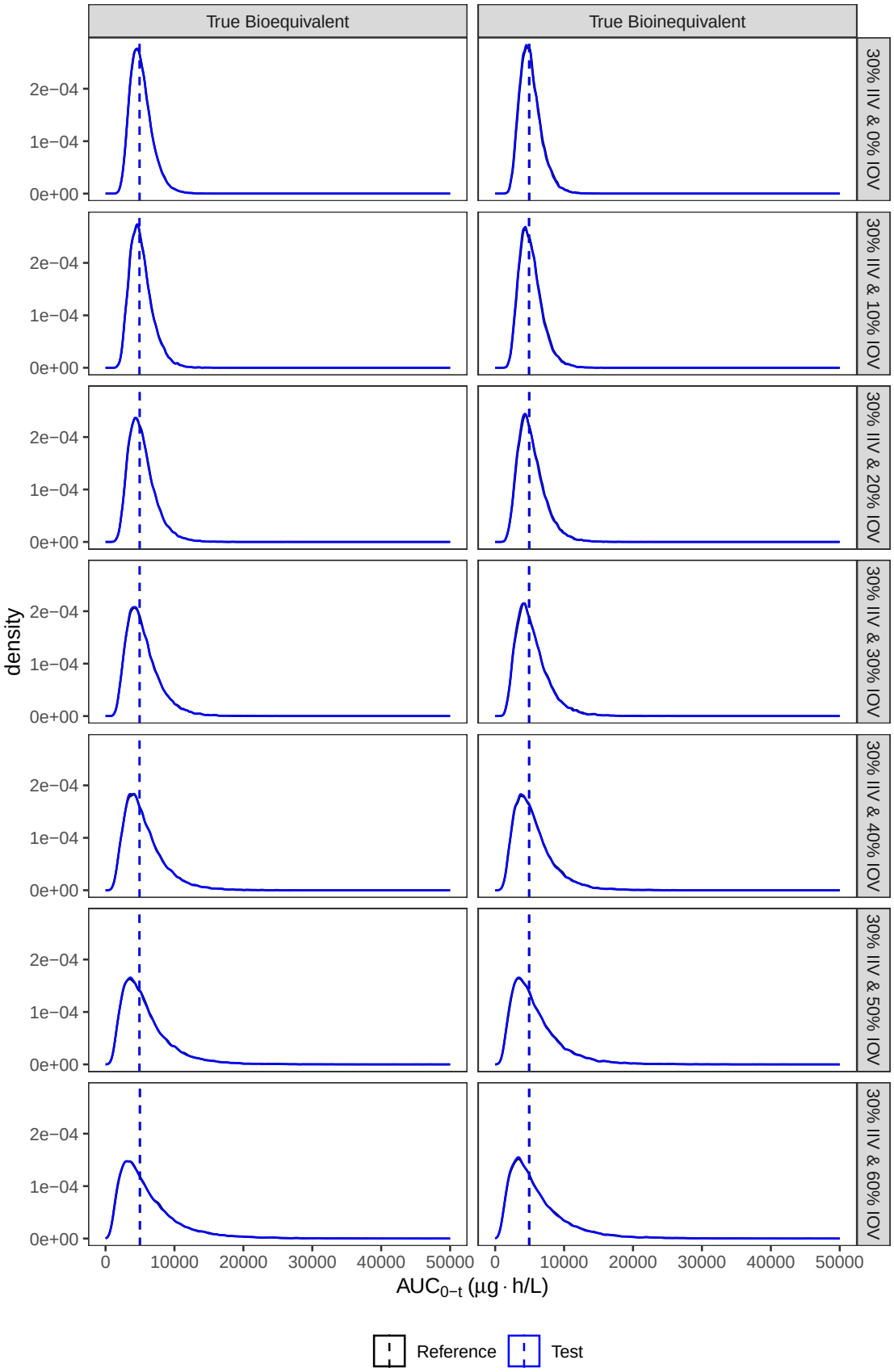

Figure S10: Distribution of Observed AUC0-t, for Simulations where Test Product Presents a Lower Bioavail-ability than the Reference Product

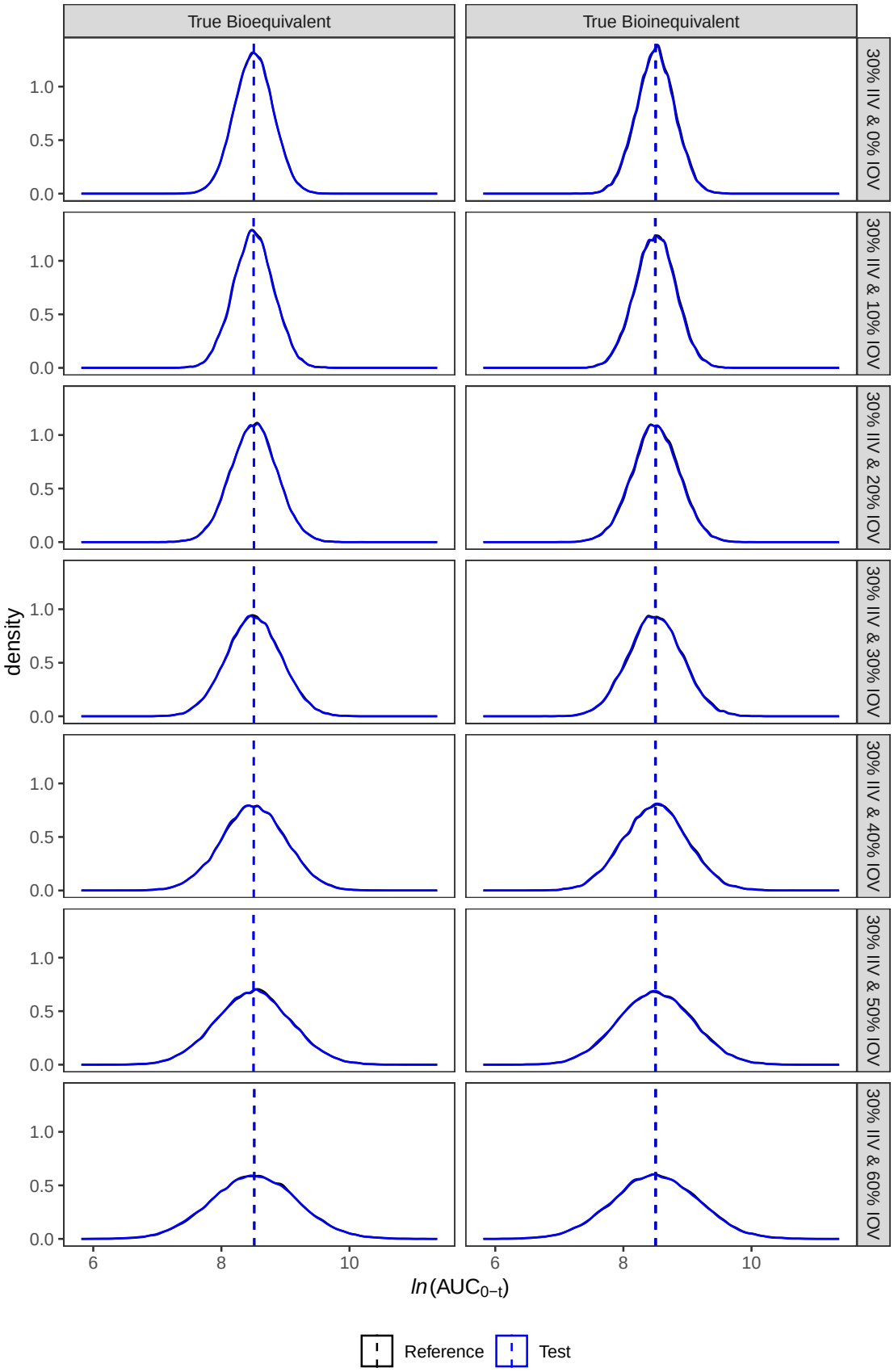

Figure S11: Distribution of *Ln*-Transformed Observed AUC0-t, for Simulations where Test Product Presents a Lower Bioavailability than the Reference Product

S.2. Simulations Where Test Product Presents a Higher Bioavailability than the Reference Product

S.2.1. Simulated Volume of Distribution

Table S5: Summary Statistics of Simulated Volume of Distribution, for Simulations where Test Product Presents a Higher Bioavailability than the Reference Product

	True Bioequivalent		True Bioinequivalent	
	Reference	Test	Reference	Test
30% IIV & 0% IOV	58.85 (30.6%) [58.77–58.92]	58.85 (30.6%) [58.77–58.92]	58.78 (30.9%) [58.7–58.86]	58.78 (30.9%) [58.7–58.86]
30% IIV & 10% IOV	58.96 (32.2%) [58.88–59.04]	58.95 (32.2%) [58.87–59.03]	58.73 (32.6%) [58.65–58.81]	58.74 (32.5%) [58.66–58.82]
30% IIV & 20% IOV	58.71 (37.1%) [58.62–58.8]	58.66 (37.1%) [58.57–58.75]	59.06 (37.4%) [58.97–59.15]	59.08 (37.4%) [58.99–59.17]
30% IIV & 30% IOV	58.9 (45%) [58.79–59.01]	58.89 (44.8%) [58.78–58.99]	58.73 (44.5%) [58.62–58.84]	58.77 (44.5%) [58.66–58.88]
30% IIV & 40% IOV	58.56 (53.1%) [58.44–58.69]	58.54 (53.2%) [58.42–58.67]	58.62 (53.1%) [58.5–58.75]	58.68 (53%) [58.56–58.81]
30% IIV & 50% IOV	58.32 (63.4%) [58.17–58.46]	58.42 (63.5%) [58.27–58.56]	58.81 (63.5%) [58.66–58.96]	58.91 (63.5%) [58.77–59.06]
30% IIV & 60% IOV	59.13 (75.1%) [58.96–59.3]	59.05 (75.1%) [58.88–59.22]	58.65 (75.8%) [58.48–58.82]	58.44 (75.9%) [58.27–58.61]

Values for V are in L, and are presented as G_{mean}, with GCV% within parenthesis, and 95% CI of the G_{mean} within square brackets.

$N = 210000$ for each group.

IIV – Inter-individual variability; IOV – Inter-occasion variability.

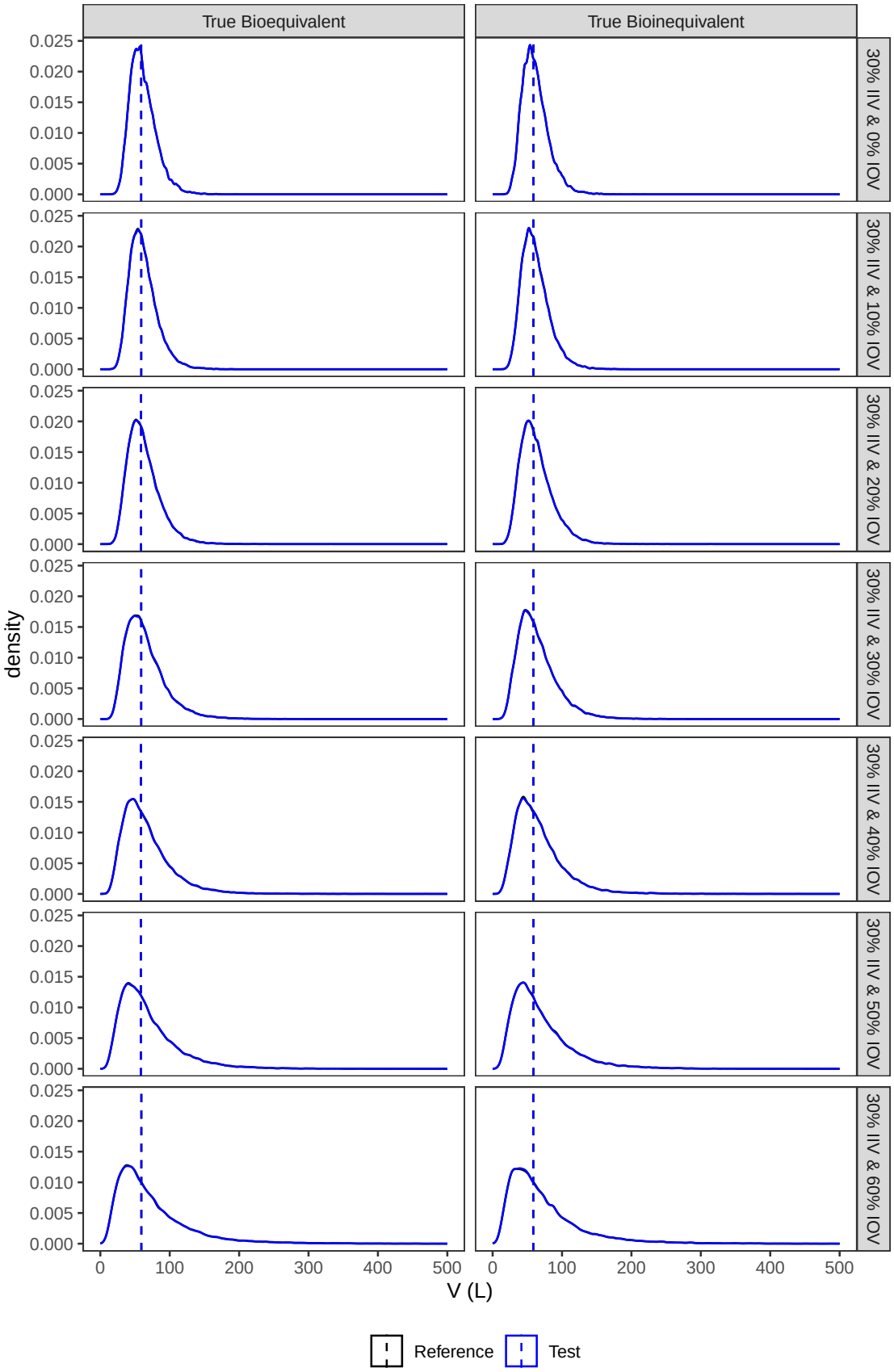

Figure S12: Distribution of Simulated Volume of Distribution, for Simulations where Test Product Presents a Higher Bioavailability than the Reference Product

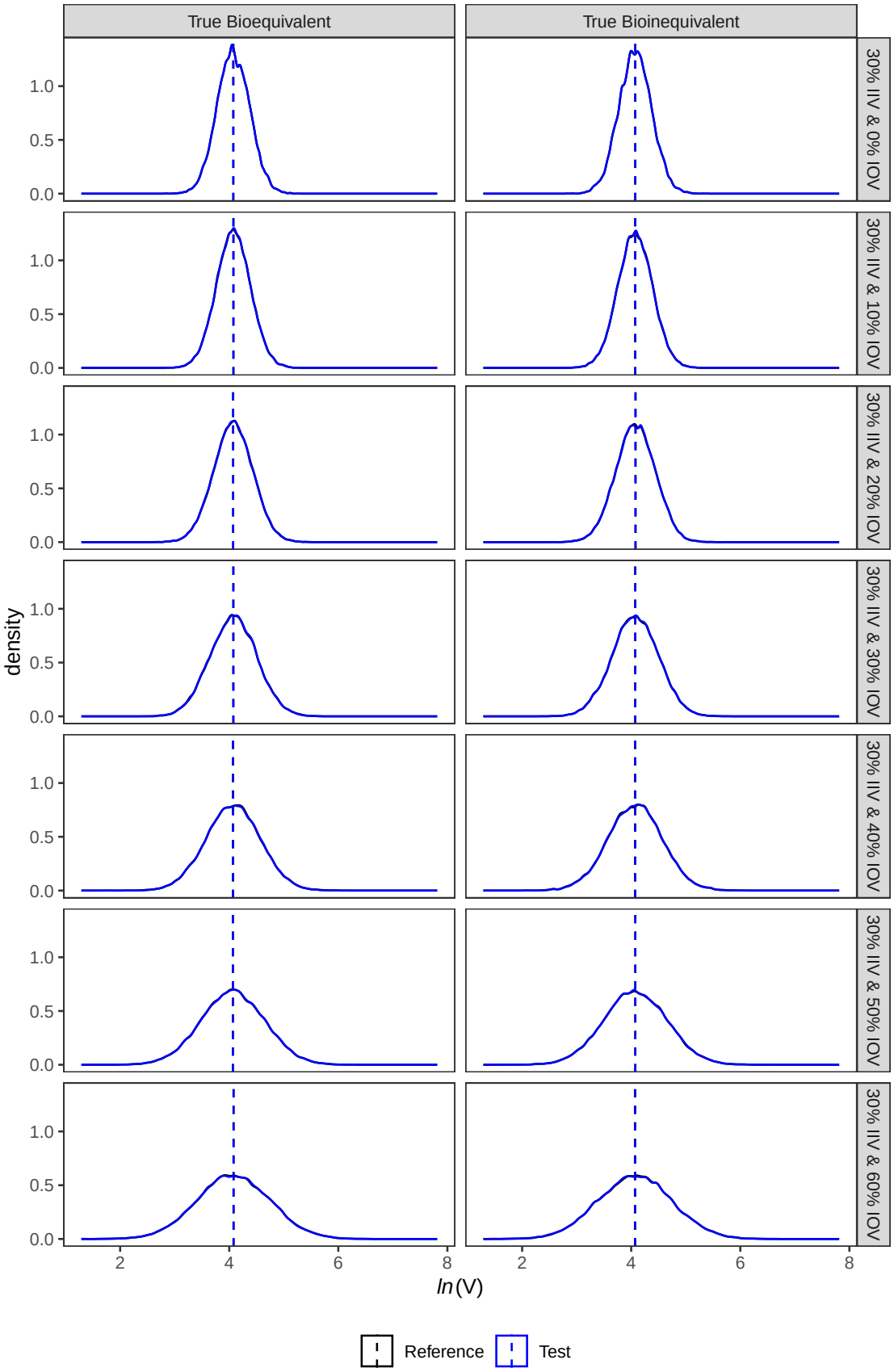

Figure S13: Distribution of *Ln*-Transformed Simulated Volume of Distribution, for Simulations where Test Product Presents a Higher Bioavailability than the Reference Product

S.2.2. Simulated Plasma Concentrations

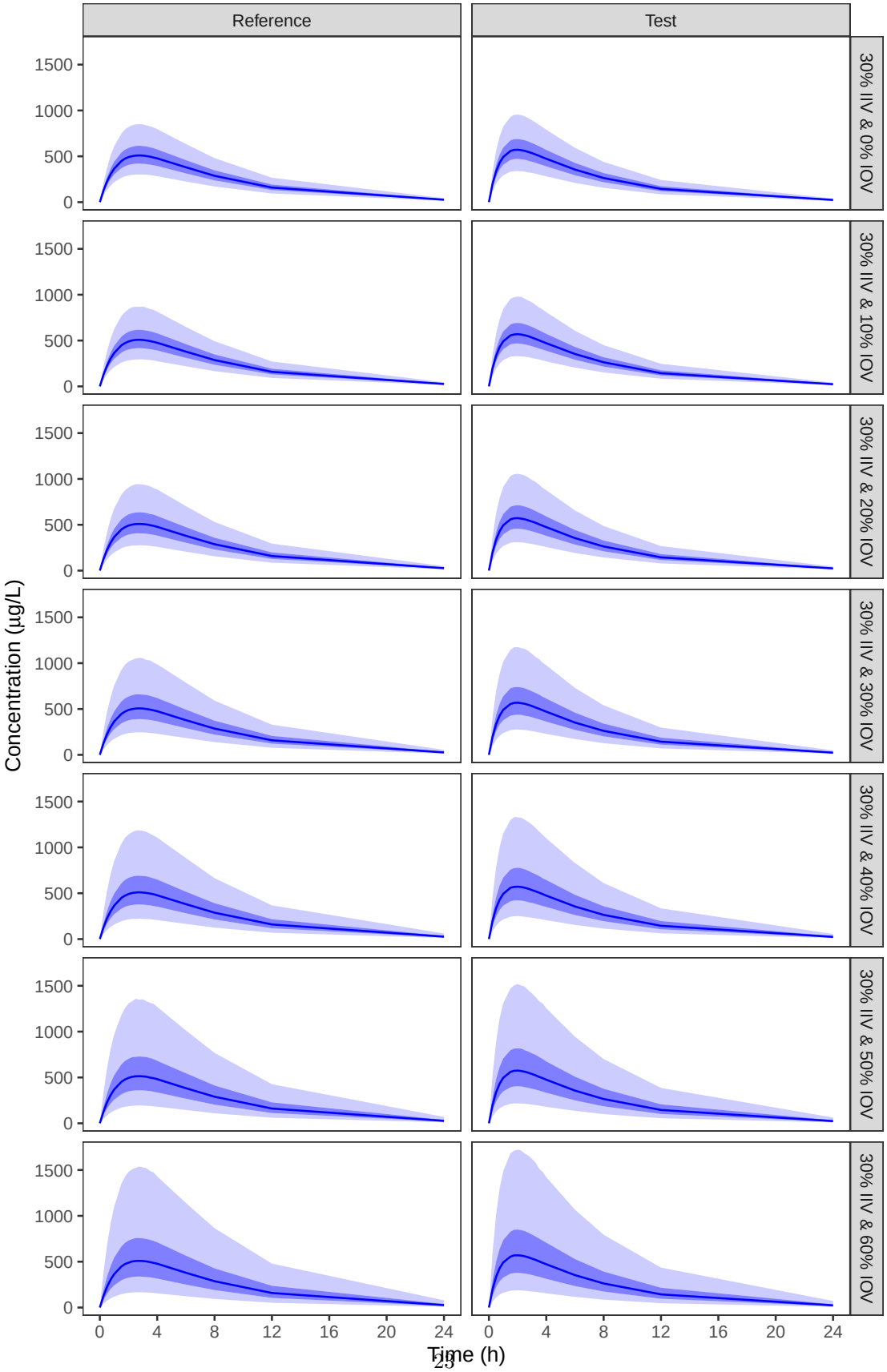

Figure S14: 90% Confidence Interval of Simulated Concentration-Time Data, for True Bioequivalent Simula-tions where Test Product Presents a Higher Bioavailability than the Reference Product – Linear Scale

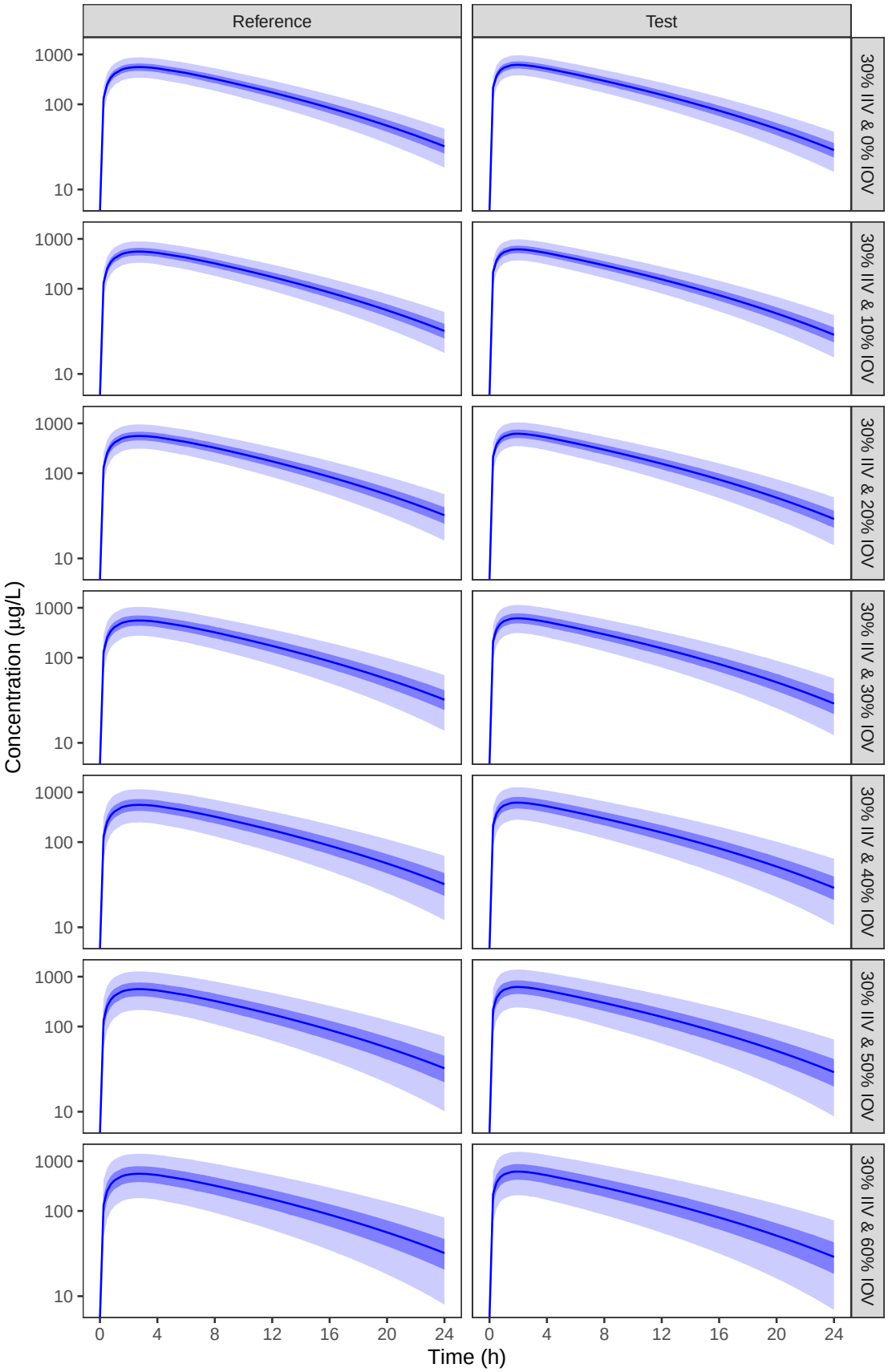

Figure S15: 90% Confidence Interval of Simulated Concentration-Time Data, for True Bioequivalent Simula-tions where Test Product Presents a Higher Bioavailability than the Reference Product – Semi-Logarithmic Scale

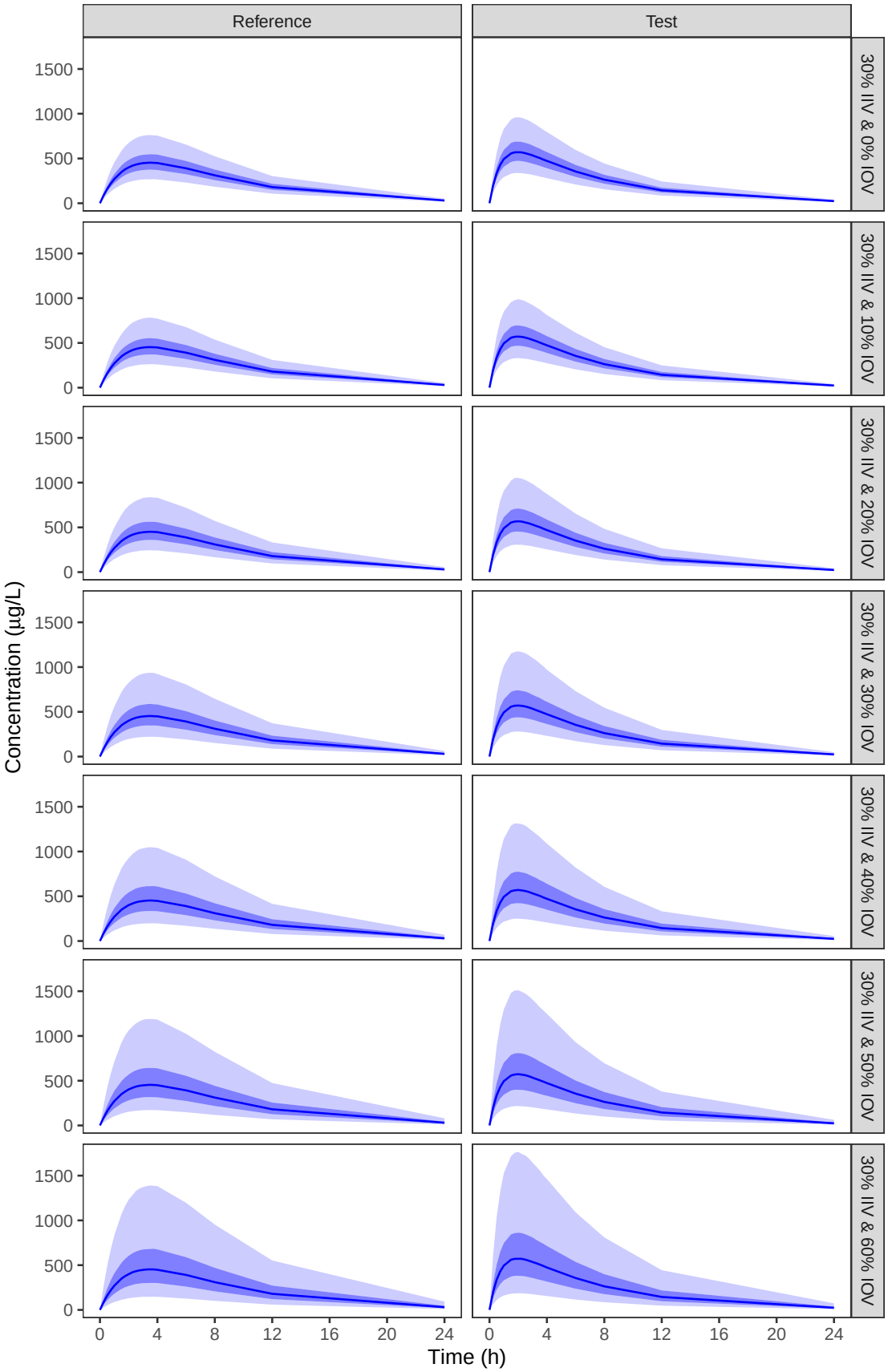

Figure S16: 90% Confidence Interval of Simulated Concentration-Time Data, for True Bioinequivalent Simulations where Test Product Presents a Higher Bioavailability than the Reference Product – Linear Scale

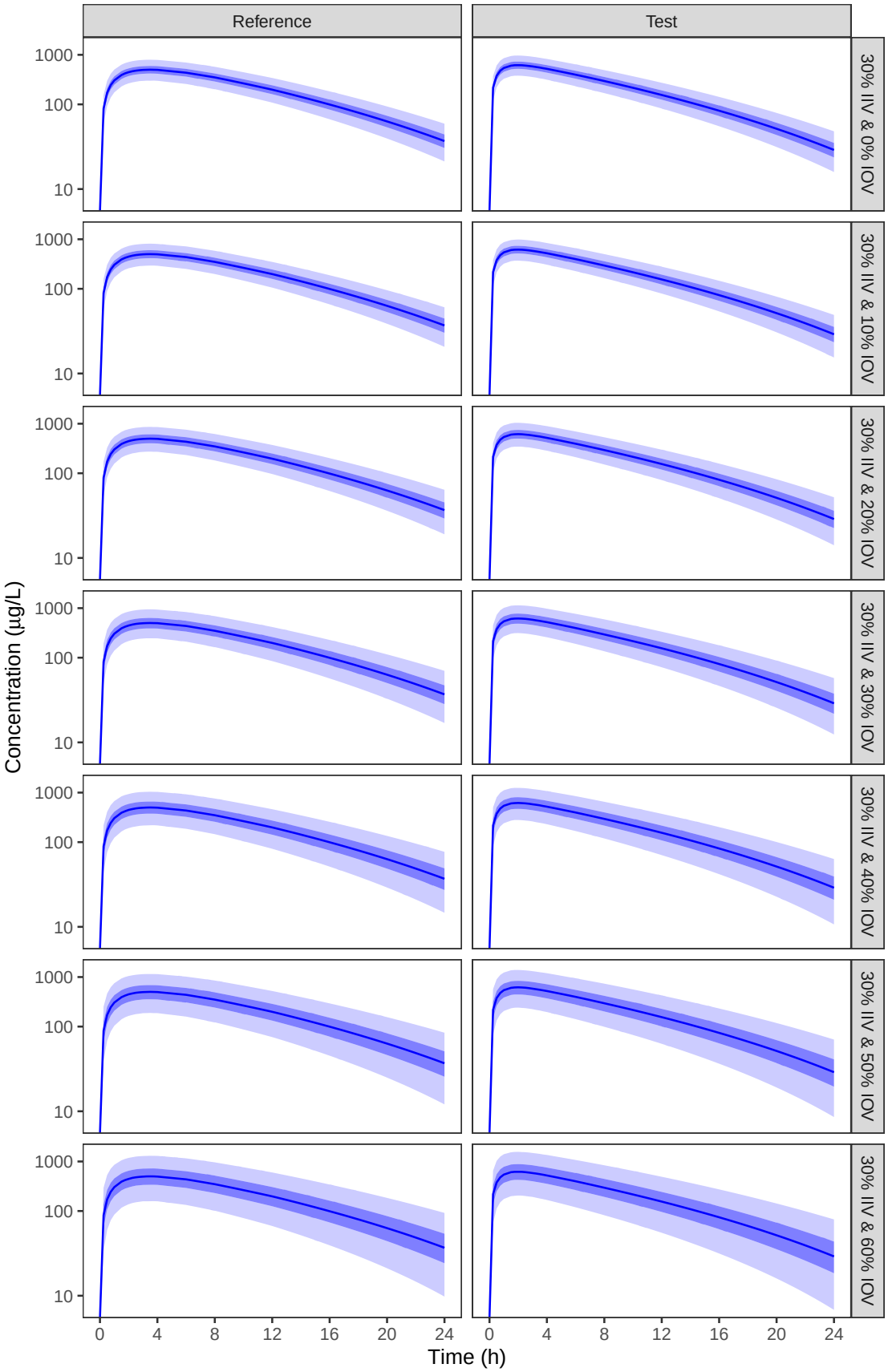

Figure S17: 90% Confidence Interval of Simulated Concentration-Time Data, for True Bioinequivalent Simu-lations where Test Product Presents a Higher Bioavailability than the Reference Product – Semi-Logarithmic Scale

S.2.3. Simulated Non-Compartmental Analysis Parameters

S.2.3.1. Maximum Observed Concentration

Table S6: Summary Statistics of Simulated Cmax, for Simulations where Test Product Presents a Higher Bioavailability than the Reference Product

	True Bioequivalent		True Bioinequivalent	
	Reference	Test	Reference	Test
30% IIV & 0% IOV	579.57 (31.2%) [578.82–580.33]	641.66 (31.3%) [640.82–642.5]	513.72 (31.6%) [513.04–514.4]	642.8 (31.6%) [641.95–643.64]
30% IIV & 10% IOV	578.73 (32.8%) [577.94–579.53]	641.22 (32.9%) [640.34–642.1]	514.2 (33.2%) [513.49–514.91]	642.82 (33.1%) [641.93–643.71]
30% IIV & 20% IOV	580.87 (37.7%) [579.97–581.78]	644.03 (37.7%) [643.03–645.04]	511.08 (37.9%) [510.28–511.88]	639.45 (37.9%) [638.44–640.45]
30% IIV & 30% IOV	578.83 (45.5%) [577.76–579.91]	641.05 (45.3%) [639.86–642.23]	513.89 (45%) [512.95–514.84]	642.57 (45%) [641.39–643.76]
30% IIV & 40% IOV	582.6 (53.5%) [581.35–583.85]	645.29 (53.6%) [643.9–646.67]	514.9 (53.6%) [513.79–516.01]	643.21 (53.4%) [641.83–644.59]
30% IIV & 50% IOV	584.74 (63.8%) [583.28–586.2]	646.39 (63.9%) [644.78–648.01]	513.59 (63.9%) [512.3–514.87]	641.53 (63.9%) [639.92–643.14]
30% IIV & 60% IOV	577.22 (75.5%) [575.56–578.88]	639.92 (75.5%) [638.08–641.76]	514.87 (76.1%) [513.39–516.36]	646.34 (76.3%) [644.47–648.22]

Values for C_{max} are in μg/L, and are presented as G_{mean}, with GCV% within parenthesis, and 95% CI of the G_{mean} within square brackets.

$N = 210000$ for each group.

IIV – Inter-individual variability; IOV – Inter-occasion variability.

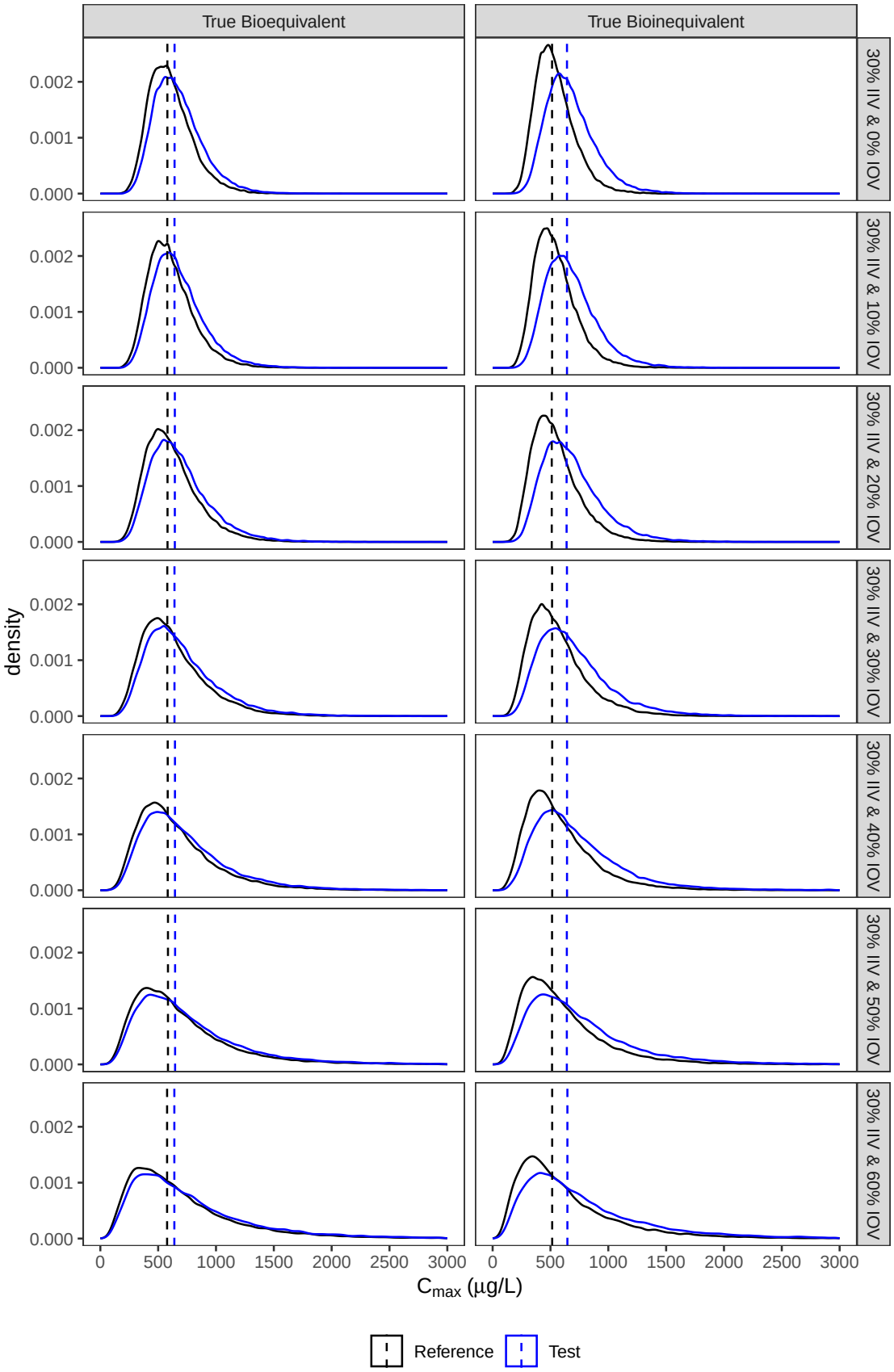

Figure S18: Distribution of Observed Cmax, for Simulations where Test Product Presents a Higher Bioavail-ability than the Reference Product

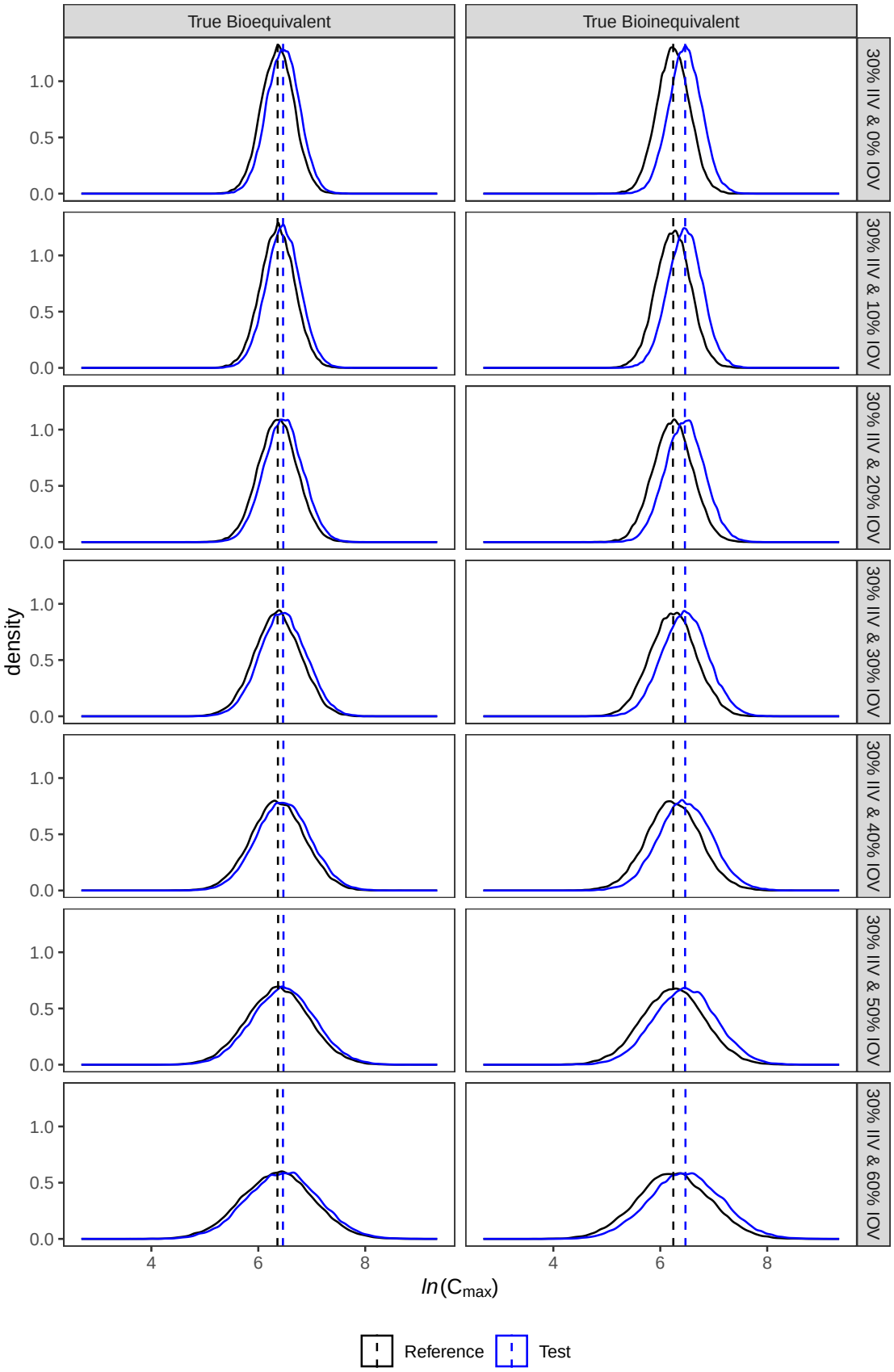

Figure S19: Distribution of *Ln*-Transformed Observed Cmax, for Simulations where Test Product Presents a Higher Bioavailability than the Reference Product

S.2.3.2. Time of Maximum Observed Concentration

Table S7: Summary Statistics of Simulated Cmax, for Simulations where Test Product Presents a Higher Bioavailability than the Reference Product

	True Bioequivalent		True Bioinequivalent	
	Reference	Test	Reference	Test
30% IIV & 0% IOV	2.75 (1–6)	2.25 (0.75–4)	3.25 (1.5–6)	2.25 (0.75–4)
30% IIV & 10% IOV	2.75 (1.5–6)	2.25 (0.75–4)	3.25 (1.5–6)	2.25 (0.75–4)
30% IIV & 20% IOV	2.75 (1–6)	2.25 (0.75–4)	3.25 (1.5–6)	2.25 (0.75–4)
30% IIV & 30% IOV	2.75 (1–4)	2.25 (0.75–4)	3.25 (1.5–6)	2.25 (0.75–4)
30% IIV & 40% IOV	2.75 (1–6)	2.25 (0.75–4)	3.25 (1.5–8)	2.25 (1–4)
30% IIV & 50% IOV	2.75 (1.5–6)	2.25 (0.75–4)	3.25 (1.5–6)	2.25 (0.75–4)
30% IIV & 60% IOV	2.75 (1–6)	2.25 (0.75–4)	3.25 (1.5–6)	2.25 (0.75–4)

Values for t_{max} are in hours (h), and are presented as median with range within parenthesis.

$N = 210000$ for each group.

IIV – Inter-individual variability; IOV – Inter-occasion variability.

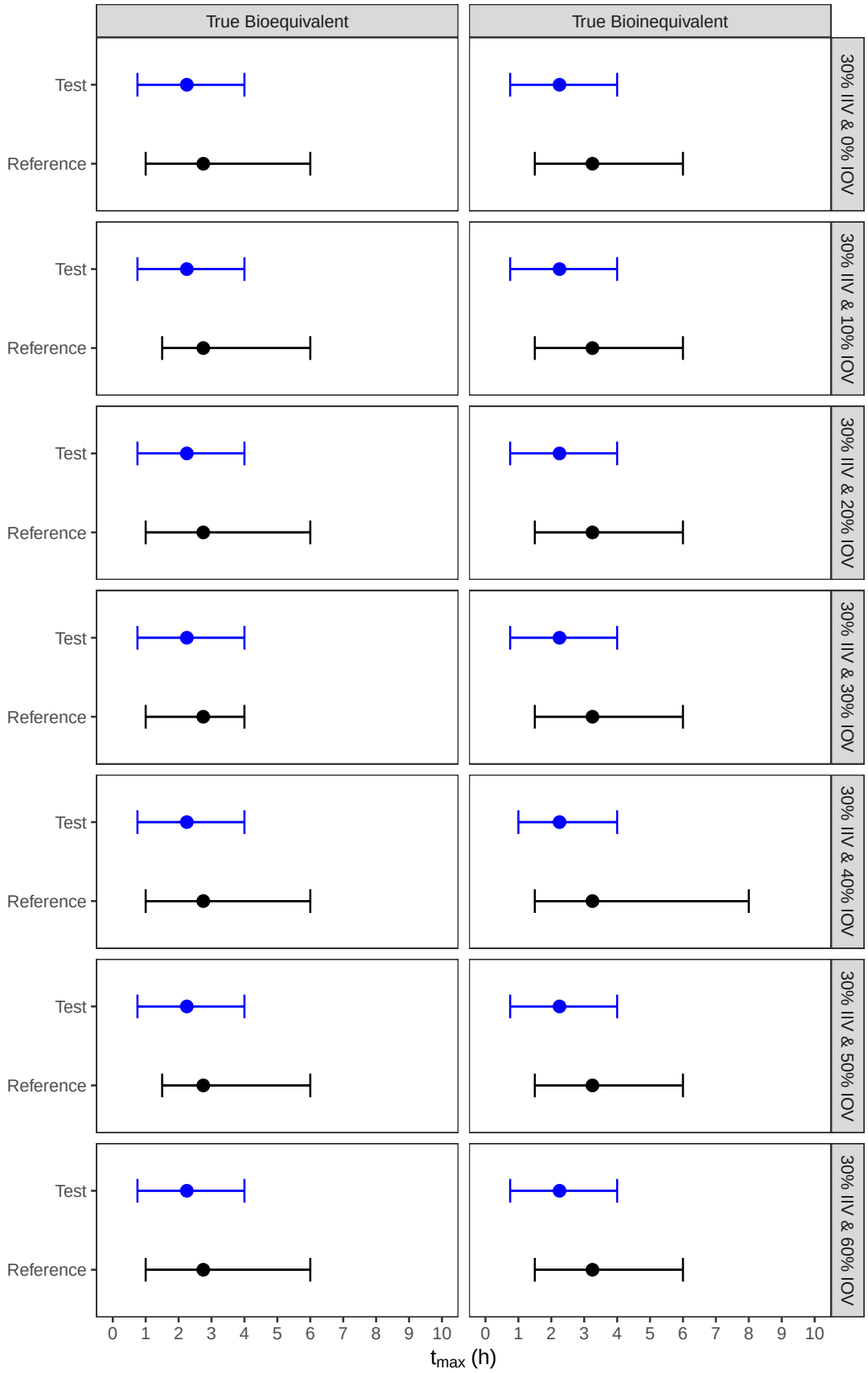

Figure S20: Distribution of Observed Tmax, for Simulations where Test Product Presents a Higher Bioavail-ability than the Reference Product

S.2.3.3. Area Under the Concentration-Time Curve

Table S8: Summary Statistics of Simulated AUC0-t, for Simulations where Test Product Presents a Higher Bioavailability than the Reference Product

	True Bioequivalent		True Bioinequivalent	
	Reference	Test	Reference	Test
30% IIV & 0% IOV	4924.2 (30.8%) [4917.87–4930.54]	4946.53 (30.8%) [4940.17–4952.89]	4891.58 (31.1%) [4885.22–4897.95]	4952.6 (31.1%) [4946.17–4959.03]
30% IIV & 10% IOV	4915.98 (32.4%) [4909.34–4922.62]	4938.35 (32.4%) [4931.69–4945.03]	4895.03 (32.8%) [4888.35–4901.73]	4953.92 (32.7%) [4947.16–4960.68]
30% IIV & 20% IOV	4935.43 (37.3%) [4927.82–4943.05]	4961.53 (37.3%) [4953.88–4969.19]	4867.23 (37.6%) [4859.67–4874.81]	4926.92 (37.6%) [4919.27–4934.58]
30% IIV & 30% IOV	4921.22 (45.2%) [4912.16–4930.3]	4943.32 (44.9%) [4934.26–4952.4]	4895.59 (44.7%) [4886.66–4904.53]	4953.01 (44.7%) [4943.98–4962.06]
30% IIV & 40% IOV	4949.14 (53.2%) [4938.58–4959.72]	4972.44 (53.3%) [4961.82–4983.09]	4904.24 (53.3%) [4893.76–4914.73]	4959.13 (53.1%) [4948.58–4969.71]
30% IIV & 50% IOV	4969.5 (63.6%) [4957.13–4981.9]	4982.45 (63.6%) [4970.04–4994.89]	4888.86 (63.6%) [4876.68–4901.07]	4941.64 (63.6%) [4929.33–4953.97]
30% IIV & 60% IOV	4900.56 (75.2%) [4886.54–4914.62]	4927.91 (75.3%) [4913.82–4942.05]	4902.43 (75.8%) [4888.31–4916.58]	4981.22 (75.9%) [4966.86–4995.61]

Values for $AUC_{0\text{-t}}$ are in μg·h/L, and are presented as G_{mean}, with GCV% within parenthesis, and 95% CI of the G_{mean} within square brackets.

$N = 210000$ for each group.

IIV – Inter-individual variability; IOV – Inter-occasion variability.

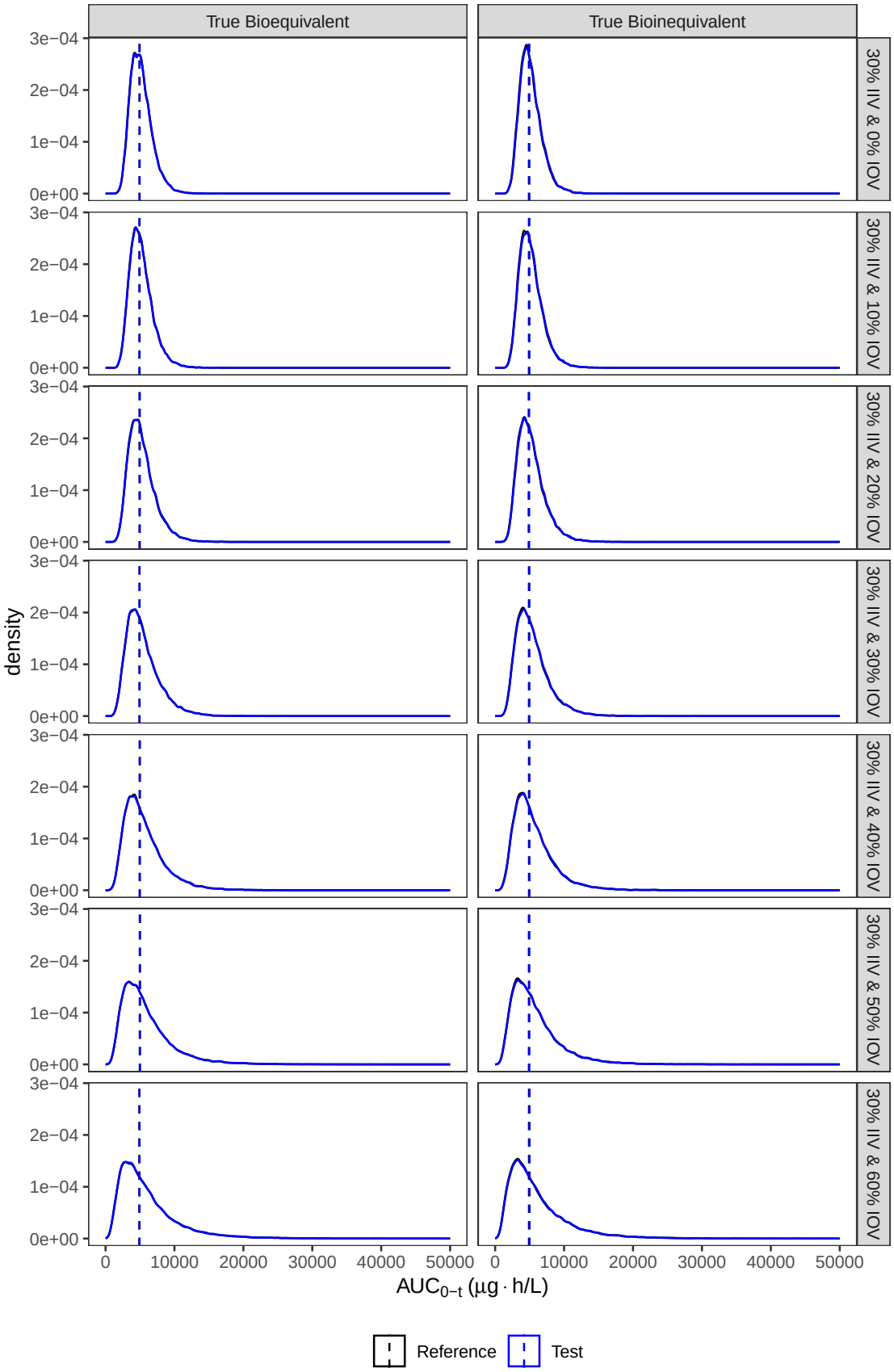

Figure S21: Distribution of Observed AUC0-t, for Simulations where Test Product Presents a Higher Bioavail-ability than the Reference Product

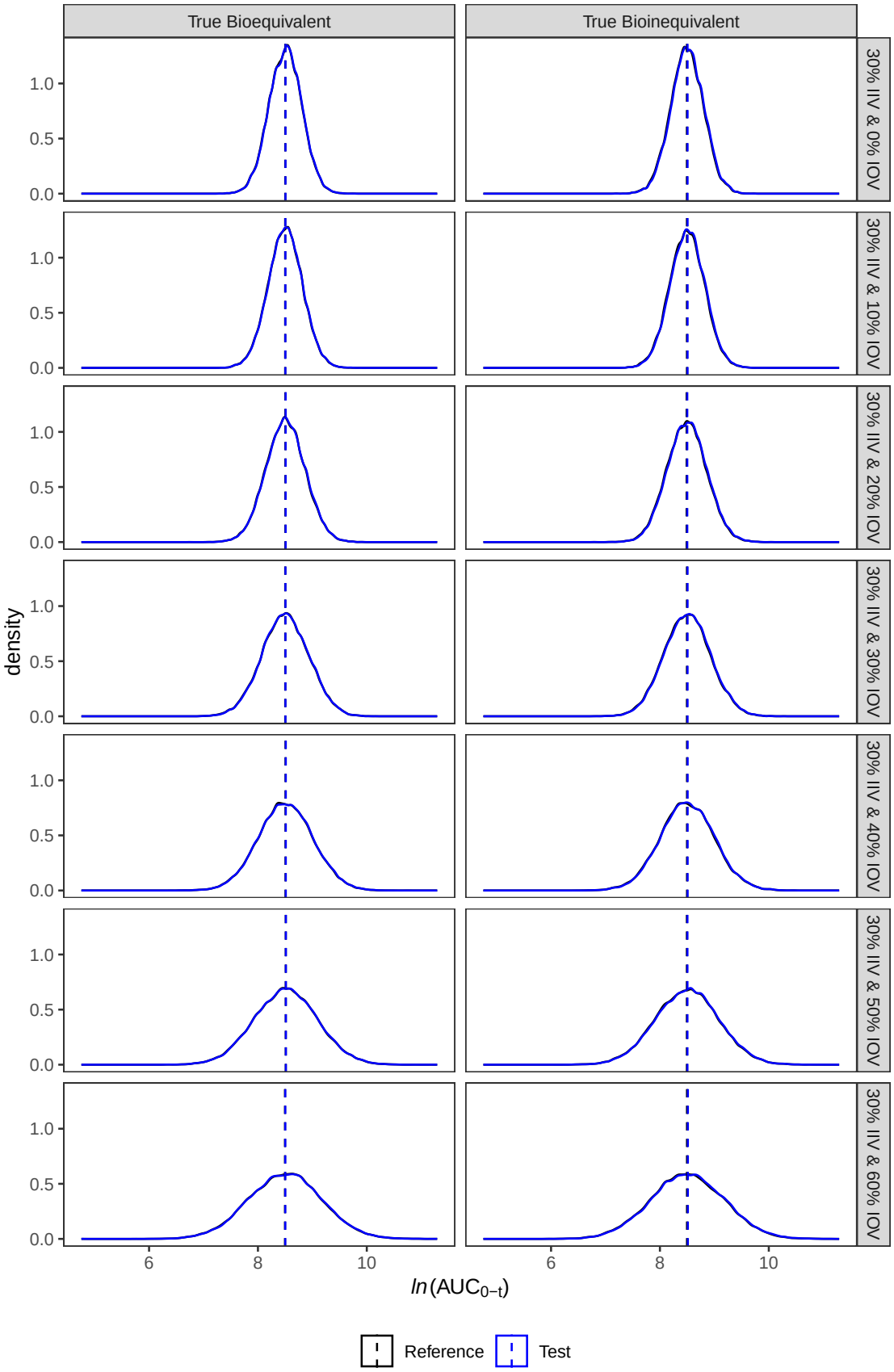

Figure S22: Distribution of *Ln*-Transformed Observed AUC0-t, for Simulations where Test Product Presents a Higher Bioavailability than the Reference Product