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Editorial

Some Thoughts on Generic API Manufacture

I recently gave a workshop at the International Generic Drug Association annual conference in Montreal, where I had the opportunity to meet many friends in that sector of the pharma industry. Since I have consulted for many generic companies on various issues, such as troubleshooting in manufacture, cost reduction of APIs (my experience in working in manufacture of agrochemicals is useful here), designing novel synthetic routes, and auditing API producers, and have given many training courses to generic companies all over the world, I think I know the sector reasonably well. There are some excellent manufacturers of high-quality APIs in this sector, but occasionally I see one or two who are not up to standard.

In the UK, and many other countries, once a drug is off patent, medical practitioners are allowed to prescribe the generic version of the drug instead of the branded version to reduce drug costs, and most times this is not noticed by the patient. Occasionally, however, patients observe side effects. A friend of mine who suffers from rheumatoid arthritis (RA) takes Voltarol (diclofenac sodium), but when the doctor prescribes a generic version she gets severe side effects, so she has to insist on the branded version; similarly, a correspondent from Denmark reported to me that a relative of his had severe side effects after a generic substitution.

I have recently had a similar problem when one generic version of a medicine I take, tamsulosin hydrochloride, was substituted by another generic brand; the second one did not work for me at all, but on reversion to the original brand after a few days, the medicine soon began to take effect (since the medicine is for prostate problems, it is easy to monitor the effect!!). When I mentioned this to the doctor, she said that many patients report problems either with generic substitution or when changing from one version of a generic medicine to another. In the UK the doctor prescribes the generic drug but cannot control which generic manufacturer; the pharmacist uses the version (manufacturer) that they stock, and this can vary from month to month, the assumption being that they are equivalent, which they clearly are not.

So why should the medicines be different? Is it in the API? Does the API contain new impurities at low levels (below 0.1%)? Since each generic manufacturer uses its own synthetic route (often a much more cost-effective route than the originator), the chances of low-level impurities at below 0.1% are quite high, but it is debatable whether such low levels of impurities could cause severe side effects (although I know that RA sufferers can be affected by trace levels of substances in foods as well as drugs). In the Danish example cited above, it was impurities which were shown to be the problem.

On the one hand, are new impurities not being detected by the analytical procedures? On one audit I noticed a small broad peak amongst sharp peaks in the HPLC of an API, which was at variable retention time and was being ignored; it actually came from the previous injection. When the retention time was worked out, it was at over 70 min; the run time being 40 min. The level of the impurity, which had a surprising structure, turned out to be over 1%!

On the other hand, is it the formulator that is the problem? In my case of an inactive material/formulation, this was probably the case, but it is hard to see how a slight difference in formulation should cause side effects. Nevertheless, formulators often change the source of API to lower costs (in my experience, some formulator audits of the API manufacturers are not rigorous enough, or at least, not as rigorous as mine!), and it seems more likely to be an API issue when side effects are involved.

My guess would be that it is trace amounts of very active impurities which are the problem. I well remember a manufacturing issue from my SmithKline days when the synthetic route to cimetidine was changed slightly by using a modified, but cheaper, reagent three steps from the end of the synthesis. Initial manufacturing batches produced a new impurity at about 0.03% that had not been seen in laboratory or pilot-plant use tests and was shown to have possible toxicity issues necessitating a modification to the process to ensure that it was kept at below 0.01%. Interestingly, the impurity had only been seen in one of two plants using the new process, though nominally they were the same process, but at different batch sizes.

I would be interested to hear of any readers who have experienced similar problems, either side effects or lack of efficacy, when their medicine has been changed from one generic drug to another, or from a branded drug to a generic drug. It seems to be a more widespread problem than I had first imagined. I would also be interested to hear from readers who have had low-level toxic impurity issues when introducing process changes. I anticipate some lively discussion.

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Editor

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