



Analytical Characterization, Safety and Clinical Bioequivalence of Recombinant Human Insulin from Transgenic Plants

Boothe J.G., Nykiforuk C.L., Kuhlman P.A., Whelan H., Pollock W.B.R., Clark S., Yuan S., Kumar R., Murray E.W., Visser F., Martens K., Wu J., Pollock E., Given B., Szarka S., Zaplachinski S., Harry I., Keon R. and Moloney M.M.

This work demonstrates the quality, safety and pharmacological equivalence of recombinant human insulin produced from transgenic safflower plants. A cGMP process was developed for the purification of insulin expressed in transgenic seed. Physical-chemical, structural, and biological analysis confirmed the identity and functionality of the resulting product. The plant-made insulin (SBS-1000) was also shown to meet all compendial specifications and to be free of host-specific impurities. Repeat dose (28-day) toxicity studies comparing the effects of SBS-1000 with Humulin®R were performed in Fischer 344 rats and Cynomolgus monkeys. Parameters evaluated included clinical signs, injection site changes, tissue/organ pathology and toxicokinetics. Data from these studies indicated that SBS-1000 had a safety profile indistinguishable from Humulin®R. A 3-way crossover study in healthy volunteers (n=23) using a euglycemic clamp was conducted to compare the pharmacokinetics and pharmacodynamics of SBS-1000 with two reference insulins, Humulin®R and Humulin®S. Results from this study showed that the three insulins displayed similar adverse event profiles. Although an analytical error resulted in a reduced concentration in the formulated SBS-1000 (accounting for lower values for the point estimate ratios), the 90% CI of all primary endpoints fell within the 80-125% range required for bioequivalence to Humulin®R. Similar results were obtained with Humulin®S for all endpoints except GIR_{max}. This difference between SBS-1000 and Humulin®S was also observed between Humulin®R and Humulin®S and was exacerbated by the greater variability observed for this parameter. Together these results demonstrate the feasibility of our transgenic plant manufacturing platform for the production of pharmaceutical-quality human insulin.

Parameter	SBS-1000:Humulin®R		SBS-1000:Humulin®S		Humulin®R:Humulin®S	
	Ratio (%)	90% CI	Ratio (%)	90% CI	Ratio (%)	90% CI
Insulin AUC 0-8 hrs.	91	87-95	90	85-95	99	95-103
GIR AUC 0-8 hrs.	92	84-100	92	85-100	101	92-110
Insulin C max	94	87-102	86	80-93	92	84-100
GIR max	93	81-108	81	68-97	87	74-103