



*International Pharmaceutical Excipients Council
Of The Americas*

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Chair**

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Mr. Nam-su Kim
Pharma Safety Bureau
Pharma Safety Policy Division
Korean Food and Drug Administration

Dear Mr. Nam-su Kim,

Re; Proposed Korean Pharmaceutical Talc Drug Master File Regulations

The following comments are submitted on behalf of the International Pharmaceutical Excipients Council of the Americas (IPEC-Americas) and the International Pharmaceutical Excipients Council of Europe (IPEC Europe) to provide feedback to the Korean Food and Drug Administration (KFDA) concerning the proposed Drug Master File Regulations for Talc which were published for comment recently. IPEC Americas and IPEC Europe are members of The International Pharmaceutical Excipients Council (IPEC) Federation which is an international industry trade association which includes IPEC-Americas, IPEC Europe, IPEC Japan and IPEC China. Many of IPEC's member companies manufacture either finished drug products or excipients used in such products for various purposes. IPEC also has a number of excipient distributors as members. IPEC represents over 300 companies worldwide.

A number of IPEC member companies or their international affiliates produce or distribute talc products (e.g. astringent powder for infants), pre-mixed excipients or drug products which contain talc (e.g. tablet lubricant) that are currently marketed in South Korea and therefore will be substantially affected by the new DMF regulations being proposed by KFDA.

The talc excipients produced or used by the member companies are manufactured to comply with compendial standards such as the United States Pharmacopeia/National Formulary (USP/NF), European Pharmacopeia (PhEur) or Japanese Pharmacopeia (JP) and are commonly used for multiple international pharmaceutical applications.

The monographs of USP, PhEur and JP include specific tests to detect asbestos in talc. The monographs are based upon a uniform text published by the Pharmacopoeial Discussion Group which is made up of all three pharmacopeias. In South Korea, the revision of the KP standards regarding talc excipients was implemented as of April 2, 2009, and we believe that this, along with an appropriate supplier qualification program is a better measure to be used to secure the quality and safety of talc substances. The problems that the Korean regulatory authorities seek to address are related to compliance with existing regulations. IPEC Americas and IPEC Europe, in the light of our considerable experience with excipients, good manufacturing practices and DMFs firmly believe that the implementation of a DMF system as proposed will not resolve these compliance-based issues.

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In our view, best practice would comprise an expectation that only “Pharmaceutical Grade” talc which meets appropriate pharmacopeial standards be used in the production of drug products, and that the talc be appropriately tested by the user prior to use. Alternatively, the user may be able to rely on the testing done by the talc manufacturer and reported on certificates of analysis to provide this assurance if the user has fully qualified that the talc manufacturer uses appropriate Good Manufacturing Practices when producing the talc. This would typically be done through supplier audits. These types of proactive controls on the part of the pharmaceutical product manufacturer would ensure that only asbestos-free talc is used in any drug product used in South Korea.

Pharmaceutical manufacturers and importers must manage the quality of all ingredients used in finished drugs as well as establishing a system of overall quality management. Since it is the responsibility of pharmaceutical manufacturers/importers to use quality excipients, they should be expected to have good supplier management programs in place to monitor whether the talc that companies use comply with the appropriate standards for talc in the relevant pharmacopoeias.

Talc excipients are very different from bulk active drug substances in that they are used in many different types of drug applications and dosage forms to provide varying types of functionality. Talc excipients are regulated quite differently from active drug substances in all countries of which we are aware. These countries neither have nor require the same level of regulatory oversight as is required for active drug substances. Most talc based excipients have been safely used in food and drug products worldwide for many years .

IPEC believes that the use of modern compendial testing and good supplier qualification practices on the part of the user of the talc provides appropriate control of talc quality as it relates to asbestos contamination and that the proposed talc DMF requirements may lead to an unnecessary increased burden on excipient manufacturers and users without actually improving quality or safety to patients.

IPEC feels that it is very important to emphasize the fact that DMFs are not required for the use of talc in any other country in the world. DMFs are not considered to be a preventative tool for controlling contamination issues such as the asbestos problem in talc. Currently, in all countries we are aware of that have an excipient DMF system in use, a DMF is simply a voluntary mechanism which can be used by an excipient manufacturer to submit that information about their process or material which may be considered confidential to regulators. Although a DMF for an excipient can be filed in the U.S. it is usually only intended for novel or formulated excipients or for use of an existing excipient in a new route of administration or at a much higher level of use than previously used in an approved drug. These DMFs contain safety data and confidential CMC information that cannot be easily shared with the pharmaceutical user due to intellectual property concerns. A DMF is not normally necessary for compendial excipients, such as talc, in the U.S.

The proposed requirement in South Korea for a DMF for talc from every supplier will not prevent problems with talc quality or safety, and could potentially cause difficulties in maintaining an adequate supply of certain pharmaceutical products in South Korea. Many talc suppliers worldwide who produce high quality asbestos-free talc may decide not to develop a talc DMF in South Korea due to the investment in time and resources it would take for them to prepare and maintain such a document.

Many global talc excipient manufacturers are companies whose primary business is in markets other than pharmaceuticals such as food or industrial applications. Only a very small portion of their business may involve marketing these chemicals as pharmaceutical excipients. These talc excipients are typically of high quality and may provide key functionality to many drug products. However, the

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volumes of many of these materials which are utilized are very small as it relates to some of these company's business priorities. Therefore, it is critical that any talc regulations which are being developed in South Korea to control these materials are reasonable and do not create significant unnecessary hurdles for these manufacturers. Otherwise, many of these companies may decide to no longer supply their high quality talc excipients into the South Korean market or to global pharmaceutical companies who plan to market their drugs in South Korea. We feel that this would be counterproductive to your efforts to improve overall drug quality. This is a possibility that must be considered, based on feedback we have had from member companies who are familiar with your current draft DMF regulation. They are concerned about the future economic viability of the South Korean pharmaceutical talc market if the regulations as currently proposed are implemented.

It appears that the proposed regulations would have a disproportionate impact on the pharmaceutical industry by imposing a requirement that is more restrictive than necessary, especially for imports.

If decisions are taken to no longer supply certain talc excipients into the South Korean market or for drugs intended to be marketed in South Korea, this would create significant problems for global and domestic pharmaceutical manufacturers who utilize these talc excipients in their drug formulations:

- Existing drug formulations may have to be reformulated which could potentially limit availability of these drugs for a period of time and increase costs significantly without any real benefit in product quality.
- The quality of some drugs may be adversely affected due to dependence on certain properties which might only be able to be achieved through the use of the original talc excipient.
- These concerns especially apply to the talc excipients and drug products which use talc grades that have been imported safely into South Korea for many years.
- There does not appear to be any real need to regulate these talc excipients to the level addressed in the proposed talc DMF regulations due to a long history of safe use in South Korea and the fact that proper use of modern compendial testing and supplier qualification on the part of the user provide adequate control to prevent the asbestos contamination problem which is what has driven this discussion.
- Since many pharmaceutical companies are developing their drugs for use globally as well as in South Korea, this type of regulation in South Korea could have significant impact in other countries as well.

KFDA has distributed copies of the current requirements in South Korea for API DMFs and asked for industry comments related to what information may not be appropriate to include in a DMF for talc excipients. Many of the data and information requirements in that document are not applicable and would not be available for use with any excipient, not just talc, because those requirements are specifically designed with APIs in mind. Talc is a mineral that is mined. For talc, any requirements expected to demonstrate the quality and safety of the material should be aligned with those required in the ICH CTD P4 section on Excipients. This is what most worldwide regulators are interested in to show that appropriate controls are in place.

IPEC has additional concerns related to how the proposed talc DMF regulations would actually work in practice, i.e.; who would file the DMF and be responsible for its' contents? It is unclear as to what exactly would be the responsibilities of the talc manufacturer, the talc importer and the pharmaceutical user of talc in their drug products. This gets more complex in situations where talc may be used in a pre-mixed excipient system which is manufactured by a company other than the talc manufacturer and this material is then used in the production of a drug product by the ultimate pharmaceutical

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manufacturer. How would the DMF reference situation work in this scenario where the talc goes through intermediary manufacturing steps by multiple companies? IPEC believes that appropriate supplier qualification and compendial testing throughout the supply chain is the best solution to address these issues and that this will give appropriate control to provide assurances to the pharmaceutical users and KFDA that any talc which is used is asbestos-free.

IPEC believes that KFDA should focus on developing practices to ensure that pharmaceutical users are, in fact, fully qualifying their talc suppliers, as opposed to developing a talc DMF system which is unlikely to solve the problem for the reasons discussed above. KFDA can periodically inspect talc manufacturers, if needed, to verify that appropriate GMP controls are in place at the manufacturer to assure that the talc is asbestos free. However, this can be done without the development of a DMF for talc since the key controls for making sure the talc is asbestos free relate to having appropriate in-process and finished product testing in place and this can easily be assessed by KFDA upon inspection. The development of a DMF for a common compendial excipient like talc provides no value.

Please take these comments as constructive feedback. Some of our IPEC member companies may also submit individual comments to KFDA which may contain additional specific information relating to their regional regulations that pertain to talc excipients. We hope that the proposed regulations can be modified to address both the needs of the excipient manufacturers, distributors and pharmaceutical users and the KFDA regulators as outlined in this letter and in the individual comments that you may receive from our IPEC members and other associated trade associations.

IPEC can assist you in your efforts to develop scientifically justified regulations for talc quality control that we believe can accomplish your initiatives while not creating unnecessary non-value-added burden for industry. Hopefully, these regulations can also be harmonized with the approaches used in the major global market regions so as to facilitate global trade of pharmaceuticals. IPEC would be glad to have further discussions with KFDA about how the regulations could be designed to improve patient safety and minimize concerns to industry.

IPEC Americas appreciates this opportunity to provide you with our comments on the proposed talc DMF regulations before they are finalized. We hope these comments will be helpful to you as you finalize your proposed regulations. Please let me know your thoughts about our comments as soon as you get a chance and whether you would like to have further discussions on these topics.

Sincerely,



Janeen Skutnik
Chair, IPEC-Americas