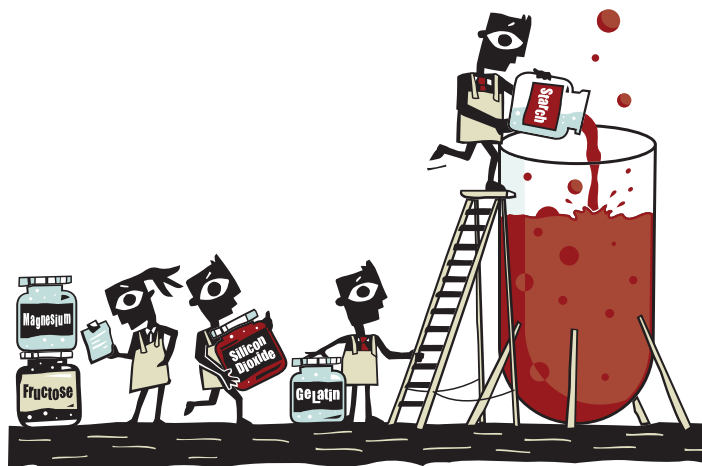


# EXCIPIENTS IN THE SPOTLIGHT

With public awareness of additives higher than ever before, the development of chemicals and excipients, and of standards to monitor their safety, is a top priority, writes SOCMA president Joseph Acker.

## Author

Joseph Acker was appointed president of SOCMA in March 2003. He previously served as president and CEO of DanChem Technologies and president of Hickson DanChem Corporation in Virginia, USA. He is the immediate past chairman of SOCMA's Board of Governors and served as its treasurer and vice chairman. He is a member of various professional associations and serves on numerous civic boards.



Current good manufacturing practice (cGMP) requirements, while never easy, present unique concerns in a speciality chemical environment. In regulating manufacturers of active pharmaceutical ingredients (APIs), intermediates and excipients, the FDA has recognised that one size does not fit all. The challenge is determining, and consistently implementing, those steps that are necessary to ensure the quality and purity of a particular chemical product.

Public awareness of additives and ingredients has focused more attention on the chemicals and excipients markets than before. As the major ingredients of pharmaceutical preparations, related safety issues have risen to the top of the list for consumers and producers.

Excipients, the ingredients other than the pharmacologically active drug included in the manufacture of pharmaceutical drugs, govern many of the characteristics exhibited by drugs in pill and capsule form. Ingredients such as microcrystalline cellulose govern the breakdown behaviour of capsules in the stomach, while substances such as fructose and aspartame give oral preparations a sweet taste.

## Excipients govern many of the characteristics exhibited by drugs in pill and capsule form

Other excipients may give a preparation greater crushability to facilitate its manufacture as a pill, or to give the drug a slow release capability. Generally, they are classified in the following groups: binders, disintegrants, compression aids, fillers/diluents, lubricants, glidants, colourings, sweeteners, preservatives, suspending/dispersing agents, film formers/coatings, flavourings and printing inks.

The importance of these types of ingredients is considerable. Some determine the delivery system for a drug, while others control its assimilation into the body. Disintegrants allow the preparation to break up into particles small enough to be taken into the blood stream, while the inks are used to clearly mark individual pills so that there is no danger from false identification of a drug treatment.

## Recently, policies on the labelling of foods and pharmaceuticals have been radically reviewed

Whether excipients directly affect how a drug performs within the body, or simply give it a more pleasant taste and texture in order to ease its use and improve patient compliance with drug regimens, they are nevertheless vital to the manufacture of pharmaceuticals as marketed today. In many cases, excipients

will make up the bulk of the total dosage, which is why they are sometimes referred to as bulking materials.

Many of the most commonly used excipients used in the US pharmaceutical industry are familiar to the general public. For example, starch, gelatin, talc and sucrose are all instantly recognisable. However, public awareness of other common excipients, such as magnesium stearate, cellulose, silicon dioxide, titanium dioxide and shellac, is growing significantly.

The extra attention being given to excipients in the public sphere is a natural extension of a trend that has seen consumers become increasingly curious and cautious about additives in food. Recently, policies on the labelling of foods and pharmaceuticals have been radically reviewed in response to this growing concern.

As a result, there is a growing emphasis on establishing appropriate standards for quality and control of excipients within the

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### CGMP COMPLIANCE CONFERENCE FOR PHARMACEUTICAL INGREDIENT SUPPLIERS

SOCMA's cGMP Compliance Conference for Pharmaceutical Ingredient Suppliers, scheduled for 5–6 October 2005 in Alexandria, Virginia, USA, will serve to underline the importance of cGMP compliance.

The conference will cover:

- Risk-based approach to cGMP compliance
- Foundation for API cGMPs: ICH Q7A
- Process analytical technology for APIs
- API facility foreign inspections
- Corrective action, preventative action
- Cleaning validation
- Current trends in EU regulations

## New excipients are always being developed, but their official recognition is dependent on rigorous qualification

pharmaceuticals industry. Bodies such as the US Pharmacopoeial Convention, an independent organisation that produces and maintains the *US Pharmacopeia*, and the *US National Formulary* control the use of these substances in the USA. International bodies such as the International Pharmaceutical Excipients Council (IPEC) also exist to monitor and address industry issues arising from the use of excipients. The *US National Formulary* currently contains legally recognised and scientifically valid standards of identity, strength, quality, purity, packaging and labelling for more than 250 excipients, vitamins, minerals and botanicals. New excipients are always being developed, but their official recognition is dependent on rigorous qualification by bodies such as the FDA.

New bulking ingredients for drug preparations are required to be officially recognised as safe, and must contain only suitable inactive ingredients that do not interfere either with the effectiveness of the drug or with the tests that are carried out to assess a drug's efficacy. Therefore, it is crucial that propositions for new drug preparations being brought to market include data on the excipients that are expected to be used in the final product.

In some cases, the long lead time needed to bring a drug to market can create uncertainty over the choice of excipients used in the test preparation and the final product, as some excipients used in tests may no longer be available or may have been superseded in the mean time. This places the onus firmly on the manufacturers of the final product to find excipients suppliers with whom they can implement a strategy that aligns with their long-term development and marketing needs.

While the availability of excipients is a concern, the likelihood that specific ingredients will be superseded is limited by the complex

nature of the process of classifying a new excipient for general use in pharmaceuticals. The difficulty of bringing new excipients to market was one of the drivers behind the formation of IPEC at the beginning of the 1990s.

IPEC, which has divisions in Europe, the USA and Japan, is an organisation that represents producers, suppliers and end users of excipients. Each of the three associations concentrates its efforts on local laws and regulations governing the excipients market, as well as on scientific research and business practices in each location.

For IPEC, safety and public health issues are of vital importance, though international trade arrangements are also a crucial area of debate. IPEC is working hard on the harmonisation of regulatory standards and the extension of pharmacopoeial monographs. Harmonisation of the international standards for monographs would make the approval and use of new excipients easier and quicker to achieve on a global scale, while preserving high standards of safety and quality control.

### Case study: Penwest Pharmaceuticals

As for the firms involved in the manufacture of excipients, there is a definite move towards consolidation, a trend that can be seen in the development of new drug treatments by a number of firms. An example of the potential impact of this trend is the decision by Penwest Pharmaceuticals, a specialist in the development of products based on new extended release drug delivery technologies, to sell its excipients business to Joseph Rettenmaier Holding for \$41.75m. The move came as part of Penwest's decision to focus on its drug delivery business.

Rettenmaier is a leading firm in the production of cellulose and organic fibre products, and has its own well-established excipients business. It will take over a wide range of different excipients from Penwest, including Emcompress, Emcocel, Explotab and Prosolv.

The Prosolv range comprises silicified microcrystalline cellulose graded in different median particle sizes to alter the ingredient's performance. It has been formulated to offer improved performance in wet granulation applications when compared to other types of microcrystalline cellulose, which exhibits reduced functionality following wet granulation and can lose up to 50 per cent of its compressibility.

Emcocel microcrystalline cellulose is a partly depolymerised type of cellulose prepared from  $\alpha$ -cellulose treated with mineral acid. With its high compactibility, microcrystalline cellulose has been widely used in the pharmaceutical industry for over 25 years. It also offers low friability, an inherent degree of lubricity, high dilution potential and enhanced compaction performance in combination with other excipients.

Explotab is a disintegrant that allows for rapid dissolution through the accelerated absorption of water, which in turn triggers a quick increase in the size of the granules that make up a tablet.

‘Over the past few years, we have increasingly turned our efforts towards expanding the company’s drug delivery pipeline through the development of pharmaceutical products internally and with third-party collaborators,’ said Tod R Hamachek, chairman and CEO of Penwest, in a statement. ‘We believe it is important to control the product development process in order to better control the product selection and subsequent development timelines, broaden our patent estate and participate more fully in the revenue stream from future product sales by assuming an equal or full share of development costs. This transaction with Rettenmaier is an important step in the continued financing of that strategy and will focus Penwest solely on growing [its] specialty pharmaceutical business.’

While Penwest turns its focus away from excipients, many in the public arena continue to train their gaze on these products to monitor their safety and ensure that sufficiently high standards are maintained around the world. Pressure in the same direction will

Many in the public arena continue to train their gaze on these products to monitor their safety

also continue to be exerted from within the pharmaceuticals industry itself.

It is likely that with concerted effort on behalf of the industry the domestic regulators in major drug-producing nations will extend their cooperation to ease the process of certifying new chemicals and excipients while pressing for the same high standards. With continued consolidation among the producers of chemicals and excipients, new business opportunities could be waiting around the corner. **END**

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EP	○	○	○	○	○
USP		○	○	○	○

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