

SHAKE RATTLE AND ROLL

Master files list information about the content of a medicinal product, providing brand protection and a regulatory system for product quality and control. Excipient manufacturers claim the European Master Files system is out of sync with the regulatory environment, and is holding back the development of innovative new pharmaceutical products. Phil Taylor investigates.

DRUG MASTER FILES ADVANTAGES

- Keeps manufacturing information confidential
- Manufacturers do not need to provide exhaustive data in their marketing applications
- Information can be easily updated
- Complex data are kept in one place

Pharmaceutical excipients are crucial components of modern medicines, but these inactive ingredients are considered somewhat homely when compared with their more glamorous, active counterparts. It is rare that a new excipient product reaches the market to the kind of fanfare that accompanies a new active substance, and rarer still for a truly novel excipient to reach the market at all. One reason put forward for this – at least in Europe – is that the regulatory environment serves as a disincentive to innovation.

Excipients have come to be considered critical but uninspiring commodities in pharmaceutical development and manufacturing, and the less-than-stellar growth forecast reinforces that view. A new report from market research firm Freedonia estimates just 5.1% annual growth between 2006 and 2011 and considerably less than that in the US and Europe. But the counterpoint to this is that the number of new active substances coming out of the industry's pipelines is diminishing year after year, and drugmakers are increasingly turning to excipients to provide an innovative edge to their products.

Excipients are critical in medicinal products in many ways, such as controlling the release of actives through novel disintegrants or coatings, making products more aesthetically pleasing or hard to copy, and even packing multiple compounds into a

single dosage form. The unfortunate reality is that while there is a desire among pharmaceutical and excipient manufacturers for excipients with novel functionality, regulatory obstacles in Europe are making both suppliers and users think twice before investing their R&D budgets in this area.

Ingredient information

In the US, when a pharmaceutical manufacturer wants to use a novel excipient in a medicinal product, it can supply information on that ingredient to the US FDA in one of two ways; either the manufacturer itself files the supporting data in its application, or it can reference a Drug Master File (DMF) that the excipient supplier has lodged with the FDA. The latter approach is invaluable to suppliers, as it allows them to keep manufacturing or formulation information confidential. It also makes life easier for the manufacturer who does not have to include exhaustive data in its own marketing applications. Information can be updated if changes are made to the excipient manufacturing process. It is also easier for the regulators to have all the complex information on the novel excipient consolidated in one place for review in conjunction with individual licence applications.

Accordingly, the US DMF system avoids multiple assessments and duplication of review efforts and thus reduces the administrative workload on excipient manufacturers, users and

agency staff, creating a more efficient regulatory process. In Europe, it is very different. Unlike the US and Japan, which have master file systems that can be applied broadly across a range of components, the European Master File system is restricted only to active pharmaceutical ingredients (APIs). In 2004, biologicals were also excluded on the grounds that they were not sufficiently 'well-defined', so now only chemical APIs can make use of this regulatory route.

Industry perspective

The International Pharmaceutical Excipients Council – Europe (IPEC Europe), has been campaigning to try to bring the European regulatory environment into line with the rest of the world on this issue. It has also been working to remove the disadvantages that novel excipient developers face in Europe compared with other territories, including the US and Japan, which implemented its own legislation on master files (see case study).

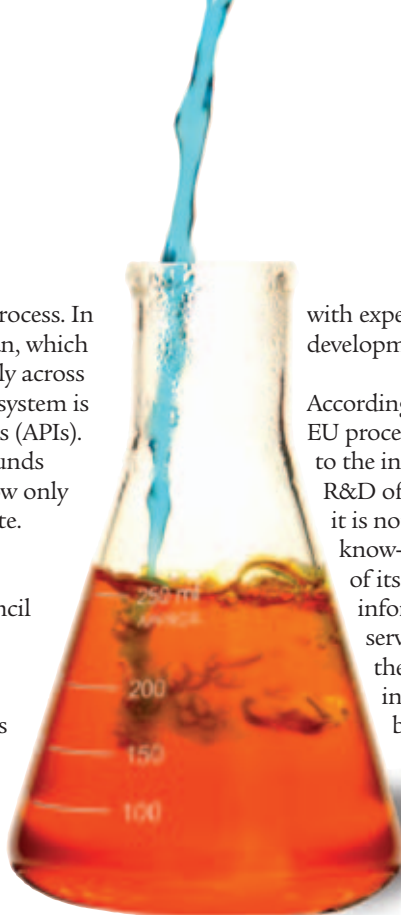
Kate Denton of Novozymes Biopharma in the UK, who serves on IPEC's Regulatory Affairs Committee, has first-hand experience of the constrictions of the European regulatory environment. Her company manufactures

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and sells the novel biotech excipient Recombumin®, a recombinant form of human albumin, which is excluded from using the European Master File route on two counts: it is not an active ingredient and it is a biological substance. The premise of the product, which is used as a component in the manufacture of protein-based pharmaceuticals, is to enhance patient safety by removing the risk of exposure to viruses or prions that could occur with the use of human or animal-derived albumin.

Presenting the case for expanding the European Master File system to include novel excipients and biologics at IPEC Europe's annual general meeting and seminar at the end of January, Denton said that the system was having a material effect on the development of the Recombumin business in Europe, despite a healthy demand for the product from pharmaceutical and medical device manufacturers.

Novozymes has been prevented from providing pertinent information directly to the European Medicines Agency (EMA) in order to support these Recombumin users, because the line of communication is limited to a channel between the EMA and the market application holder. A Master File for Recombumin in Europe (as has been filed in other countries including the US, Canada, Australia and New Zealand) would allow for direct communication between the EMA and Novozymes, and so provide the agency with information first hand from the body



with expert knowledge of the excipient's process development and control.

According to Denton, the restrictions of the current EU processes 'are surely creating unnecessary barriers to the industry's ability to undertake collaborative R&D of new biological products in Europe, because it is not able to protect effectively the commercial know-how relating to the manufacture and control of its novel products or manage its own product information in a practicable way. Our experiences serve as an indicator of the negative impact of the master file system on Europe's capability for innovation and competitiveness in the biopharmaceutical arena. It is now widely acknowledged that the centre of gravity for worldwide R&D investment is gradually moving towards the US and emerging markets such as India and China. Extending the master file system in Europe would be a positive step towards alleviating that shift.'

IPEC Europe has set up a taskforce to promote the case for broadening the scope of the European Master File system to include biological agents and excipients, and set out its stall on the issue via a position paper published in August 2007. The group is now trying to get this on the agenda of the EC and EMA. IPEC Europe's US counterpart is also supporting this effort, in the spirit of achieving a harmonised approach to excipients around the world. Dave Schoneker, director of global regulatory affairs at Colorcon and chairman of IPEC Americas, also believes there are problems with the way the EU system is operated.

'European regulators are not given access to the same level of information on excipients as their counterparts in the US and many other regions,' says Schoneker. 'For instance, in the US DMF there is detailed information on manufacturing processes that regulators in Europe never have access to via the usual regulatory channels – they are only given the minimum.'

Schoneker believes that Europe should move closer to the US situation by allowing not just novel excipients to use the master file system, but also mixtures and co-processed excipients that still depend on confidential and often proprietary processes and may provide novel or improved functionality.

EC view

IPEC's interpretation of the EC's public position is that there are avenues open to excipient and biological ingredient developers wishing to protect their intellectual property. One possibility is the Certificate of Suitability scheme, operated by the European Directorate for the Quality of Medicines & HealthCare (EDQM, part of the Council of Europe), and another is through the use of confidentiality agreements. However, Dr Susanne Keitel, director of EDQM, emphasises that the certification scheme is not workable for novel excipients, as it is only applicable to components for which a monograph

already exists in the *European Pharmacopoeia* – namely, well-known, standard excipients and chemical APIs. ‘Although the certification scheme is open to excipients covered by *European Pharmacopoeia* monographs, when one looks at the documentation required in marketing authorisation applications, it is not attractive,’ says Keitel. ‘A simple reference to the pharmacopoeial monograph is sufficient, so who would submit an application for certification of an excipient?’

There are also clear issues with confidentiality, not least that biopharmaceutical companies tend to be small or medium-sized entities with fewer resources at their disposal to enforce confidentiality of their proprietary information. A master file approach would help them reduce their regulatory affairs workload thereby encouraging innovative product development.

Keitel also pointed out that the EC is concerned that the use of master files limits the amount of information available to the marketing authorisation holder of a medicinal product, and that this is not in line with the need for license holders to take responsibility for their products, especially in the case of complex substances such as biologicals where the characterisation and determination of the quality may not only require a combination of physico-chemical and biological testing, but also extensive knowledge of the production process and its control.

That aside, there are indications that the EC is open to the concept of positive change in the regulatory environment, and to expanding the boundaries of the master file system. In fact, the EU authorities have already accepted that master files are capable of applying to certain biological materials as is demonstrated by their extension of the system to include plasma products and vaccine antigens. There has even been a proposal to encompass herbal medicinal products in the future. While the information in plasma master files and vaccine antigen master files still has to be made available to marketing authorisation holders, at least the concept has been recognised. As the production of these components is often less well-defined and controlled than those based on recombinant technology, there seems to be a clear disparity in the authorities’ treatment of biological substances.

The EC is in the midst of a public consultation, launched last year entitled ‘The Future of Pharmaceuticals for Human Use in Europe: Making Europe a Hub for Safe and Innovative Medicines’. This has given the pharmaceutical industry an opportunity to put forward its position on master files and explain why Europe needs to bring itself in line with other parts of the world.

European precedent

Professor Henk de Jong, chair of the European Pharmacopoeia Commission, points out that there is a clear example of how the master file system has been adopted for non-active ingredients,

CASE STUDY: JAPAN

Japan recently amended its 1948 Pharmaceutical Affairs Law to allow for the filing of master files for novel excipients and pre-mixed excipients (JP-DMF), but the implementation is not without its critics. For example, IPEC Americas maintains the system requires too much detailed information and only allows for a limited number of related products to be included in one JP-DMF. It is also not easily applied to pre-mixed excipients. IPEC Americas says it will be proposing changes to the JP-DMF system in the future to make it work in a similar way to the DMF systems in the US and Canada.



when there is a strong political will to do so. This is for the approval of hydrofluoroalkane propellants, used to replace ozone-depleting CFCs in inhaled medicines. The procedure was efficient and quick, to the extent that the EU led the world in making the wholesale transition from ozone-depleting propellants in metered dose inhalers.

‘At that time, IPEC thought the way had been opened for excipient master files,’ says de Jong, a former chair of IPEC Europe. ‘But this has proved not to be the case.’

His belief is that the adoption has been stalled because EC officials believe that master files act as barriers to free trade and are used by industry to achieve monopolies. ‘It is crucial that this perception is changed, and to explain that it is not the intent,’ he says. ‘Rather it is the protection of intellectual property, in reasonable measure, and the promotion of flexible and wider use of new products that serve the public health and the growth and development of the biopharmaceutical industry in Europe.’

Another key regulatory development is the establishment of the Advanced Medicinal Therapy Product (AMTP) regulation to provide a regulatory framework for gene and stem cell therapy and other complex treatments. In an accompanying paper, the EC acknowledges the benefit of having a centralised assessment for such products because it allows for pooling the expertise of all the member states to ensure a high level of scientific evaluation. The same principles should apply to novel excipients and components, according to IPEC. The AMTP regulation is going to necessitate a revision to the Annex I requirements for pharmaceuticals registration, so this provides a good opportunity to update legislation on master files.

‘The climate and time is right for European regulators to consider extending the European Master File system,’ says Denton.

It is worth noting that the EU is just two years from the culmination of the Lisbon Agenda, a 10-year programme aimed at making the continent ‘the most competitive and the most dynamic knowledge-based economy in the world’. But at least in the area of master files, the regulatory environment seems to be at odds with this objective. **WPF**