
Insulin Opportunity: Technical Presentation

Patent Portfolio

Patent Estate

There is a solid IP Portfolio for the regular insulin process

Intellectual Property Portfolio				
Title	Katten Ref.	Application / Patent #	Filing/ Issue Date	Application Data/ Status
hGh and Methods for Preparation	◆ 343445-00006	◆ 61,305,451	◆ 2/17/2010	◆ Provisional App.; To convert on 2/17/2011
Insulin Production Methods and Pro-Insulin Constructs	◆ 343445-00005	◆ 7,790,677	◆ 5/20/2007(FD) ◆ 9/7/2010 (ID)	◆ Issued ◆ 1st Maintenance Fee due 3/7/2014
Insulin Production Methods and Pro-Insulin Constructs	◆ 343445-00013	◆ 12/658,852	◆ 2/16/2010	◆ Continuation of 11/715,731 ◆ Published 8/19/2010
Improved Insulin Aspart Analog Preparations and Methods of Manufacturing and Formulating Same	◆ 343445-00014	◆ TBD	◆ In progress	◆ In preparation
Improved Insulin Glargine Analog Preparations and Methods of Manufacturing and Formulating Same	◆ 343445-00016	◆ TBD	◆ In progress	◆ In preparation
Liquid Insulin Compositions and Improved Methods of Manufacturing Liquid and Crystalline Insulin Preparations and Formulations	◆ 1343445-00015	◆ TBD	◆ In progress	◆ In preparation

Physiochemical Properties

Our generic meets the Doctrine of Equivalence for USP Grade Insulin-Humulin

Technical Data

Physiochemical Composition	
Physiochemical Property	Value
◆ Amino acid sequence	◆ Equivalent to insulin hormone, USP
◆ Amino acid composition	◆ Equivalent to insulin hormone, USP
◆ Peptide map	◆ Equivalent to insulin hormone, USP
◆ Disulfide bridges	◆ Equivalent to insulin hormone, USP
◆ Molecular weight	◆ Equivalent to insulin hormone, USP
◆ Isoform pattern	◆ Equivalent to insulin hormone, USP
◆ Electrophoretic patterns	◆ Equivalent to insulin hormone, USP
◆ Liquid chromatographic patterns	◆ Equivalent to insulin hormone, USP
◆ Potency	◆ Equivalent to insulin hormone, USP



Insulin Specifications

Technical Data

As the data shows, our generic has specifications that are equivalent to USP Grade Insulin

Component Specifications		
Attribute	Analytical Method	Acceptance Criteria
Appearance	♦ Visual	♦ Clear, colorless solution with no visible particulates
Identity	♦ RP-HPLC USP	♦ Retention time (R_T) of the major peak in the chromatogram of the assay preparation corresponds to that in the chromatogram of the standard preparation, as obtained in the Assay
Bacterial Endotoxins	♦ USP <85>	♦ NMT 80 USP Endotoxin Units/100 Insulin Human Units
Sterility	♦ USP <71>	♦ Meets requirements when tested as directed for <i>Membrane Filtration under Test for Sterility of the Products to be Examined</i>
Particulate Matter	♦ USP <788>	♦ Meets requirements for small volume injections
Limit of High Molecular Weight Proteins	♦ RP-HPLC USP	♦ NMT.1.7%
pH	♦ USP <791>	♦ 7.0 to 7.8, determined potentiometrically
Zinc	♦ USP<591>	♦ 10 to 40 ug/100 USP Insulin Human Units
Assay	♦ RP-HPLC USP	♦ 3.30 to 3.64 mg/mL
Potency		♦ 95.0% to 105.0% of label claim expressed in USP Insulin Human Units/mL
Degradation Products		♦ Report all individual impurities >0.1% - Report Result ♦ Identify all individual impurities >0.5% - Report Result ♦ Total degradation products: All peaks above reporting threshold ≤3.0%
Other	♦ USP<1>	♦ Meets requirements for injections
APET	♦ USP<51>	♦ Bacterix NLT 1.0 log reduction from the initial calculated count at 7 days, NLT 3.0 log reduction from the initial count at 14 days, and no increase from the 14 days' count at 28 days ♦ Yeast and molds: no increase from the initial calculated count at 7, 14, and 28 days

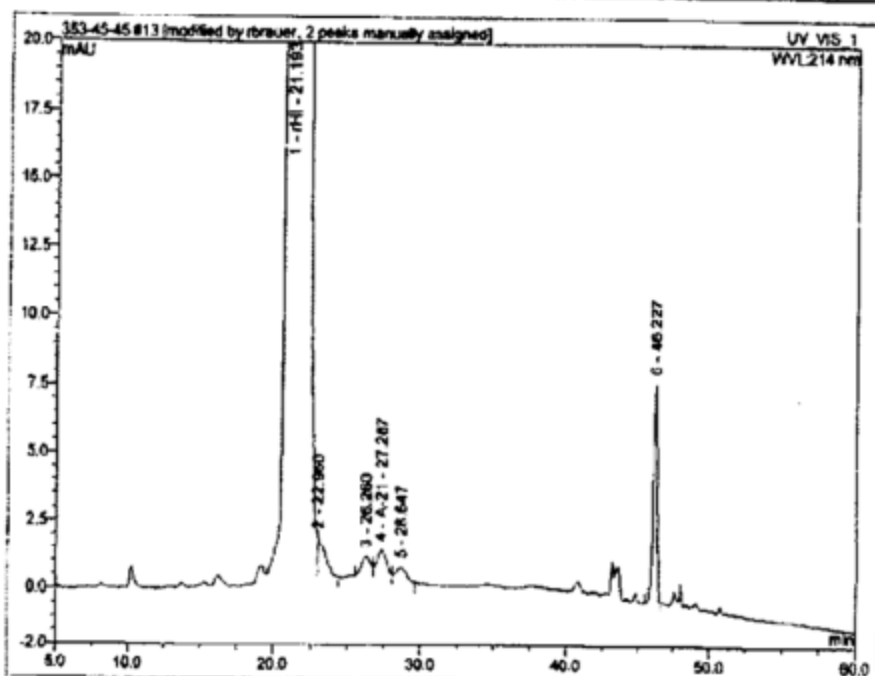
HPLC Results

Technical Data

As the graphs illustrate, our generic is able to produce higher purity insulin with less polymeric forms than USP Grade Insulin

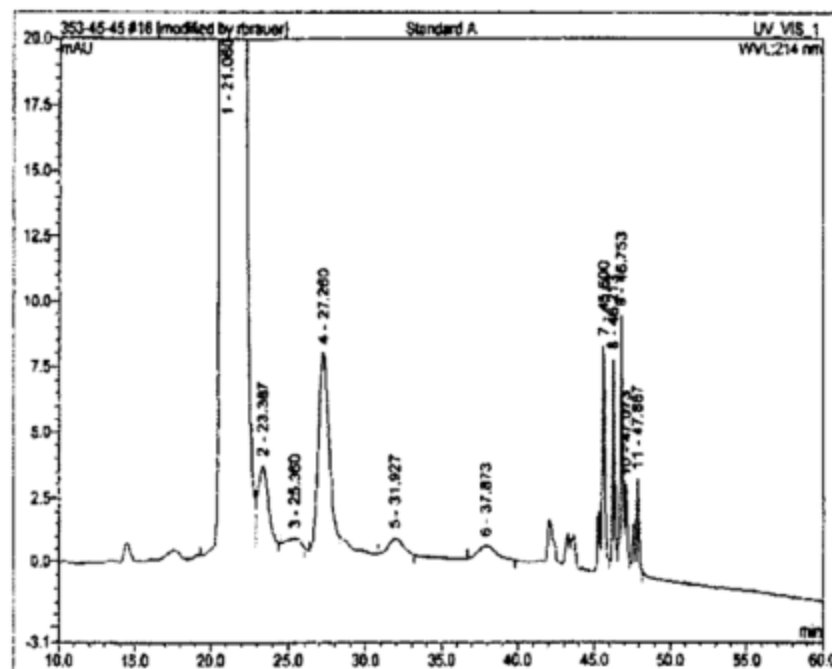
13 QCS-09-155 Filtered – Our Commercial Grade Insulin

Sample Name:	QCS-09-155 Filtered	Injection Volume:	10.0
Vial Number:	RA7	Channel:	UV_VIS_1
Sample Type:	unknown	Wavelength:	214
Control Program:	USP related Sub	Bandwidth:	n.a.
Quantif. Method:	Insulin ACN PO4 SO4	Dilution Factor:	1.0000
Recording Time:	12/2/2009 7:04	Sample Weight:	1.0000
Run Time (min):	60.00	Sample Amount:	1.0000



16 Standard A – USP Grade Insulin

Sample Name:	Standard A	Injection Volume:	20.0
Vial Number:	RA5	Channel:	UV_VIS_1
Sample Type:	unknown	Wavelength:	214
Control Program:	USP related Sub	Bandwidth:	n.a.
Quantif. Method:	Insulin ACN PO4 SO4	Dilution Factor:	1.0000
Recording Time:	12/2/2009 11:05	Sample Weight:	1.0000
Run Time (min):	60.00	Sample Amount:	1.0000



R & D Insulin Drug Substances

Technical Data

As the related substances analysis shows, our generic has the same peaks as USP Insulin, however, it has fewer contaminants

Related Substances			
R & D Insulin Drug Substances			
Identity	Retention Time	Peak Area	Relative Area %
Insulin	♦ 21.19	♦ 884.701	♦ 99.11
A5/B4 Desamido	♦ 22.96	♦ 0.842	♦ 0.11
	♦ 26.3	♦ 0.508	♦ 0.07
A21 Desamido	♦ 27.29	♦ 0.808	♦ 0.10
	♦ 28.65	♦ 0.360	♦ 0.05
Multimer	♦ 46.23	♦ 2.575	♦ 0.29
Insulin Human USP Standard			
Identity	Retention Time	Peak Area	Relative Area %
Insulin	♦ 21.06	♦ 1275.883	♦ 98.35
A5/B4 Desamido	♦ 23.29	♦ 3.084	♦ 0.23
	♦ 25.36	♦ 0.330	♦ 0.05
A21 Desamido	♦ 27.26	♦ 5.746	♦ 0.49
	♦ 31.93	♦ 0.350	♦ 0.05
	♦ 37.87	♦ 0.330	♦ 0.05
Multimer	♦ 45.60	♦ 1.440	♦ 0.14
Multimer	♦ 46.21	♦ 1.086	♦ 0.11
Multimer	♦ 46.75	♦ 1.155	♦ 0.13
Multimer	♦ 47.07	♦ 0.383	♦ 0.06
Multimer	♦ 47.89	♦ 0.360	♦ 0.05

Peptide Mapping

Technical Data

As the data shows, the amino acid bonds in our generic are localized in the identical place as the USP Standard Reference

Non-Reduced Peptide Map Using V8 Protease

Peptide Fragments		
Fragment Number	USP Reference Standard	R&D Insulin
I	Achain gln-cys-cys-thr-ser-ile-cys-ser-leu-tyr-gln-leu-glu Bchain phe-val-asn-gln-his-leu-cys-gly-ser-his-leu-val-glu	Achain gln-cys-cys-thr-ser-ile-cys-ser-leu-tyr-gln-leu-glu Bchain phe-val-asn-gln-his-leu-cys-gly-ser-his-leu-val-glu
II	Achain asn-tyr-cys-asn Bchain ala-leu-tyr-leu-val-cys-gly-glu	Achain asn-tyr-cys-asn Bchain ala-leu-tyr-leu-val-cys-gly-glu
III	Arg-gly-phe-phe-tyr-thr-pro-lys-thr	Arg-gly-phe-phe-tyr-thr-pro-lys-thr
IV	Gly-ile-val-glu	Gly-ile-val-glu

Reduced Peptide Map Using V8 Protease

Peptide Fragments		
Fragment Number	USP Reference Standard	R&D Insulin
I	Gly-ile-val-glu	Gly-ile-val-glu
II	Gln-cys-cys-thr-ser-ile-cys-ser-leu-tyr-gln-leu-glu	Gln-cys-cys-thr-ser-ile-cys-ser-leu-tyr-gln-leu-glu
III	Asn-tyr-cys-asn	Asn-tyr-cys-asn
IV	Phe-val-asn-gln-his-leu-cys-gly-ser-his-leu-val-glu	Phe-val-asn-gln-his-leu-cys-gly-ser-his-leu-val-glu
V	Ala-leu-tyr-leu-val-cys-gly-glu	Ala-leu-tyr-leu-val-cys-gly-glu
VI	Arg-gly-phe-phe-tyr-thr-pro-lys-thr	Arg-gly-phe-phe-tyr-thr-pro-lys-thr

Electrophoretic Patterns

Technical Data

As the graphs illustrate, our generic has the identical electrophoretic patterns as USP grade insulin

Figure 3.2.S.6: Non-Reduced Gel (run on Nupage 4-12% Bis-Tris gel with a MES SDS Running Buffer)

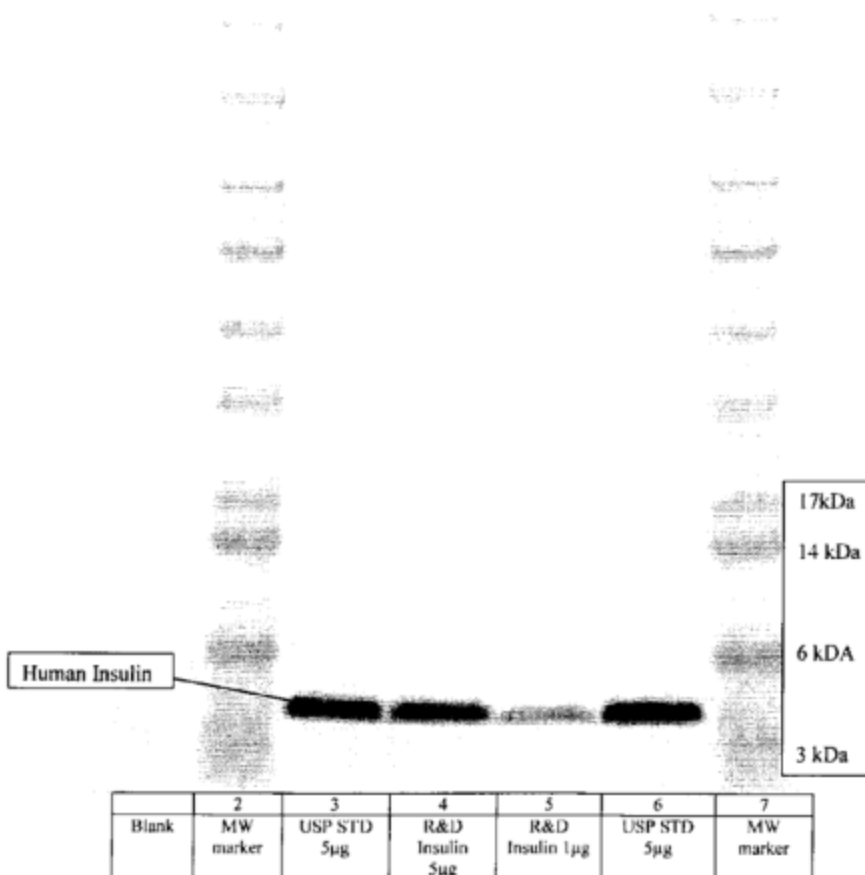


Figure 3.2.S.7: Reduced Gel (run on Nupage 4-12% Bis-Tris gel with a MES SDS Running Buffer)

