Comparison of the Rabbit, Diabetic Miniature Swine, and Non-human Primate to Evaluate the Clinical Biopotency of Insulin Products
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Purpose
The potency of human insulin has classically been evaluated following the U.S. Pharmacopeia (USP) guideline for comparison to an international standard (IS) of activity (IU). However, since insulin analogues are intentionally different and cannot be standardized against an IS, there is a need for a bioassay to assess clinical specific activity (U).

Methods
To this extent, we compared the biopotency (U) of different insulin products in rabbits, in type 1 diabetic miniature swine and in normal non-human primates, and used human and pork insulin as reference standards. New Zealand White rabbits were fasted and injected subcutaneously (s.c.) at a dose level of 0.5 U/kg. Yucatan miniature swine (Sus scrofa) were made diabetic by intravenous administration of alloxan and insulin products were injected s.c. at a dose level of 0.1 U/kg in overnight fasted animals (no feed or insulin for 18 h). Normal insulin suppression tests (nIST) were conducted in fasted male cynomolgus primates (Macaca fascicularis) receiving a bolus intravenous (i.v.) infusion of glucose (ivGTT; 0.25 g/kg) and treated with somatostatin. Insulin products were given at a dose level of 0.05 U/kg. Glucose levels were recorded using handheld glucometer devices. The blood glucose kinetics (BGPK) and the blood glucose area under the curve (BGAUC) were used to assess biopotency in the rabbit, the diabetic miniature swine, and the non-human primate. The slope of the blood glucose clearance (kG) was used to assess biopotency during the nIST.

Results
The BGPK for short-acting human and pork insulin were similar in the rabbit assay but their respective BGAUCs were different (ratio of 1.2). Accordingly pork insulin was more potent during nIST in the non-human primate (slope of -0.012 vs. -0.010; pork and human, respectively).

Conclusion
Our data indicate that the biopotency of insulin products can be assessed using BGAUC and kG, but that only the type 1 diabetic miniature swine can discriminate between differences in biopotency for all aspects of BGPK.