IPEC EUROPE FOLLOW UP PAPER ON THE NEED FOR EXTENDING THE EUROPEAN ASMF SYSTEM TO NOVEL EXCIPIENTS

For a number of 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. A novel excipient is defined as new chemical or biological entity that has not been through a regulatory assessment for pharmaceutical use. By its very nature, a novel excipient is not listed in a national pharmacopoeia or in other well established ingredient compendia such as the FDA's Inactive Ingredients database.

Despite the lack of a pre-approved functional role in drug products and the associated regulatory risk of using them, novel excipients are desired by the pharmaceutical industry. They are needed to increase the bioavailability of poorly soluble active substances or as the basis for new drug delivery systems. Novel excipients can help to re-formulate drugs in order to improve their quality and safety or to reduce their manufacturing costs. Accordingly they foster innovation and ultimately improve treatment options for patients.

For a first time approval, the information on chemistry, manufacturing and control as well as the toxicological data has to be made available to users and health authorities in a suitable format. As novel excipients tend to be more complex than their well-established counterparts they have a stronger need for a Master File system to provide their data.

IPEC Europe has presented its position in two papers available on their website: IPEC Europe approach to the lack of a Master File system for excipients in Europe and IPEC Europe proposed outline for an Excipient Master File system in Europe. These papers include a comprehensive description of the current unmet needs of both developers and users of novel excipients in Europe compared to other world regions such as the US, Japan, Australia, New Zealand and Canada upon which IPEC Europe's position is based. In addition, the latter paper clarifies that IPEC Europe advocates a voluntary approach for the excipient manufacturer as it is recognised that a master file would not necessarily be of value for compendial excipients for which a Certificate of Suitability (CEP) can be granted by the EDQM. However, when used, it is intended that the excipient manufacturer would be able to protect his confidential information within the Closed Part of a master file and that 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 Open Part, i.e. as for an active substance master file (ASMF).

The EMA/HMA(CMDh and CMDv)/EDQM established an ASMF Working Group in June 2010 who published their Mandate in May 2011 EMA Active Substance Master File Working Group. The aim of this joint initiative is to improve and optimise the use of the ASMF system through various measures such as:

- a worksharing procedure for ASMF assessment
- a procedure for a coordinated and harmonised use of ASMF assessments, independent of the licensing procedure being used (CP, MRP/DCP, nat.)
- a guidance document on procedural rules for a common use of ASMF Assessment Reports (ARs)
- an EU numbering system for all ASMFs
- a centralised database for all ARs of ASMF

This initiative focuses on better use of regulatory resources when assessing ASMFs and acknowledges the value of worksharing procedures. IPEC Europe's view is that these aims also apply to novel excipient review and that therefore this initiative offers a good opportunity to address this issue by extending the use of the ASMF system to novel excipients. The basis for applying the ASMF system to novel excipients is premised by the fact that in terms of regulatory requirements novel excipients are treated the same as active ingredients, i.e comprehensive quality and safety data as specified in Directive 2003/63/EC Section 3.2.2.4 (d) (see below). Accordingly we believe that it makes sense for novel excipients to be treated the same in terms of their assessment procedure and that therefore submission via a master file procedure should be possible.

Directive 2003/63/EC Section 3.2 Content: basic principles and requirements (8) (page L 159/61) allows the manufacturer of a well-defined active substance to provide manufacturing and quality information in a separate document directly to the competent authorities as an ASMF. In addition Directive 2003/63/EC Section 3.2.2.4 (d) (page L 159/66) specifies that information in relation to a novel excipient must be supplied according to the active substance format previously described. We believe that a pragmatic interpretation of these two sections of Directive 2003/63/EC of the current legislation could allow regulators to apply the ASMF procedure to novel excipients, i.e. that no changes to the legislation would be required. We understand that such a pragmatic interpretation is legally possible and furthermore that a precedent has been set in that a master file type approach has already applied for the assessment of metered dose inhalers and container closure stoppers (please see point 3 below).

Given that data requirements for active substances and novel excipients are equivalent, the rationale for allowing manufacturers of active substances significant advantages that are not open to novel excipient manufacturers is unclear. Appendix 1 lists some aspects of API and novel excipient review in the context of a Marketing Authorisation Application (MAA) and shows that certain considerations (e.g. IP protection, worksharing) which are equally valid for both APIs and novel excipients are possible for the former but not the latter.

In addition to the points that IPEC Europe has already presented in its previous excipient master file position papers, we would like to make the further observations below which, in our view, support the benefits of extending the use of the ASMF procedure to novel excipients in line with the current

initiative.

1. There would be a decrease in the workload for the regulatory authorities, as multiple assessments would no longer be necessary.
2. Given that an optimisation process for the ASMF system is already ongoing, the changes needed to extend the procedure to novel excipients could be done in parallel thus establishing such a process with minimum workload.
3. The precedent has already been set for the use of a worksharing procedure for evaluation of information, firstly in the 1990s in relation to the replacement of the Freons (chlorofluorohydrocarbons) in Metered Dose Inhalers (aerosol cans) by propellants that do not hurt the ozone layer through the International Pharmaceutical Aerosol Consortium (IPAC) and secondly in 2008 for changes in the quantitative and qualitative composition of rubber stoppers West Pharmaceutical Services Public Assessment Report. This shows that the EU regulatory authorities are open in principle to harmonised assessment and thus this approach should be possible for novel excipients.
4. The recommendations as a result of the ASMF initiative, as well as revision of the Variation Regulation 1234/2008, are likely to necessitate changes in the legislation. Therefore, those required in order to extend the ASMF procedure to novel excipients could be made at the same time.
5. Regarding the implementation of the new variation classification guidelines, it is clear that significant detail is required in support of some of the changes in relation to novel excipients, e.g. *B.II.c.4 Changes in synthesis or recovery of a non-pharmacopoeial excipient or a novel excipient* and *B.II.c.5 b) Introduction of a new manufacturer of a novel excipient that requires a significant update to the relevant novel excipient section(s) of the dossier*. IPEC Europe considers that it is not possible to provide the required level of detailed information without being able to use the master file system as significant amounts of this information are confidential to the excipient manufacturer. Therefore we would argue that it will not be possible for the MAH to comply with the new variation regulations without a workable system in place for novel excipients.
6. In addition, novel excipient manufacturers need to be able to use a master file system to be in compliance with other current regulatory standards in Europe. The EMA has issued various guidelines clarifying their expectations for specific aspects of the dossier requirements for excipients, e.g:
   - EMEA/CHMP/QWP/396951/2006 Guideline on Excipients in the Dossier for Application for Marketing Authorisation of a Medicinal Product
   - EMEA/CHMP/SWP/4446/2000 Guideline on the Specification Limits for Residues of Metal Catalysts or Metal Reagents
   - EMEA/CHMP/QWP/251344/2006 Guideline on the Limits of Genotoxic Impurities

   As above, a significant proportion of the requested information is of a highly sensitive nature

and therefore only possible to submit directly to the authorities in the form of a master file.

7. The use of the ASMF system would enable direct communication between the manufacturers of novel excipients and the assessors as is the case for API manufacturers. Such direct communication could mitigate the risk of a delayed drug product registration for first time users of novel excipients. We believe that this is beneficial for the overall review of the novel excipient information within the context of its application to ensure the safety and quality of the finished medicinal product.

IPEC has several member companies whose businesses are being negatively impacted by the inability to be able to use a master file in Europe. For example, IPEC member company A has potentially new excipients offering advantages in performance, safety and sustainability which they would like to be available to the EU market. However they cannot introduce these new excipients into Europe due to the absence of a suitable master file system. Likewise, IPEC member company B supplies novel biotechnologically-derived proteins and polymers for use as pharmaceutical ingredients. This company's business is also hindered in Europe compared to other countries where the products can be supported by comprehensive master files.

In addition, IPEC member company C markets novel copolymers used for tablet coating applications which offer advantages of flexibility, low viscosity and rapid rate of dissolution. Due to their superior technical performance, there has been global interest within the pharmaceutical industry in these products and the company has submitted master files worldwide to support their launch in many regions. However, only in Europe, one of the company's major market places, drug product manufacturers hesitate to use these innovative products due to the above-mentioned lack of suitable master file system. The ability to use the ASMF system in Europe would encourage pharmaceutical companies to use such novel excipients, as such a system increases the level of confidence that the necessary -and at the same time confidential- manufacturing details are available for review by the competent authorities in context of a marketing authorization application.

In conclusion, IPEC Europe believes that, should the EU decision makers be open for the extension of the ASMF system to novel excipients, the cost of implementing this change would be minimal as it could be done in parallel to the forthcoming ASMF optimisation. However, the benefit would be considerable as it would allow novel excipient developers, especially SME companies, to protect their know-how thereby dramatically increasing their business opportunities. A workable regulatory mechanism for 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. Regulatory reviewers would also benefit through a reduced workload for assessment.

Appendices

Appendix 1: Comparison of Active Substance and Novel Excipient Regulatory Requirements and Processes

Topic	Active Substance	Novel Excipient
Requirement for Marketing Authorisation regarding pharmaceutical dossier Module 3	Comprehensive data regarding manufacture and control	Comprehensive data regarding manufacture and control **(same requirement as for API)** Directive 2003/63/EC Section 3.2.2.4 (d) Novel excipients: For excipient(s) used for the first time in a medicinal product or by a new route of administration, full details of manufacture, characterisation, and controls, with cross references to supporting safety data, both non-clinical and clinical, shall be provided **according to the active substance format previously described.** A document containing the detailed chemical, pharmaceutical and biological information shall be presented. This information shall be formatted in the same order as the chapter devoted to Active Substance(s) of Module 3.
Protection of intellectual property	**Possible** via ASMF procedure The main objective of the Active Substance Master File (ASMF) procedure, formerly known as the European Drug Master File (EDMF) procedure, **is to allow valuable confidential intellectual property or 'know-how' of the manufacturer of the active substance (ASM) to be protected,** while at the same time allowing the Applicant or Marketing Authorisation (MA) holder to	**Not possible** as cannot use ASMF This means manufacturers of novel excipients do not have the same legal possibility to protect their IP, which is a significant disadvantage compared to API manufacturers. As the need to fulfil the documentation requirements is a significant investment, this is a serious issue especially for small and medium sized enterprises. This is an important hurdle for innovation in Europe.

Topic	Active Substance	Novel Excipient
	take full responsibility for the medicinal product and the quality and quality control of the active substance (Guideline on Active Substance Master File Procedure Final, 31 May 2013)	
Workload for regulatory authorities (EMA, EEA National Competent Authorities, EDQM)	**Possible** to use worksharing procedure and significantly reduce workload for regulatory authorities The corrections introduced to this guideline aim to improve the ASMF procedure across the European Regulatory Network. The long term objective of these administrative amendments is to have a unique version of an ASMF for one active substance valid for the whole EU/EEA, and consequently one AR of the ASMF recognized by all Competent Authorities (Guideline on Active Substance Master File Procedure Draft, 17 January 2012)	**Not possible** Cost impact on regulatory authorities
Workload for API / excipient manufacturer	**Possible** to reduce workload due to harmonised assessment procedure	**Not possible** Cost impact on manufacturer
Workload for applicants **(finished product manufacturers)**	**Possible** to reduce workload due to harmonised assessment procedure	**Not possible** Cost impact on applicant, hurdle to use novel excipients for medicinal products, resulting in marketing disadvantage for novel excipients manufacturers

18 November 2013