Regulatory Information Sheet

Colorcon provides enhanced customer support for Regulatory Submissions – New approach for Drug Master Files (DMFs) and Regulatory Filing Packages

Background

Drug Master Files (DMF) are submissions to regulatory agencies that contain confidential or trade secret information about drug substances, excipients, container closure systems, etc. The confidential information held in a DMF is intended to be information that is essential to the use of the material in a regulated product. DMFs are a mechanism used in the US and Canada to allow Sponsors to incorporate by reference the confidential information in their regulatory filings and allows the regulatory agency to review this information in the context of an Investigational Drug Application/Submission, New Drug Application/Submission, Abbreviated New Drug Application/Submission or other regulatory filing. **There is no legal requirement for excipients used in pharmaceutical products in the US or Canada to have a DMF. DMF submissions are not reviewed independently nor are they approved or disapproved.** Typically regulatory agencies only review the information in a DMF in the context of a drug application/submission.

When a DMF is used to hold confidential information, the Sponsor must request a Letter of Authorization (LOA) from the DMF Holder before they can reference the DMF in their application/submission. The LOA authorizes the Sponsor to reference the DMF in their application/submission and authorizes the regulatory agency, on behalf of the Sponsor, to review the information in the DMF during their review of the application/submission. If during the review, the regulatory agency finds deficiencies in the information provided in a DMF, a letter describing the deficiencies is sent to the DMF holder. The Sponsor is also notified about the deficient DMF but no details of the deficiency are disclosed to the Sponsor. DMF deficiencies can be cause to delay regulatory action on an application/submission or be cause for an unfavorable action. Every day approval is delayed is money lost by the Sponsor.

A DMF can be useful if there is confidential information that is not provided directly to a Sponsor in support of their regulatory filing. However, the use of a DMF should be limited to the protection of confidential information that will not be shared with the Sponsor. The use of a DMF is completely at the discretion of the holder of the confidential information. Alternatively, the confidential information can be provided directly to the Sponsor under a confidentiality agreement for inclusion directly in their application/submission. There is no regulatory advantage to having a DMF and some drawbacks of DMFs can be avoided by eliminating their use wherever possible.

Colorcon DMFs

Colorcon has maintained DMFs for our dispersion products (ex.; Opadry, Opacode, Lake Blends, etc.) for many years. These products are mixtures of commonly used compendial excipients and/or colorants. These DMFs contain only quantitative disclosures and a very brief explanation of the locations of our facilities and manufacturing processes. Recently Colorcon has concluded that the utility of holding basic information about these products in a DMF has significantly diminished. This information is now routinely provided by Colorcon to Sponsors directly under confidentiality agreements for inclusion in their regulatory filings rendering the use of these types of DMFs redundant. As a result Colorcon is closing Colorcon DMFs that cover basic

dispersion products. Colorcon DMFs for other products will continue to be maintained. Customers that have been issued LOAs to DMFs that will be closed will be notified. In the future, new DMFs will only be utilized to share information with regulatory agencies that cannot be shared with Sponsors under a confidentiality agreement.

By providing regulatory filing information directly to our customers, we feel we can improve and streamline the service we provide to our customers and reduce unnecessary intermediate steps. This approach will offer the following benefits, creating a partnership that minimizes unnecessary regulatory transactions and supports successful regulatory actions for our customers.

Benefits

- Will streamline the systems needed to support the use of Colorcon products in drug products.
- Provides direct customer access to the key information needed for regulatory filings such as quantitative formulations and compendial/regulatory grade information
- Facilitates quicker, easier review of film coating information by regulators potentially speeding drug product approvals
- Eliminates concerns about delays resulting from potential DMF deficiencies
- Eliminates unnecessary regulatory transactions
- Improves transparency between Colorcon, our customers and regulators

FAQs

Do regulatory agencies expect film coating manufacturers to have a DMF?

No. Regulatory agencies in North America actually discourage the use of DMFs for compendial excipients unless they are manufactured by a novel process. DMFs containing only information already held by the Sponsor are also discouraged. The US FDA has commented publically that often DMFs for compendial excipients are not even consulted during the review of a drug application even when an LOA is provided. Additionally, the US FDA has stated to Colorcon that they don't see the need for a DMF reference for many of Colorcon's standard dispersion products in an NDA or ANDA since the sponsors already typically include the quantitative formula for the Colorcon product in their filings.

Why are you closing some of Colorcon's DMFs?

The U.S. FDA has determined that all DMFs must be converted to electronic DMFs in eCTD format by 15 May 2017. Colorcon has assessed whether to convert each of our U.S. DMFs to the eCTD format or simply provide the information directly to our customers. Colorcon has decided that some of our DMFs will be converted to the eCTD format where there is a need for confidentiality beyond what can provided under a confidentiality agreement. However, it has also been determined that several of our DMFs, which refer to dispersion products, are no longer needed since the same information that is contained in our DMF is routinely provided to customers under confidentiality agreements.

Which DMFs in the United States are being closed?

DMF 721 & DMF 2948 are being closed as of 01 April 2017. No new LOAs will be issued for these DMFs from 15 October 2016. Customers that have had LOAs for this DMF in the past will be notified by letter during October 2016.

What about Colorcon's other US DMFs?

Colorcon DMFs 9822 - Aqueous Ethylcellulose Dispersion, DMF 20131 Starcap 1500 Co-Processed Starch Excipient, and DMF 967 Polyvinyl Acetate Phthalate (PVAP) will be converted from paper to eCTD by the 15 May 2017 deadline. Customers requiring LOAs to these DMFs will be provided LOAs electronically as soon as the files are converted.

Will Colorcon provide Sponsors equivalent information to what is currently held in the DMFs that are being closed?

Yes. This information has been and can be provided to Sponsors under a confidentiality agreement.

How do I request this information from Colorcon?

Information can be requested via our online request system: http://www.colorcon.com/regulatory-compliance/request-information. Colorcon also provides Regulatory Filing Packages for selected regions that allow users to request all the documents needed for filing with one click.

How will this impact approved drug products?

In all cases, necessary actions should be minimal. This will depend on how the original filing was done and how much information about the film coating was included directly in the drug application. Each company should consult their Regulatory Department for specific actions needed for impacted drug filings.

What if a company has an application or submission under review currently or are planning to file an application or submission in the near future and already have an LOA?

The DMF will remain open for several months beyond the notification of closure to accommodate in process filings.

Which DMFs in Canada were closed?

DMF 1968-036 (also known as PR-MF-6836) was closed as of 31 March 2016. No new LOAs will be issued for this DMF from 9 March 2016. Customers that have had LOAs for this DMF in the past were notified by letter during March 2016.

Why did you close the Canadian DMF?

Health Canada announcement of October 5, 2015 stated that all current paper DMFs must be converted to electronic format by 31 March 2016. Immediately after becoming aware of the notice, Colorcon began discussions with Health Canada regarding our DMFs. Health Canada was made aware of our plans and agreed on the closure of DMF 1968-036 but would not give any extension to the timeline previously announced.

What about Colorcon's other Canadian DMFs?

Colorcon DMFs 2006-006 - Aqueous Ethylcellulose Dispersion and 2007-068 - Starcap 1500 Co-Processed Starch Excipient are being converted from paper to eCTD at this time. Customers requiring LOAs to these DMFs will be provided LOAs electronically as soon as the files are converted.

What if I have additional questions?

Additional questions can be submitted as a General Regulatory Request via our online request system: http://www.colorcon.com/regulatory-compliance/request-information or by contacting your local Colorcon representative.

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