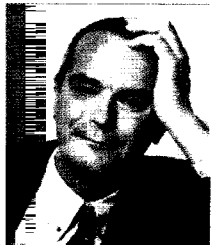


Nutraceutical

THMPD and novel foods approval

Companies seeking to develop such drinks can find new opportunities for regulatory approval in the European Union, writes Dr John Wilkinson.



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The development of functional foods and nutraceuticals is now an established industry with companies spending million of dollars on new development programmes to come up with new exciting innovative products. In the soft drinks industry, this has so far been slow to develop, and one of the reasons for this is the uncertainty of how to get regulatory approval. With nutraceuticals in general, there is no doubt that it is a tricky and complex task, deciding what regulations are appropriate for a product that may be considered a medicinal product or that may be viewed as just a food.

Most nutraceuticals are plant derived. Many of these have folklore associated with them that indicates that they have medicinal effects, such as for example, common sage (*Salvia officinalis*). This herb is used in cooking (mainly sage and onion stuffing) and is considered by the regulatory authorities as a food. However, its folklore uses indicates that it can cure a sore tongue, and also help with memory loss. This latter effect has been validated with recent scientific research conducted on mice and in vitro assays among other experiments. To develop sage as a nutraceutical one could use an extract of the plant, but if it is used in pharmacologically active levels the regulatory authorities may consider it a medicinal product rather than a food. It is this kind of confusion that is putting off drink manufacturers from developing functional or nutraceutical drinks.

Understanding the process

However, in the EU there have been a number of recent developments, which are making it easier for companies to understand the approval process and decide which is the most appropriate way forward for their product. For example, in October 2005 the Traditional Herbal Medicinal Products Directive (THMPD) was introduced into the UK, which has a 'phase in' period of five years before it becomes compulsory, with mutual recognition in other member states in the EU. So a functional drink that contained pharmacologically active amounts of a herb and also had "traditional" medicinal claims on the bottle, would need approval through this route. There is however a proviso, and this is that the herb in question must have significant use for the past 30 years in commerce, of which 15 years of that must have been in the EU. Any herbs that do not fall within this requirement are considered pharmaceuticals and would have to be developed as a drug.

Opportunities to innovate abound despite the constraints. For example new EU member states such as the Cyprus and Estonia have many unique species and folklore that are unknown to the rest of Europe and that could be approved under the THMPD. Also the production of novel extracts from existing herbs, protected by patents, is another area that could and is being exploited



Sage can help with memory loss according to folklore. Under this directive. In principle, 'old herbs' used in the 19th century, but long forgotten about, could be resurrected, developed by drink companies and still comply with the THMPD.

The novel foods route

Companies that want to develop nutraceutical drinks that are not medicinal, but are to be used for their potential anti-aging/antioxidant effects or can demonstrate other health benefits, should consider the novel foods approval route. The beauty of this is that one application in a single member state can be submitted and if this is approved, then the company can market the product throughout the whole of the European Union. Again there are limitations on what herbs/botanicals can be considered under this directive.

Any plant that has not been traded to a significant degree in the EU prior to 1997 will immediately be considered novel and a full application will be needed. The costs can be substantial; US\$500,000 – 1 million is not untypical and some companies have spent much more on this if you include all the R&D as well. Alternatively, if you can demonstrate that a history of safe use in the country of origin exists, then in theory the need for safety and toxicological studies could be reduced substantially, enabling companies to get approval at much lower cost.

However, if the herb/food has been on sale prior to 1997 in the EU but your product is a modification of this, say through a novel extraction process, then there is an opportunity to get approval through the substantial equivalence procedure. Providing you have good data for the product, approval costs for the preparation of the dossier and the application fee, can be as low as a US\$20,000 – 40,000. The equivalence route can be used when a company wants to incorporate a herb or botanical into a drink, but is using a different solvent extraction system to produce the botanical extract. This was recently demonstrated with astaxanthin, a potent antioxidant that provides salmon with their pink flesh colour, but

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which is now commercially derived from *Haematococcus* algae.

The dried algae had been on sale prior to 1997 in Europe and an American company, US Nutra (now called Valensa), developed a super critical carbon dioxide extract of the algae which concentrated the astaxanthin content and produced an oil/water soluble oleoresin. This was recently given novel foods approval through the substantial equivalence route and is now being taken up by various companies in the EU for use in capsules and tablets. It could also be put into drinks, but further approval would be needed because the approval was based on astaxanthin contained in capsules and tablets as opposed to a drink.

Points to bear in mind

When a company is thinking of getting approval through the novel foods directive several points need to be kept in mind:

- Does the herb/botanical have any folklore uses for its medicinal properties? If so, this needs to be evaluated beforehand otherwise the application could be referred to the MHRA borderline unit and could be regarded as a medicine.
- Could you use the extract of the plant at below its concentration for medical uses but still retain an element of functionality? Providing the functionality is for health-promoting effects it could be approved through the novel foods directive, although the directive is primarily involved in safety rather than what claims you want to make.
- Do you have good analytical data and safety studies? If it is a substantial equivalence application you can use the scientific literature to support its safety profile.

Apart from the above points, the novel foods directive contains a list of criteria which have to be included in the application, as outlined below.

Table 1: Points to consider when seeking novel foods approval for a functional drink.

The following is a list of criteria and descriptions that has to be met when applying for novel foods approval in the EU:

1. **The specification of the novel food** This includes information such as its botanical name, the composition of the plant, such as its phytochemical profile, pesticide content, etc.
2. **The effect of the production process applied to the novel food** Does it alter the composition of the novel food, such as, for example, when using a novel extraction process?
3. **The history of use of the organism as a source of the novel food** This needs to document the use of the novel food in the countries where it is grown and consumed.
4. **The anticipated intake/extent of use of the novel food** This section needs to include the amount of the novel food intended to be used in the final product (usually per mgs) and the food matrix, for example a soft drink or juice.
5. **Information from previous human exposure to the novel food or its source** This can include folklore use and also new information gleaned from clinical trials or existing products that are similar to the novel food.
6. **The nutritional information on the novel food** This includes information such as the protein and fat content.
7. **Microbiological information on the novel food** The presence of pathogenic organisms in the product and their levels.
8. **Toxicological information** This includes data such as clinical trials, animal studies etc, to demonstrate the safety of the product.

—More and more drinks companies are developing nutraceutical and functional drinks, a recent example being the new antioxidant wellness drink from Coca-Cola, Ipsei, which contains an extract of the South African rooibos plant. Newer developments include Phytotrade Africa, a company that develops nutraceuticals from African-derived plants and which has spent a lot of money developing baobab fruit pulp as an ingredient for possible use in smoothies. In the USA, researchers in Florida have now developed a way of producing commercial quantities of limonoids, potent cancer chemopreventative

compounds found in citrus fruits such as orange and grapefruit juices. This exciting development means that it won't be long before we will see nutraceutical versions of grapefruit juice, standardised to 0.5% limonoids, on the supermarket shelves – that is once they have obtained novel foods approval.

There are other further developments to the directive that are being lobbied for in Brussels and will help companies become more innovative. These include changes to the legislation that will allow producers of exotic fruits in developing countries to include a history of safe use from their respective countries in the application procedure. This, in principle, will circumvent a lot of expensive toxicity and safety studies that would have been required in the existing legislation.

As it stands, there are still plenty of opportunities for drink companies to develop functional drinks. It can be relatively inexpensive if you can

submit a substantial equivalence application, or cost tens of thousands through the THMPD, tens of thousands to a few million through a full application via the novel foods directive, or hundreds of millions if it is considered a drug.

Taking the right path in terms of regulatory approval can and will enable the drinks industry to produce innovative drinks, but be warned – make sure you consider the regulatory approval process early in the development process. Otherwise you could find that you may be unable to market the product legally, or that the unexpected regulatory costs make the product uneconomic to produce. ■



Baobab fruit pulp (above), dried plants and herbs (left) and the antioxidant wellness drink Ipsei (below).



Changes to legislation will allow producers of exotic fruits ... to include a history of safe use from their respective countries in the application procedure.