Literature review:

01. David Q et al (2008) Identified two novel metabolites of the dipeptidyl peptidase inhibitor sitagliptin (MK-0431, \((2R)-4\text{-oxo-4-[3-(trifluoromethyl)-5,6-dihydro[1,2,4]triazolo[4,3-a]pyrazin-7(8H)-yl]-1-(2,4,5-trifluorophenyl)-butan-2-amine}\), from dog urine after purification and then characterized by hydrogen/deuterium exchange tandem mass spectrometry and NMR spectroscopy nuclear Overhauser effect experiments as the \emph{cis} and \emph{trans} stereoisomers formed by cyclization of the primary amino group with the alpha carbon of the piperazine ring, following oxidative desaturation.

02. Zeng Wei et al (2007) developed method using turbulent flow online extraction and tandem mass spectroscopy for Sitagliptin in human urine and hemodialysate. After the urine assay, the LOQ was 0.1 mg/ml, the linear calibration range was 0.1 to 50 microg/ml, the interday precision (R.S.D.\%, n=5) was 2.3-6.5\%, and the accuracy was 96.9-106\% of the nominal value. From the urine quality control samples (QCs), the intraday precision (R.S.D.\%, n=5) and accuracy were 1.8-2.6\% and 96.2-106\% of the nominal value, respectively. The interday precision (R.S.D.\%) for 56 sets of urine QCs over a 6-month period varied from 3.8\% to 5.5\% and the accuracy from 102\% to 105\% of the nominal value. For the hemodialysate assay, the LLOQ was 0.01 ng/ml, the linear dynamic range was 0.01-5.0 ng/ml, the interday precision was 1.6-4.1\%, and the accuracy was 89.8-104\% of the nominal value. For hemodialysate QCs, the intraday precision and accuracy varied from 2.3\% to 8.9\% and from 99.8\% to 111\% of the nominal value, respectively.

03. PK Sahoo et al (2008) developed a HPTLC method for Simultaneous estimation of metformin hydrochloride and pioglitazone hydrochloride from combined tablet dosage form. The detection of the combined dosage form was carried out at 230 nm and a flow rate employed was 1 ml/min. The mobile phase has a combination of acetonitrile:water:acetic acid \((60:40:0.3)\) and the pH adjusted to 5.5 by adding triethylamine. Linearity is obtained in the concentration range of 0.015 to 0.120 mg/ml of pioglitazone hydrochloride and 0.5 to 4.0 mg/ml of metformin hydrochloride with a correlation coefficient of 0.9992 and 0.9975.

84.9 kg]) were enrolled, providing 10 subjects for each dose group. After administration the mean fraction of unchanged drug excreted in urine ranged from 0.21 to 0.34 and mean renal clearance was 15.5 to 23.6 L/h. The dose-normalized AUC exhibited dose-linearity over the range of 50 to 400 mg. All doses of LC15-0444 =200 mg had been found to inhibit 80% of DPP IV activity for 24 hours. High-fat diet did not significantly influence the AUC of LC15-0444. LC15-0444 has generally well tolerated.

05. Ramakrishna Nirogi et al (2008) developed Sensitive liquid chromatography tandem mass spectrometry method using liquid-liquid extraction for the quantification of sitagliptin, a DPP-4 inhibitor, in human plasma. After liquid-liquid extraction, the analytes were separated using an isocratic mobile phase on a reverse-phase column and analyzed by MS/MS in the multiple reaction monitoring mode using the respective [M + H](+) ions, m/z 408-235 for sitagliptin and m/z 310-148 for the internal standard. The assay exhibited a linear dynamic range of 0.1-250 mg/mL for sitagliptin in human plasma. The lower limit of quantification had been 0.1 ng/mL with a relative standard deviation of less than 6%. Acceptable precision and accuracy had been obtained for concentrations over the standard curve range. A run time of 2.0 min for each sample made it possible to analyze more than 300 human plasma samples per day.

06. Tesfaye Biftu et al (2007) identified orally bioavailable cyclohexylamine DPP-4 inhibitor and designed a novel and potent DPP-4 inhibitor by application of molecular modeling and X-ray crystallography of Sitagliptin. The X-ray crystal structure of sitagliptin bound to DPP-4 suggested that the central beta-amino butyl amide moiety could be replaced with a cyclohexylamine group. This has confirmed by structural analysis and the resulting analog 2a was synthesized and found to be a potent DPP-4 inhibitor (IC(50)=21 nM) with excellent in vivo activity and pharmacokinetic profile.

07. Armagan Anal et al (2009) developed three Spectrophotometric methods and one HPLC method of rosiglitazone maleate and Metformin Hcl both anti-diabetic drugs, in pure form and in pharmaceutical preparations. The two spectrophotometric methods has based on the reaction of rosiglitazone (RSG) with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) and bromocresol green (BCG). Linear relationship between the absorbance at lambda(max) and the drug concentration has found to be in the ranges 6.0-50.0 and 1.5-12 ug/ml for DDQ and BCG methods, respectively. The third spectrophotometric method consists of a zero-crossing
first-derivative spectrophotometric method for simultaneous analysis of RSG and metformin (MTF) in tablets. The calibration curves are linear within the concentration ranges of 5.0-50 ug/ml for RSG and 1.0-10.0 ug/ml for MTF. The fourth method is a rapid stability-indicating HPLC method developed for the determination of RSG. A linear response was observed within the concentration range of 0.25-2.5 ug/ml.

08. Stephen M et al (2003) reviewed a clinical focus on dual therapy of Metformin Hcl in the treatment of type 2 diabetes mellitus. Metformin is the only currently available oral antidiabetic/hypoglycemic agent that acts predominantly by inhibiting hepatic glucose release. As patients with type 2 diabetes often have excess hepatic glucose output, use of metformin is effective in lowering glycosylated hemoglobin (HbA1c) by 1 to 2 percentage points when used as monotherapy or in combination with other blood glucose-lowering agents or insulin. Also other metabolic variables (eg, dyslipidemia, fibrinolysis) may be improved with the use of metformin. Body weight is often maintained or slightly reduced from baseline. Metformin is well tolerated and is associated with few clinically deleterious adverse events.

09. Dinesh K. et al (2008) reviewed Sitagliptin a New Class of Oral Drug for Type 2 Diabetes. The conclusion is Sitagliptin, an oral dipeptidyl peptidase-4 (DPP-4) reversible inhibitor, improves glycaemic control by inhibiting DPP-4 inactivation of the incretin hormones glucagon-like peptide-1 and glucose-dependent insulinotropic polypeptide. It increases active incretin and insulin levels, and decreases glucagon levels and postglucose-load glucose excursion. Sitagliptin, which can be used as monotherapy or in combination with other antidiabetic drugs, is a promising new treatment option, especially for patients with early-stage type 2 diabetes and more severe hyperglycemia, although experience with this noble drug will further help it to establish its supremacy as oral drug for Type -2 DM.

10. Vishvas G et al (2010) Identified risks and benefits of sitagliptin and saxagliptin monotherapies and metformin combination therapies. It demonstrates that the new DPP-4 inhibitors, sitagliptin and saxagliptin, have a good general safety and efficacy profile. These drugs have been approved worldwide including in places such as India, USA, and Europe. However it was found that no formal economic evaluation of sitagliptin and saxagliptin has been conducted till date in India. And, for saxagliptin, it was found that no economic evaluation has been conducted anywhere in the world, till date.
11. K.S. Lakshmi et al (2009) developed reversed phase HPLC method for Simultaneous determination of metformin and pioglitazone in bulk and pharmaceutical dosage forms. A Gemini C18 column (150x4.6mm, 5μ) had been used with a mobile phase containing a mixture of Acetonitrile and Ammonium Acetate buffer (pH-3) in the ratio of 42: 58. The flow rate was kept 0.3ml/min and effluents were monitored at 255nm and eluted at 5.17min (MET) and 8.1min (PIO). Calibration curve is plotted with a range from 0.5-50 μg/ml for MET and 0.3-30 μg/ml for PIO.

12. M. B. Shankar et al (2005) developed Derivative Spectrophotometry and Liquid Chromatographic Methods for Estimation of Pioglitazone Hydrochloride and Metformin Hydrochloride in Tablets. PIO and MET in combined preparations (tablets) were quantified using the second-derivative responses at 227.55 nm for PIO and 257.25 nm for MET in spectra of their solutions in a mixture of methanol and acetonitrile (30 + 70). The calibration curves were linear [correlation coefficient (r) = 0.9984 for PIO and 0.9986 for MET] in the concentration range of 8-40 microg/mL for PIO and 4-12 microg/mL for MET. In the LC method, analysis is performed on a Hypersil ODS-C18 column with 5 microm particle size using the mobile phase acetonitrile-water-acetic acid (75 + 25 + 0.3), adjusted to pH 5.5 with liquor ammonia, at a flow rate of 0.5 mL/min. Measurement is made at a wavelength of 230 nm. Both the drugs are well resolved on the stationary phase, and the retention times were 8.5 min for PIO and 16.0 min for MET. The calibration curves is linear (r = 0.9933 for PIO and 0.9958 for MET) in the concentration range of 4-20 microg/mL for PIO and MET.

13. N.R Lad et al (2003) developed Concurrent assay by RP-HPLC of metformin and glimepiride in tablets with wavelength programming. The HPLC determination is carried out on a μBondapak C18 (300x3.9m m) 10μm with use of a flow rate of 1.0 ml/min. The programming regime is, 0-5.8 min at 265 nm, 5.8-9.0 min at 230 nm and 9.0-11 min again at 265 nm. The calibration graphs are linear in the range of 400-600 and 1.6-2.4 μg/ml for metformin and glimepiride respectively with correlation coefficient of 0.9999 for both.

14. Setter SM et al (2003) focused on Metformin HCl in the treatment of type 2 diabetes mellitus. Metformin is the only currently available oral antidiabetic/hypoglycemic agent that acts predominantly by inhibiting hepatic glucose release. As patients with type 2 diabetes often have excess hepatic glucose output, use of metformin is effective in lowering
glycosylated hemoglobin (HbA1c) by 1 to 2 percentage points when used as monotherapy or in combination with other blood glucose-lowering agents or insulin. Other metabolic variables (e.g., dyslipidemia, fibrinolysis) may be improved with the use of metformin. Body weight is often maintained or slightly reduced from baseline. Metformin is well tolerated and is associated with few clinically deleterious adverse events.

15. Gallwitz B et al (2007) received Sitagliptin a novel DPP-4 inhibitor for the treatment of type 2 diabetes. A general islet-cell dysfunction including insulin- and glucagon-secretion defects contributes to the pathophysiology of type 2 diabetes. Improving islet function by incretin hormone action is a novel therapeutic approach. Glucagon-like peptide-1 (GLP-1) and glucose-dependent insulino tropic peptide (GIP) are important incretin hormones contributing to 50-70% of the stimulation of insulin secretion after a meal. Dipeptidyl-peptidase IV (DPP-4) inhibitors inhibit the degradation of GLP-1 and GIP as well as that of other regulatory peptides. Sitagliptin, a DPP-4 inhibi tor, is orally active and has been shown to be efficacious and safe in clinical studies. Sitagliptin has received approval in Mexico, the United States and other countries. Like other DPP-4 inhibitors, sitagliptin reduces hemoglobin A1c (HbA1c), fasting and postprandial glucose by glucose-dependent stimulation of insulin secretion and inhibition of glucagon secretion.

16. Patel Kishan D et al (2010) reviewed the Role of DPP-4 inhibitor in treatment of type 2 diabetes. Emerging as an epidemic of the 21st century type II diabetes has become a major health problem throughout the globe. Known treatments of type II diabetes mellitus have limitations such as weight gain and hypoglycaemias. A new perspective is the use of incretin hormones and incretin enhancers. Incretin mimetics are a new class of pharmacological agents with multiple antihyperglycemic actions that mimic the actions of incretin hormones such as glucagon-like peptide (GLP)-1. DPP-4, a protease that specifically cleaves dipeptides from proteins and oligopeptides after a penultimate N-terminal proline or alanine, is involved in the degradation of a number of neuropeptides, peptide hormones and cytokines, including the incretins GLP-1 and GIP.

17. Hess et al (2010) developed electrospray ionisation liquid chromatography-mass spectrometry method for Simultaneous identification and validated quantification of 11 oral hypoglycaemic drugs in plasma. The LC-MS/MS assay had allowed the simultaneous identification of 14 oral antidiabetics and quantification of 11 oral antidiabetics in plasma in
the ESI mode in a single run. Linearity is shown up to overdose concentrations. The limits of detection with a signal-noise-ratio is greater than 3 were below 1 ng/ml for all analytes. Recoveries ranged from 78 to 105%; for vildagliptin and saxagliptin recoveries were worse (45%) owing to their hydrophilic character. Intraday and interday precision and accuracy were below 20% for 11 drugs at three concentrations. For the gliptins, several validation parameters are out of range and, therefore, quantitatively this method is inappropriate.

18. G. Hendriks (2008) identified theoretical models in LC based bioanalytical method development. The Bioanalytical method development largely depends on the experience and the preference of the developer. Mathematical models helped in selecting the proper conditions to develop a selective and robust method, using liquid chromatography, liquid–liquid extraction, solid phase extraction and protein precipitation. It reviewed the literature providing relevant equations and algorithms to model LC based bioanalytical methods for the quantification of small molecules. By using the cited references, it has been possible to build models to describe the analytical methods either as an approximate impression or in a detailed way, incorporating many experimental variables.

19. Stella et al (2007) identified metabolism and excretion of the DPP 4 inhibitor sitagliptin in humans. The metabolism and excretion of [14C]sitagliptin, an orally active, potent and selective dipeptidyl peptidase 4 inhibitor is investigated in humans after a single oral dose of 83 mg/193 μCi. Six metabolites are detected at trace levels, each representing <1 to 7% of the radioactivity in plasma. These metabolites are the N-sulfate and N-carbamoyl glucuronic acid conjugates of parent drug, a mixture of hydroxylated derivatives, an ether glucuronide of a hydroxylated metabolite, and two metabolites formed by oxidative desaturation of the piperazine ring followed by cyclization.

20. M. Jadzinsky et al (2009) identified Saxagliptin given in combination with metformin improves glycaemic control in patients with type 2 diabetes in initial therapy compared with either monotherapy. A randomized controlled trial in multicentre is been carried out. At 24 weeks, saxagliptin 5 mg þ metformin and saxagliptin 10 mg þ metformin demonstrated statistically significant adjusted mean decreases vs. saxagliptin 10 mg and metformin monotherapies in HbA1c (_2.5 and _2.5% vs. _1.7 and _2.0%, all p < 0.0001 vs. monotherapy) and FPG (_60 and _62 mg/dl vs. _31 and _47 mg/dl, both p < 0.0001 vs. saxagliptin 10 mg; p ¼ 0.0002 saxagliptin 5 mg þ metformin vs. metformin; p < 0.0001
saxagliptin 10 mg þ metformin vs. metformin). Saxagliptin þ metformin in initial therapy led to statistically significant improvements compared with either treatment alone across key glycaemic parameters with a tolerability profile similar to the monotherapy components.

21. Tina vilsboll et al (2007) reviewed DPP 4 inhibitors for current evidence and future directions. Glucagon-like peptide-1 (GLP-1) and glucose dependent insulinotropic polypeptide (GIP) are responsible for the higher insulin response after oral versus intravenous glucose administration. This effect is called the incretin effect. An impaired incretin effect in patients with type 2 diabetes has focused attention on the possible importance of GIP and GLP-1 in diabetes mellitus. Metabolic control is to be markedly improved by administration of exogenous GLP-1, but the native peptide is almost immediately degraded by the enzyme dipeptidyl peptidase IV (DPP IV) and, therefore, has little clinical value. Orally active inhibitors of DPP IV have now been developed and have been shown to enhance endogenous levels of GLP-1, resulting in improved glucose tolerance, lasting improvement of HbA1C and improved beta-cell function. In general the DPP IV inhibitors are weight neutral, and well tolerated.

22. Zander m et al (2002) studied type 2 diabetes with glucagon-like peptide 1 on glycaemic control, insulin sensitivity, and beta-cell function. Glucagon-like peptide 1 (GLP-1) had been proposed as a treatment for type 2 diabetes. It has investigated the long-term effects of continuous administration of this peptide hormone in a 6-week pilot study. One patient assigned saline was excluded because no veins were accessible. In the remaining nine patients in that group, no significant changes were observed except an increase in fructosamine concentration (p=0.0004). In the GLP-1 group, fasting and 8 h mean plasma glucose decreased by 4.3 mmol/L and 5.5 mmol/L (p<0.0001). Haemoglobin A(1c) decreased by 1.3% (p=0.003) and fructosamine fell to normal values (p=0.0002). Fasting and 8 h mean concentrations of free fatty acids decreased by 30% and 23% (p=0.0005 and 0.01, respectively). Gastric emptying is inhibited, bodyweight decreased by 1.9 kg, and appetite was reduced.

23. M. Shawn Mcfarland et al (2009) determined the prevalence of the potentially inappropriate initial dosing of sitagliptin based on estimated glomerular filtration rate (GFR) at baseline for pharmacist versus nonpharmacist prescribers in an internal medicine department of a private physician-owned multispecialty clinic that included a pharmacist-
managed diabetes program. Of the 290 patients prescribed sitagliptin for the first time between October 17, 2006, and June 5, 2008, 35 (12.1%) received a potentially inappropriate initial dose according to product labeling regarding renal function; 21 were over-dosed and 14 were under-dosed. Potentially inappropriate initial dosing of sitagliptin based on assessment of renal function was more likely to occur with nonpharmacist prescribers than with a pharmacist prescriber.

24. Girishma M. et al (2010) reviewed the Role of sitagliptin in treatment of type 2 diabetes. Emerging as an epidemic of the 21st century type II diabetes has become a major health problem throughout the globe. Known treatments of type II diabetes mellitus have limitations such as weight gain and hypoglycaemias. A new perspective is to use of incretin hormones and incretin enhancers. Incretin mimetics are a new class of pharmacological agents with multiple antihyperglycemic actions that mimic the actions of incretin hormones such as glucagon-like peptide (GLP)-1. DPP-4, a protease that specifically cleaves dipeptides from proteins and oligopeptides after a penultimate N-terminal proline or alanine, is involved in the degradation of a number of neuropeptides, peptide hormones and cytokines, including the incretins GLP-1 and GIP.

25. G. Bolli et al (2007) compared the efficacy and tolerability of vildagliptin vs. pioglitazone as add-on therapy in patients with type 2 diabetes inadequately controlled with metformin monotherapy. They added to a stable dose of metformin (mean dose at baseline >2000 mg/day), both vildagliptin and pioglitazone decreased A1C (AMD ¼ _0.9 _ 0.1% and _1.0 _ 0.1%, respectively) from identical baseline values (8.4 _ 0.1%). The between-group difference in AMD A1C was 0.1 _ 0.1%, and non-inferiority of vildagliptin to pioglitazone was established at both 0.4 and 0.3% margins for upper limit of the 95% confidence intervals. Adverse events (AEs) were reported by 60% of vildagliptin-treated patients and by 56.4% of pioglitazone-treated patients; serious AEs were reported by 2.0 and 4.6% of patients receiving vildagliptin and pioglitazone respectively.

26. Janaki pathi P et al (2011) developed two simple accurate rapid and sensitive methods have been developed for the estimation of Atazanavir in the pharmaceutical dosage forms. The method A based on reaction of Atazanavir with moderant black III to form an ion association colored complex at pH 2.4.