The separation of biomolecules from aqueous solutions has been a major area of emphasis in the production of biopharmaceuticals and other high value products. Numerous creative and cost-effective solutions have been developed and integrated into biopharmaceutical manufacturing facilities over the last 20 years. A new set of challenges is now emerging as technologies for cost-effectively producing small molecules from cellulosic materials are being developed. These small molecules range from ethanol and related alcohols that could be used as biofuels, to fermentation products that may also be useful as precursors for the chemical industry. All have a common denominator in that they are produced in aqueous environments, and require cost-effective methods for their recovery and purification at relatively dilute concentrations. This paper addresses some of the challenges in processing fermentation-derived products from aqueous fermentation broths, as well as the role of separations in achieving cost-effective, aqueous-based manufacture of small molecules. Examples will include recovery of ethanol from fermentation broth, biobutanol, and monosaccharides that may be derived from non-food, renewable resources that have a low carbon footprint, and would develop from platforms that provide inexpensive, fermentation derived, precursor molecules. These renewable resources include cellulosics such as wood, corn stover, and residue obtained from the processing of corn grain to ethanol. The impact of liquid/solid separations, novel adsorption methods, and chromatographic separations will be discussed.