originally approved for the treatment of HIV infection in 1996. By 1998, however, it became clear that manufacturing processes were producing a previously unknown polymorph that did not meet the solubility specification approved for clinical application. The decreased solubility led to a substantial decrease in oral bioavailability and eventually forced the manufacturer (Abbott Labs, now Abbvie) to temporarily withdraw the Norvir® (Ritonavir) from the market while a new formulation was developed and tested.[15] As this example clearly demonstrates, it is important to ensure that manufacturing processes lead to not only the desired compound, but also that they reliably produce the same crystal form every time and that the crystal form is stable under the proposed storage conditions.

Environmental and waste disposal issues also become a major concern. Laboratory-scale reaction can employ solvents that have known safety and waste disposal issues such as methylene chloride (carcinogen, highly volatile), ethyl ether (highly volatile, highly flammable, peroxide former), and benzene (carcinogen, toxic, highly volatile, highly flammable). Industrial-scale procedures designed to prepare material for human consumption (i.e., medication), however, are often limited to more benign solvents (e.g., ethanol, 1,4-dioxane, toluene, ethyl acetate). The sheer volume of waste produced is also significantly higher and must be considered as a process is moved to an industrial scale. A 10,000-fold increase in production scale would lead to a 10,000-fold increase in waste generation if no changes were made on moving from the lab scale to manufacturing. If a lab-scale procedure requires 5 L of solvent to produce 20 g of material, a 10,000-fold increase to produce 200 kg would require 50,000 L of solvent in the absence of procedural changes. All of this solvent would be considered hazardous waste and would require proper disposal. Modifications to minimize solvent utilization can significantly reduce the environmental impact. These factors will also reduce production costs, which will, in turn, lower the cost of the product once it reaches the market. Minimizing solvent use is environmentally important and can help contain the cost of new medicines as they approach the market.

There are additional factors beyond scalability of the chemistry that must also be considered. Changes in synthetic pathways often result in the formation of different impurities or side products with unknown properties, even if the change is as simple as producing a new salt form of the parent compound. Consider, for example, a new synthetic method for the production of a candidate compound that also generates a small but quantifiable amount of an Ames positive impurity. The presence of this new impurity would represent a major issue for the new route. Identification, characterization, and monitoring methods to detect impurities in the final products must be established in order to ensure that the clinical material is truly suitable for human study.