Vitamin D prescribing: the issues with unlicensed products

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Vitamin D is an important regulatory hormone and evidence is emerging of its beneficial role beyond bone health. With the industrialisation of the modern world, studies reveal an increasing incidence of vitamin D deficiency that in turn has been associated with co-morbidities besides fractures and falls. In consequence, there has been an exponential rise in the prescription of vitamin D$_3$ products in the UK, yet many of these prescriptions are being met by unlicensed products. This may, in part, be related to the previous lack of licensed vitamin D$_3$ products, yet with the emergence of licensed formulations, there should no longer be the need to issue unlicensed products against a prescription. Similarly, there are reasons as to why only licensed preparations should be dispensed against prescriptions for vitamin D.

In the UK, the licensing of pharmaceutical products is undertaken by the Medicines Healthcare Products Regulatory Authority (MHRA). Marketing authorisation is based upon stringent review with a focus on quality, efficacy and safety, in order that the public is protected. Thus, MHRA market authorisation provides a ‘kite mark’ to reassure both public and prescriber that a medicine achieves these standards. In the case of vitamin D this may seem rather trite as the product is often available on the shelf of a local supermarket, so why worry with regard to which product is dispensed?

The answer may be found when in the MHRA remit of quality, safety and efficacy together with pricing in relation to unlicensed vitamin D products.

Quality and efficacy
The manufacture of vitamin D is not a straightforward process. Recent studies reveal a wide variation in the actual vitamin D content of products, particularly unlicensed formulations versus the stated dose. Garg et al analysed 14 formulations of vitamin D$_3$; only eight were within 10 per cent of the stated dose. The actual dose in the formulations ranged from 8 per cent to 201 per cent of the claimed dose. The two licensed formulations had vitamin D concentrations of 90±4 per cent and 97±2 per cent of stated dose.

Similarly, Leblanc showed that of 15 vitamin D$_3$ preparations analysed, there was discrepancy between the stated dose and measured dose in pills from the same bottle (52–136 per cent of expected dose) and between separate preparations (9–140 per cent of stated dose). Only five preparations were within 10 per cent of the stated dose. Of these, the licensed products revealed the greatest accuracy with least variation compared with the stated dose.

A recent study from India revealed similar analytical results of 14 commercially available vitamin D$_3$ preparations with only four preparations having actual doses within the accepted range of the stated dose. The majority of prescribers would feel that when they prescribe a product that the stated dose is the actual dose. However, if patients are being treated for vitamin D deficiency, the failure of symptoms to resolve due to inadequate dosing from manufacturing error may prompt the clinician to consider further investigation for potential malabsorption.

Safety
It is not just inadequate dosing that is a problem. There are increasing reports of vitamin D intoxication due to manufacturing error of unlicensed products. These patients presented with life threatening hypercalcaemia requiring hospitalisation and the reports revealed that the actual dose exceeded stated dose by a factor of hundreds or thousands. However, to the authors’ knowledge, no such reports of vitamin D intoxication due to errantly manufactured vitamin D have emerged in the UK but could in the future.

A recent UK report of direct blood spot analysis of 25-hydroxy vitamin D concentrations (25(OH)D), revealed that of 4480 samples analysed, 69 users (1.5 per cent) had 25(OH)D concentrations in the toxic range (>220nmol/litre). On further analysis, only two of these were under medical supervision and the one had been taking 10 000IU daily, against the advice of the consultant. However, 55 per cent of the correspondents reported that they had been taking 10 000IU daily or less of vitamin D. Clearly, this points to errant manufacturing of the vitamin D consumed, as it has been demonstrated that toxicity did not occur in doses of 10 000IU daily or less.

Cost
One would assume that unlicensed products should be cheaper than their licensed alternatives and hence in the current climate of austerity, arguably these unlicensed preparations may offer better value to the NHS. However, prescription cost analysis data of all prescribed vitamin D products reveals that the licensed formulations are multiples cheaper in the low dose range as well as in the higher treatment dose range than their unlicensed counterparts. While it may appear counter-intuitive, the high costs associated with the use of unlicensed ‘specials’ may contribute to the higher pricing.

Conclusion
Vitamin D deficiency is a common problem in the UK and there is increasing prescription of vitamin D supplements. In the
main, this has been fulfilled by unlicensed preparations, yet unlicensed preparations are, by their very nature, uncontrolled and may expose the patient to clinical risk. Based on the MHRA standards of quality, efficacy and safety, together with possible favourable pricing, the data support the use of licensed vitamin D₃ preparations against a prescription.

References
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Declaration of interest
Dr Davies is a medical adviser for Internis Pharmaceuticals and also provides consultancy work for Menarini, Meda, Prostrakan and Sandoz. Dr Eligar has nothing to declare.

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