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IPEC EUROPE POSITION PAPER ON THE NEED FOR A MASTER FILE SYSTEM FOR NOVEL EXCIPIENTS IN EUROPE

A novel excipient is an excipient which is being used for the first time in a drug product, or by a new route of administration. It may be a new chemical entity that has not been through a regulatory assessment for pharmaceutical use, or it may be a well-established one that has not yet been used for human administration and/or for a specific route of administration.

Novel excipients play a crucial role in the pharmaceutical industry worldwide. They are needed by innovator companies and generic industry alike to increase the bioavailability of poorly soluble active substances or as the basis for new drug delivery systems, both oral and parenteral. Novel excipients can also help to re-formulate drugs in order to improve their quality and safety and/or to reduce their manufacturing costs and complexity. Accordingly, they foster innovation and ultimately improve treatment options for patients. However, while workable regulatory systems for novel excipients exist in many regions, the current regulatory situation in Europe serves as a hindrance to innovative product development[1].

The information required to support novel excipients is, correctly, much more extensive than for established excipients. In fact, in terms of regulatory requirements, novel excipients are treated the same as active substances and comprehensive manufacturing, quality and safety data are needed. A significant proportion of this information, comprising commercially sensitive and proprietary details, is therefore the intellectual property (IP) of the novel excipient manufacturer and represents their investment in the novel excipient. Unlike Active Pharmaceutical Ingredients, excipients are not made exclusively for pharmaceutical use and many novel excipients are already in use in other industries (e.g. cosmetics). Therefore, the novel excipient manufacturer does not want to give all the details on how to make his product to a third party.

Many countries, including all of the IPEC Federation regions except for Europe, have drug master file (DMF)-type systems that are open to excipients whereby excipient manufacturers can achieve adequate IP protection. While US, Canada, Japan and most recently China have established Excipient Master File (EMF) systems, many other regions including Australia, New Zealand, Canada, India and Korea allow a customised approach to submitting proprietary manufacturing information on excipients directly to the regulatory authorities. However, in Europe there is no way to do this for use of an excipient in a centrally-authorised product, though some EU competent authorities may be willing to accept such information on a case-by-case basis for a single national approval. This lack of flexibility is considered a significant disadvantage compared to the other regions. Accordingly, the needs of both developers and users of novel excipients

are not being met in Europe as for these other countries and this represents a significant barrier to innovation.

For many years IPEC Europe has advocated the need for a master file system in the European Union that can be used for excipients, especially for novel excipients [2, 3,4]. For novel excipients that are new chemical entities, reference to former approvals is not possible because these are not listed in pharmacopoeias or other ingredient compendia such as the FDA's Inactive Ingredients Database (for which there is no equivalent in Europe). We recognise that an EMF would not be needed for Ph. Eur. compendial excipients where either reference to the Ph. Eur. monographs or an EDQM Certificate of Suitability (CEP) is usually sufficient, both of which provide IP protection for the excipient manufacturer. For excipients included in compendia other than the European Pharmacopoeia, authorities would not usually see these as novel and a reduced amount of information is required. For all other cases with novel excipients, IPEC Europe envisages that the excipient manufacturer would be able to protect his confidential information within the Closed Part of an EMF. The excipient user/Marketing Authorisation Holder (MAH) would have access to all the information needed to take full responsibility for its intended use in their drug product in the EMF Open Part, i.e. exactly the same way of working as for an active substance master file (ASMF).

Given that data requirements for active substances and novel excipients are equivalent, and that the European legislation specifies that information in relation to a novel excipient must be supplied according to the active substance format[5], IPEC Europe believes that novel excipients should be treated the same in terms of their submission and assessment procedures via a master file procedure. The rationale for allowing manufacturers of active substances significant advantages that are not open to novel excipient manufacturers is unclear. Therefore, we believe that the ASMF system should be extended to novel excipients to redress the balance. This would allow the MAH to cross-reference an EMF for their Marketing Authorization Application and ensure a full review by the authority. At the same time, the manufacturer of the novel excipient would have the assurance that his IP is protected.

A precedent has been set in that a master file-type approach has already been applied for the assessment of metered dose inhalers[6] and container closure stoppers[7]. This, together with the recently implemented worksharing procedure for the assessment of ASMF[8], shows that the EU regulatory authorities are open to harmonised assessment for non-active pharmaceutical ingredients. Therefore, in principle this concept should also be applied to novel excipients.

The ASMF worksharing procedure focuses on better use of regulatory resources when assessing ASMFs and acknowledges the value of worksharing practices. IPEC Europe's view is that these aims also apply to novel excipient review. Currently if a novel excipient is introduced and approved via a first marketing authorisation, the EU authorities are required to reassess all of the excipient information fully for each subsequent use in further product applications. This

system leads to duplication of efforts for the reviewers, using considerable resource for very little or no benefit. It also raises concerns regarding the handling of reviewer objections that may arise from later reviews and their impact on the earlier assessments. This could be addressed by extending the use of the ASMF system (and the associated worksharing assessment procedure) to novel excipients. We recognize that this would necessitate a further change in legislation however the European Commission have already made similar changes in the context of the recently established ASMF worksharing procedure for identical reasons, namely to reduce the regulatory burden and avoid duplicate assessments of the same substance, be it an active substance or an excipient.

In addition to the reasons given above, the lack of a functional regulatory pathway for novel excipients in Europe is a strong hindrance to pharmaceutical product development. It limits innovator companies wanting to use novel excipients to formulate active substances where conventional drug formulation platforms are not successful. Likewise, pharmaceutical manufacturers are reluctant to develop their products containing novel excipients because of the perceived regulatory hurdles associated with their review. Furthermore, the developers of novel excipients that could improve the safety and/or efficacy of medicines are discouraged from commercializing their products as they do not have an adequate means of protecting their IP. Therefore, it would appear that the EU regulators are not acting for the benefit of EU patients with the lack of EMF system in Europe.

IPEC Europe believes that the significant advantages of using EMFs for novel excipients include:

- Providing innovative and safe excipients for improving medicines for European patients.
- Allowing sufficient IP protection for novel excipient developers in the EU.
- Decreasing the workload for the regulatory authorities as multiple assessments would no longer be necessary.
- Encouraging pharmaceutical companies to use products containing novel excipients in Europe as well as other world regions.
- Enabling direct communication between excipient manufacturers and assessors to optimise the review process and ensure the safety and quality of the finished medicinal product.
- Securing that EU reviewers receive the authentic information directly from the excipient manufacturer and have access to the same level of detailed information on novel excipients as their counterparts in other countries thereby ensuring the safety and quality of the finished medicinal product.

In conclusion, implementing an EMF system in Europe by extending the use of the ASMF to novel excipients would benefit a large proportion of the pharmaceutical industry (both manufacturers and users alike) by reducing the barrier to innovation in this area and bringing Europe in line with other global markets. This would encourage the development of improved drug products thereby increasing EU citizens' access to better safer medicines.

References

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