“New improved chemical entities” (NICE) were developed by improving either the quality or scalability or physicochemical properties, particularly solubility of the existing drug candidates (Innovator APIs). HPLC methods were developed for separation of racemic APIs and purification of chiral isomers in order to scale up these processes using Varicol technology (a variant of simulated moving bed [SMB] technology). Six impurities – which were found to be in range of 1-2% in the lab batches of the benzimidazole intermediate synthesis – were synthesized and characterized to control them in the final API of candesartan and azilsartan syntheses. Thermal and photosensitive Z-E isomerization in sunitinib was investigated to address inconsistency in chromatographic analysis. In addition, five novel sunitinib salts were identified, which exhibited variable water solubility.

HPLC methods were developed for separation of enantiomers of racemic clopidogrel, lansoprazole, omeprazole, EPB-1 and voriconazole using chiral stationary phases (CSPs). The effect of column loadings and flow rates on the separation profiles in terms of resolution and selectivity were investigated for developing scalable separation processes. A few of these separations were also scaled up using Varicol technology. In addition, HPLC method was developed for separation of pneumocandin isomers using silica gel. The effect of column loadings and flow rates on the separation profiles in terms of resolution and selectivity were investigated for development of scalable continuous separation in Varicol process.

Six impurities were identified in the lab development batches of benzimidazole intermediate (1) synthesis by reverse phase HPLC methods. Intermediate 1 is used as a common advanced intermediate in the synthesis of candesartan and azilsartan. All the impurities were characterized by IR, NMR, LC/MS and CHN analyses, which include an isomer of intermediate 11 (impurity 19), desethyl analogue of 1 (impurity 20), desethoxy analogue of 1 (impurity 21), methyl analogue of 1 (impurity 22),
cyanobiphenyl benzimidazole (impurity 25) and cyanobiphenyl derivative of 1 (impurity 26). The synthesis and characterization of these impurities are presented.

Z-E isomerization in sunitinib, an anticancer drug, is investigated, which is synthesized in two steps. The influence of light, heat and solvent is studied and the isomerizations were monitored by HPLC. As expected, the extent of Z-E isomerization (conversion into the undesired E-isomer) is found to depend on these parameters. Both reversible and irreversible isomerizations were observed when the solutions were kept in dark after subjecting them to light exposures. These observations have implications in the analysis of sunitinib samples using HPLC methods. In addition, polymorph, co-crystal and salt screening experiments were carried out to identify novel solid forms with the improved physicochemical properties, particularly, water solubility in the present case. Co-crystal formation was evaluated with urea and nicotinamide. These coformers do not have any ionic groups that favor formation of salts. Sunitinib malate salt is being currently sold in the market. It is poorly soluble in water. Salt screening experiments were conducted with adipic acid, glutaric acid, nicotinic acid, 4-hydroxy benzoic acid and saccharin. The salts with 1:1 ratios were obtained with these acids, except for adipic acid, which yielded a 2:1 solid form. The solubility of these salts in DI water was found to be 6 to 10 times greater than that of the marketed salt (sunitinib malate).