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Editorial

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Innovation in Generic API Synthesis and Manufacture

My colleagues and I do a lot of consulting, and surprisingly, some of the most interesting discussions happen when working with generic pharmaceutical companies. Generic companies often get bad press in newspapers and even in the chemical/pharmaceutical trade press, with the words "copycat drugs" being bandied about, the implication being that there is no innovation in the generic world; this is a long way from the truth. Of course, the reality is that the drug substance, i.e. the active pharmaceutical ingredient (API) in a generic product is not new, but the chemical process to make the API may be extremely innovative. Thus, we see many process patents for generic drugs (often highlighted in this journal's patent highlights).

There are different types of generic companies; first those that buy in the API from elsewhere and formulate. Other than offering an assurance that the formulation does not infringe on anyone else's patent and that the API is made at low cost (and within specification, of course), these companies have no interest in the synthetic route or process to make the API. As a chemist, I have little interest in this type of company. The second type is one that invests time and money looking for an innovative synthesis and low-cost process to manufacture the API, and either sells the API or formulates the drug product itself and sells that. There are other types of generic companies more focussed on innovative formulations or combination drugs, but it is not my purpose to discuss these here. Of course, there are also fine-chemical companies who make and sell generic APIs as well as do contract work for large pharma, managing to keep a foot in both camps (as pharmaceutical companies such as Novartis/Sandoz and Sanofi have done in recent years). Many of these companies are European and rely on innovation to generate profits from generic API sales.

These days many generic APIs are made in India and China, where the labour and overhead costs are low. What may be surprising to some readers, however, is that a considerable proportion of APIs for generic drugs are still made in UK, Germany, Switzerland, Italy, Israel, Canada, etc., where labour and overhead are high, and that companies in Europe can still compete on cost of goods as well as security of supply. This can only be the case if the synthetic route to the API uses low-cost raw materials and an innovative synthesis, where rigorous process development has produced an efficient manufacturing process with good space-time-yield and few isolated intermediates. In many ways the process R&D for generic APIs is similar to that in fine chemicals, agrochemicals, and colour chemicals, where a high-specification product has to be made at low cost but with high quality. It is also similar to the second-generation process R&D that many large pharmaceutical companies are currently doing on their blockbuster drugs, aiming to maintain some profits in the wake of patent expiry and generic competition.

Every synthetic route has a cost-of-goods minimum below which one can never go, namely the cost when all yields in the synthesis are 100% and there are no labour and overhead costs included. So when beginning research into routes to make generic drugs, a quick option to help prioritise R&D effort is to cost out "paper" routes based on 100% yield in each step, making assumptions about the key reagents and solvents. Process R&D can then begin to evaluate the routes in priority order.

There is no doubt that the choice of starting materials and the design of the synthetic route are critical, particularly the number of synthetic steps and the amount of convergence in the synthesis. The most successful companies start with the ideal starting material (the maximum amount of functionality present in the API that you can buy for the lowest cost) and try to relate this to the final product in the minimum number of steps, even if they have to invent new chemistry to carry out a particular transformation. Only after the best synthetic route has been decided upon can the task of yield and process optimisation begin, preferably using statistical methods to examine the progress of the development towards cost, yield, and quality targets.

However, in many of the processes for generic APIs (even some of those published in U.S. patents!) I can see that there is minimal innovation, particularly where the generic company has changed certain parts of the innovator's process (functional or protecting group, intermediate, reagent, solvent, etc.) but essentially keeps the synthesis and number of steps the same, with the sole aim of "patent busting". (Of course, one reason for this approach is the importance of the 6-month exclusivity in being first-to-file a generic drug with the U.S. Food and Drug Administration [FDA].) Since the innovator's process is rarely the optimal one in terms of cost, it usually follows that the generic "me too" process will also not be optimal. Nevertheless, in many countries the low labour and overhead costs can mean that this "me too" process can be profitable, especially if it enables the generic company to be first on the market after a blockbuster reaches patent expiry.

However, what happens when labour and overhead costs start to rise, as they are doing now in India and China? Asian and other companies will have to focus much more on innovation in synthesis, possibly doing second-generation process development themselves to produce low-cost APIs. Only those who are the most innovative and have the most highly qualified and well-trained chemists and engineers will be able to survive as the market demands lower and lower prices for generic drugs. Innovative, low-volume continuous processes (see a future issue of *Organic Process Research & Development* for a special feature section on this subject) might also be applicable in the generics field.

Hence, my message to generic API manufacturers is "innovation is the way to future profits".

Trevor Laird, Editor

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