Whitepaper

Approaches to include drug substance quality information in a drug product application

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The end goal of Drug Product (DP) development is to receive approval for the DP by one or multiple Health Authorities. This enables the company to bring the DP to the market. Collecting all quality, safety and efficacy information required for the application is usually quite complex. This whitepaper aims to support you with deciding on the optimal approach for providing the required drug substance (DS) quality information to Health Authority(ies). To understand the pros and cons of the following three most commonly used approaches, detailed information is provided in a questions and answers format.

The approaches:

1. **Referring to a Certificate of Suitability to the monographs of the European Pharmacopoeia (CEP)**
2. **Referring to a Drug Master File (DMF)**
3. **Adding the quality information about the DS in the DP application dossier**

Usually, several companies are involved in providing the required DS quality information about a particular drug product to Health Authorities. The same company can be responsible for DS and DP manufacture, and act as the applicant/DP registration holder, CEP holder and/ or DMF holder (for definitions, see Glossary). However, these roles are often performed by multiple companies or multiple legal entities belonging to the same company.

Health Authorities in for example the European Union (EU), United States (US) and Canada are members of the International Council for Harmonization of Technical Requirements for

Pharmaceuticals for Human Use (ICH). They request applicants to provide a dossier in Common Technical Document (CTD) format, which is an ICH standard described in ICH guidance M4. In a CTD dossier, the full set of quality information about the DS is located in Module 3.2.S and a summary in Module 2.3.S. In, for example, Southeastern Asian countries and Eurasian Economic Union (slightly) different dossier formats are as well in use. In this whitepaper, we provide information applicable to applications in CTD format by ICH.

Approach 1: CEP

Q1: What is a CEP?

The CEP is a certificate issued by the European Directorate for the Quality of Medicines & HealthCare (EDQM) to the CEP holder after review of the suitability of the monograph for the control of the chemical purity and microbiological quality of the DS described in their application. A CEP is valid for 5 years and valid indefinitely after the 5-year renewal.

An applicant for a DP registration can refer to the CEP in their application. A significant advantage of doing so for applicants in the EU is that the CEP replaces all information covered by the CEP in the DP application. Only required quality information which is not covered by the CEP needs to be provided by the applicant themselves.

Q2: Where can I use this approach?

This approach can be used in the European Union (EU). Additionally, Health Authorities in several other countries accept the CEP as a replacement of the content in the CTD, sometimes on different terms than used in the EU. The website of the EDQM shows that CEPs are currently recognized by Canada, Australia, New Zealand, Tunisia and Morocco.

Q3: For which type of DS?

A CEP can be issued for DS described in a monograph of the European Pharmacopoeia.

Q4: Which parties are involved to make use of a CEP?

Companies/ Legal entities: applicant/ DP registration holder, CEP holder

Reviewing agencies: local Health Authority, EDQM

Q5: What are the steps to make use of a CEP in a DP application in the EU?

New application: The CEP holder submits an application to the EDQM to obtain a CEP. When the CEP is granted and issued, the CEP holder fills the Declaration of access box at the CEP to authorize the applicant of the DP to use the CEP in support of their DP application. In the EU, the signed CEP is added in Module 1 and Module 3.2.R of the DP application and submitted to the Health Authority. The Health Authority evaluates the DP application and the market access is granted or rejected.

Post-approval changes to the DS: When the manufacturer of the DS plans to change the manufacturing process, specification, an analytical procedure or else, the dossier at the EDQM may not reflect the intended post-change situation. If the assessment in the change control procedure shows that update of the dossier is required, the CEP holder should submit the updated dossier to the EDQM for review. Once the updated dossier is accepted by the EDQM, a revised CEP will be issued in case information on the CEP requires to be changed. Otherwise, a letter accepting the application will be issued. If a revised CEP is issued by the EDQM, a DP registration holder in the EU should submit a variation in accordance with the EU "Variation Guidelines"[1] to implement the updated CEP. This is a minor variation which is not reviewed in detail by the Health Authority. If a letter is issued, there is no action required from the DP registration holder.

When the DP registration holder in the EU wishes to implement a new DS manufacturer to which a CEP was issued, or wishes to replace a DS manufacturers DMF by a CEP, a variation application should be submitted as well.

Q6: What is the content of Module 2.3.S and Module 3.2.S?

CEP application: The content of Module 2.3.S and Module 3.2.S is expected to be in accordance with ICH guidance M4.

DP application: Module 2.3.S of the DP application generally contains a summary of the DS information in Module 3.2.S. However, when making use of a CEP, the applicant of the DP may not have the required information to provide a full summary. In the EU, Module 3.2.S of the DP application is largely replaced by the CEP. Only information which is not covered by the CEP application should be added here. For example, information about an additional test that is required to ensure the quality of the DS for manufacture of the DP at hand, or information to register a retest period when this isn't included at the CEP.

Q7: When would this be the optimal approach for registration of DS information?

This is the preferred approach in the EU when the DS is tested and controlled in accordance with the monograph of the European Pharmacopoeia. The approach can be considered a "win-win situation" for the CEP holder and applicant/DP registration holder, especially when different companies are involved. The CEP holder can keep its intellectual property confidential while the applicant/DP registration holder needs less resources to provide and maintain up-to-date DS information in their application.

[1] European Medicines Agency: 'Variations guidelines' - Guidelines on the details of the various categories of variations, on the operation of the procedures laid down 'Variations guidelines' - Guidelines on the details of the various categories of variations, on the operation of the procedures laid down in Chapters II, IIa, III and IV of Commission Regulation (EC) No 1234/2008 of 24 November 2008 concerning the examination of variations to the terms of marketing authorizations for medicinal products for human use and veterinary medicinal products and on the documentation to be submitted pursuant to those procedures

Approach 2: DMF

Q1: What is a DMF?

A DMF is a standalone dossier in CTD format with detailed scientific information about the DS; general information, manufacture, characterization, control, reference standards and stability. The main objective of the DMF procedure is to allow the applicant/DP registration holder to refer to this information without disclosure of the confidential DMF content. In this way, the confidential intellectual property of the DMF holder is protected while the applicant/ DP registration holder is able to provide all required information to the Health Authority in support of their DP application. The DMF holder has the obligation to inform the applicant/DP registration holder about updates to the DMF.

Q2: Where can I use this approach?

This approach can be used in countries worldwide. The details of the procedure may differ per country/ region. For example, the DMF is named Active Substance Master File (ASMF) in the EU. The ASMF is divided in two separate parts. The Applicants Part (AP) should contain information needed to enable the applicant/ DP registration holder to take responsibility for the quality of the DS for use in their DP. The Restricted Part contains the remainder of the information (primarily parts of Module 3.2.S.2 Manufacture) which is kept confidential to the applicant/DP registration holder. In the United States (US), the DMF procedure is available for information about DS as well as DS intermediates, packaging materials, excipients, and other FDA-accepted reference information.

Q3: For which type of DS?

This approach is generally accepted for so called “small molecule” DS. Usually, the DMF procedure cannot be used for biologically active substances. In the EU and US, extensive knowledge about, and control over the manufacturing process is considered required to ensure the quality of the DS for use in the DP. The applicant is expected to submit the required information about the DS in the DP application.

Q4: Which parties are involved to make use of a DMF?

Companies/ Legal entities: applicant/ DP registration holder, DMF holder

Reviewing agencies: local Health Authority

Q5: What are the steps to make use of a DMF?

New application: The DMF holder prepares and submits the DMF to the Health Authority where their customer wishes to register their DP. The DMF contains a letter of access/ letter of authorization (LOA) in which the DMF holder authorizes the Health Authority to review the DMF in relation to the DP application of their customer. The LOA is provided to the customer who adds the LOA to their DP application. With the same LOA in both the DMF and DP application, the Health Authority has all required information about the DS and DP to evaluate the DP application.

In the EU, the ASMF holder has the obligation to share the AP with the applicant as the applicant should include the AP in the DP application.

Post-approval changes: When a change will be made to, for example, the manufacturing process of the DS, its specification, or the analytical procedures used, the DMF may not reflect the new situation. In this case, the updated DMF should be submitted to the relevant Health Authority(ies). In addition, the DP registration holder should be informed and receive sufficient details to evaluate the impact of the change to their DP. Information in the DP application might need to be updated as well. In any case, when the DMF is updated, the DP registration holder should ask the Health Authority(ies) to review the updated DMF in relation to the DP application irrespective of whether the DP application itself is updated or not. An updated LOA is only submitted in case details at the current LOA are not correct any longer. After the evaluation, the DMF holder and DP registration holder each receive questions about their own dossier. Usually, the DMF holder submits their responses first and informs the DP registration holder about their filing. The DP registration holder refers to response by the DMF holder in their own response letter.

Q6: What is the content of Module 2.3.S and Module 3.2.S?

DMF: The content of Module 2.3.S and Module 3.2.S is expected to be in accordance with ICH guidance M4.

DP application: The content of Module 2.3.S and Module 3.2.S depends on the details available to the applicant per the procedure set up in the country/ region where the DP application is submitted. In the EU, the applicant should include the AP of the ASMF in the DP application while in the US this isn't required. The applicant might set additional specifications or claim another retest period than in the DMF. In such cases, a separate Module 2.3.S and Module 3.2.S authored by the applicant should be included.

Q7: When would this be the optimal approach for registration of DS information?

In comparison with the CEP procedure, this approach requires more resources of both the DMF holder and the applicant/ DP registration holder. Still, it can be quite efficient. It enables the DMF holder to keep details about manufacture confidential, while all required information is available for review of the DP application. Moreover, a DMF procedure is in place at most Health Authorities. Therefore, the same or a similar DMF can be submitted in multiple countries/ regions.

Approach 3: DS documentation in DP application

Q1: What is a DP application with DS documentation?

This is so to say "the default approach". The dossier of the DP application contains the required scientific information about the quality of the DS as well as information about quality, safety and efficacy of the DP.

Q2: Where can I use this approach?

This approach can be used with any Health Authority worldwide.

Q3: For which type of DS?

This approach can be used for all DS; small chemically synthetized substances and large biologically active molecules, DS used in well-established DP and new products.

Q4: Which parties are involved in the regulatory procedure?

Company/ Legal entity: applicant/DP registration holder

Reviewing agencies: local Health Authority

Q5: What are the steps to take?

New application: The applicant submits the DP application including scientific information about the DS. To do so, the applicant should have access to all required information about the quality of the DS. The application is reviewed by the Health Authority and approved or rejected at the end of the procedure.

Post-approval changes: When a change will be made to the DS, for example the manufacturing process or specification, the dossier at Health Authority may not reflect the new situation. If the assessment of the change shows so, the DP registration holder should prepare an updated dossier and submit it to the Health Authority for approval.

Q6: What is the content of Module 2.3.S and Module 3.2.S of the CTD?

Content of Module 2.3.S and Module 3.2.S is expected to be in accordance with ICH guidance M4. Module 2.3.S of the DMF, generally contains the summary of Module 3.2.S. Module 3.2.S is filled with the required scientific information about manufacture, characterization, control, reference standards, packaging, and stability.

Q7: When would this be the optimal approach for registration of DS information?

For innovative DPs, this is the optimal approach in the period of market exclusivity. Often, the company was involved in development of both the DS and DP and all knowledge and study data is available in-house to author the complete dossier. The same applies for older biological DPs. This could also be the best approach for older DPs with a chemically synthesized DS for which the CEP and DMF procedures cannot be used. The same or a similar DS quality information can be submitted in multiple countries/ regions.

Summary

Quality information about the DS is an important part of DP registration applications. In this whitepaper, three approaches to provide DS quality information are described in more detail. The

"default" application contains information about the quality of the DS and DP. However, the DS manufacturer and DP manufacturer not having the same legal entity nor belonging to the same company can lead to issues to provide all information in the DP application. The CEP and DMF approaches can then provide a "win-win situation" for both parties. These give DS manufacturers the opportunity to limit disclosure of confidential information about the DS, while DP manufacturers get the required information to evaluate the quality of the DS for use in their DP and submit the application to gain and maintain the registration.

STARoDub B.V.'s team looks forward to providing you with advice on the optimal approach and a regulatory strategy for your situation as well as to supporting the planning and execution of the strategy.

Glossary

CEP holder	Holder of the Certificate of Suitability to the monographs of the European Pharmacopoeia (CEP). Usually, the CEP holder is the owner of the intellectual property about the DS. The CEP holder has various responsibilities towards their customers, applicants and/or DP registration holders, at the time of the application and during the post-authorization period (see guidance PA/PH/CEP (21) 57 by EDQM).
DMF holder	Holder of the drug master file (DMF). Usually, the DMF holder is the owner of the intellectual property of the DS. The DMF holder has the obligation to inform their customers (applicants and/ or DP registration holders) and Health Authorities in case of changes.
Applicant/ DP registration holder	The applicant is a legal entity that applies for approval from a Health Authority. When the initial registration is granted, this legal entity becomes the DP registration holder.
DS manufacturer	Manufacturer of the DS. This may be the same legal entity as the CEP or the DMF holder.
DP manufacturer	Manufacturer of the DP. This may be the same legal entity as the applicant/ DP registration holder, and also as the CEP or DMF holder.

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