Regulatory challenges are hindering the use of novel excipients

Europe needs a more standardised and consistent approach for supplying excipient information to the regulators.

Novel materials, such as biological, biotechnological and new chemical excipients, play a crucial role in bringing new, improved and potentially safer medicines to the pharmaceutical market. They can enhance product design or performance by increasing either the stability of intermediates or the shelf life of finished drug products, and the capability of these substances to extend half-life, stability and efficacy of drugs is driving their use across the pharmaceutical industry. However, there are significant challenges to the development of innovative products because of the absence of globally aligned regulatory mechanisms for reviewing new excipients.

Increasingly, the nature of excipients is changing from traditional, simple inert materials to more complex and specialised substances designed to perform highly specific functions within the drug product. As a result, more and more pharmaceutical companies are turning to these novel materials to assist in the development of more complex dosage forms and leading-edge products, and to improve existing products through reformulation. In fact, the reformulation of products is an increasingly common product lifecycle management technique as drug manufacturers strive to maintain or grow revenues in the face of patent expiries and competitive pressures.

Novel excipients have some clear advantages for drug manufacturers. Historically, excipients were not manufactured specifically for the pharmaceutical industry. However, novel materials are now being increasingly developed purely for pharmaceutical use. Accordingly, they tend to be made by rigorously controlled processes to more stringent standards with superior quality controls resulting in very consistent products with appropriate documentation systems to support their use. Furthermore, many novel materials are animal-free, thereby conferring significant benefits by minimising viral and prion concerns. Thus, pharmaceutical manufacturers can be assured of a guaranteed supply fit for purpose, which may not always be the case for traditional excipients. This is especially important given that recent high profile safety issues have highlighted that the use of high purity, quality and consistent components can be critical in ensuring final drug product quality, safety and efficacy, leading the authorities to introduce tighter regulations for the control of both excipients and APIs. In this rapidly changing regulatory environment, although the regulators have begun to recognise the evolving trend in the use of novel materials, systems have not yet adapted to adequately address the regulation of new excipients.

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Why doesn't the regulatory system support these materials?

Although new excipients are being developed specifically for pharmaceutical use, "novel" excipients by their definition have not yet been used and

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proven by the pharma industry. The established procedures listed for well-known excipients and APIs, such as compliance with a pharmacopoeial monograph, use of the *Ph.Eur.* Certificate of Suitability scheme or reference to food additive/GRAS status, depend on previous pharma use and, as such, novel excipients cannot use these procedures. Inevitably reviewers want to see more detailed information about these novel materials than for established excipients, which can lead to the perception amongst drug manufacturers that the use of a novel excipient could cause delays in their regulatory review and approval process. Another key issue for excipients is that, unlike APIs, there is no legally defined GMP standard or independent review procedure. Again, this presents difficulties — especially for novel excipient manufacturers who have to provide full and potentially confidential information directly to the user.

Overall the current regulatory environment can reduce incentives for both excipient manufacturers to develop, and pharmaceutical manufacturers to use, novel ingredients for the manufacture of innovative new products. This situation needs to be overcome and measures put in place to facilitate and standardise excipient review so that the advantages of novel materials can be utilised for the benefit of the consumer.

To this end, significant efforts by the biopharmaceutical industry and The International Pharmaceutical Excipients Council (IPEC) are ongoing, which are directed at standardising excipient manufacture, along with harmonising quality and safety assessment and data packages, a fundamental part of which is a proposal for Excipient Master Files (EMFs) in Europe. Master files allow for a more standardised and consistent approach for supplying excipient information to the regulators, and their use simplifies the system for excipient manufacturers, users and reviewers. They are invaluable to excipient manufacturers because they allow them to protect their confidential manufacturing know-how and manage their own product information. Unlike in many regions, such as the US and Japan, where master files can be submitted for a broad range of drug ingredients, the EU master file system is more restrictive and cannot be used for excipients. Establishing an EMF system in Europe would help reduce current EU regulatory burdens, removing the disadvantages compared with other territories in this area while also further aligning EU regulations with other global systems.

The current system for excipients is inadequate, especially for novel ingredients. The lack of globally aligned regulatory mechanisms for reviewing new excipients is currently creating significant challenges to the development of innovative, new pharmaceutical products. Therefore, harmonised global standards and a workable regulatory mechanism are needed to facilitate market and overall regulatory acceptance of these critical pharmaceutical components. **PTE**

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