The 99% guggulsterones tragedy

Its similarity to the ephedra (Ma Huang) disaster in the dietary supplement industry

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THE "SYNTHETIC HIGH" SYNDROME

There was a time in the not too distant past, when the ephedra plant was used widely and successfully in numerous dietary supplement preparations in the US for weight loss and body weight management. The application of this botanical, known and practiced by humans for approximately 5,000 years, has also been supported by science. However, the clinical studies also indicated that use of this herb was not free of side effects; and added to this, the use of synthetic material by some suppliers and manufacturers will lead to the demise and ultimate removal of ephedra from the supplement industry.

The question now before the industry is this – are the painful outcomes learned from the ephedra experience, which reduced several prominent dietary supplement companies to become bystander victims of bankruptcy, about to be repeated again? Or, can the "synthetic high" syndrome be prevented in the case of another millennia old natural product?

Gugulipid® is an extract from the sap of the *Commiphora mukul* tree and is fast becoming a promising hypolipidemic (cardiovascular health) dietary supplement in this country. This ancient product has a 15 year long history of successful dietary supplement use in the US and is the subject of two IND (Investigational New Drug – FDA) approved US clinical studies. Besides the investigated clinical effects on dyslipidemia, Gugulipid® appears to have other potentially important systemic effects in prevention of cardiovascular disease in reducing fasting glucose and insulin with an increase in sensitivity to insulin. Gugulipid® may also decrease C-reactive protein and oxidized low density lipoprotein. An additional positive finding from the studies indicates that this compound may reduce serum uric acid, a recently recognized risk factor in cardiovascular disease.

This evolving success story of Gugulipid® should, however, be safeguarded in view of the controversy that purged ephedra from many dietary supplements. The above described "synthetic high" syndrome is at work again in the dietary supplement industry. Recently, due to the growing popularity of natural Gugulipid®, this product is now replaced in several product applications by a cheaper, synthetic product standardized for up to 99% guggulsterones with the claim that it is similar to the 2.5-7% guggulsterones E and Z present in the clinically tested natural extract from tree sap. Despite the self-styled advantage on paper of synthetic over natural, the facts on the synthetic version are discouraging, if not precluding, to its use as a safe dietary supplement.

The synthetic product:

1. Has no clinical or safety studies available;
2. Is not included in the Indian Pharmacopoeia (IP), unlike the natural Gugulipid®, which is listed in the IP;
3. Does not provide other components from the tree sap, several of which may be pharmacologically active and beneficial;
4. Was developed by a major Indian pharmaceutical company several years ago, but was eventually

Gugulipid® is a registered trademark of Sabinsa Corporation; US Patent #6,436,991

published by B5 srl
Via Cesare da Sesto, 10
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declined registration by the Indian health authorities for commercialization;

5. Was intended to be used as a drug. The dietary supplement industry should not peddle steroidal drugs as a dietary supplement.

Based on available information, there were several reasons why the synthetic product was not registered and subsequently not marketed as a pharmaceutical drug. The initial clinical trials conducted in India involving synthetic guggulsterones were submitted in 2001 to the Drugs Controller of India for regulatory approval. The clinical data on the synthetic product showed no advantage of using it over the natural Gugulipid®. Ultimately, the drug application was rejected because Phase I and Phase II studies had not been done. Therefore, the important and fundamental questions pertaining to the safety of synthetic guggulsterones, i.e. LD_{50}, mutagenicity, teratogenicity and long-term toxicity, were never answered and remain unknown. A failed synthetic drug, high purity Guggulsterones 99% is now being marketed as a natural product – the classic FDA definition of an adulterated product!

In addition, analysis of the composition of synthetic guggulsterones revealed that it differs in proportions of guggulsterones E and Z from the naturally occurring product. In the natural product, guggulsterone E comprises nearly 20% and Z the remaining 80% in a specific natural matrix of related compounds. The synthetic material has varying ratios of guggulsterones E and Z. Therefore, the ultimate pharmacological effects for the respective products could be different.

Incidentally, reliable standardization of gum guggul extract is the key to the safety and efficacy of the preparation. This point was previously brought to the attention of the dietary supplement industry in 1999 by Sabinsa.

The analysis of standardization of gum guggul extracts includes an inexpensive, less accurate ultraviolet (UV) spectrophotometry method and a more costly, precise high pressure liquid chromatography (HPLC) method. The UV method, in addition to assessing guggulsterones content, yields the total amount of sterone, sterol and steroidal components and all compounds similar in chemical structure to guggulsterones present in the gum guggul extract, giving an inflated and incorrect value collectively reported as "guggulsterones"; while the more accurate HPLC analysis yields a guggulsterones E and Z content, with each component quantified separately, for a legitimate total guggulsterones reading. Based on this, the HPLC analytical procedure should be applied preferentially to validate and safeguard the natural and clinically tested product that belongs to the nutritional industry.

Common sense, rooted in good science, must prevail to prevent another unfortunate "synthetic high" story from happening again.

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