Drug substances in the drug product dossier

Quality documentation requirements for marketing authorizations of medicinal products in Europe

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Drug substances for drug products sold on the European market are now manufactured around the world. Regardless of the substance's origin, the documentation of its pharmaceutical quality forms an important part of the drug product dossier and thus the prerequisites for a successful marketing authorization procedure. There are several standards that must be complied with when preparing drug substance documentations.

Marketing authorization of medicinal products in Europe

Before a medicinal product can be launched on the market in Europe, it must receive authorization from a responsible regulatory authority. This involves the authority reviewing the efficacy, safety and pharmaceutical quality of the drug product on the basis of a large body of submitted documentation.

There are several possible routes to marketing authorization in Europe. One is the centralized procedure, which constitutes a common authorization procedure for all countries in the European Economic Area (EEA, i.e. EU member states plus Iceland, Norway and Liechtenstein). Others are the decentralized procedure, whereby authorization is sought simultaneously in multiple European countries, and the national procedure, which is offered for individual European countries. The responsible authority for the centralized procedure is the European Medicines Agency (EMA) in London. Responsible national regulatory authorities include the Federal Institute for Drugs and Medical Devices (BfArM) in Germany or the Medicines & Healthcare Products Regulatory Agency (MHRA) in the UK. The authorization path chosen depends both on the drug product type and on the number of countries in which it is to be brought to market.

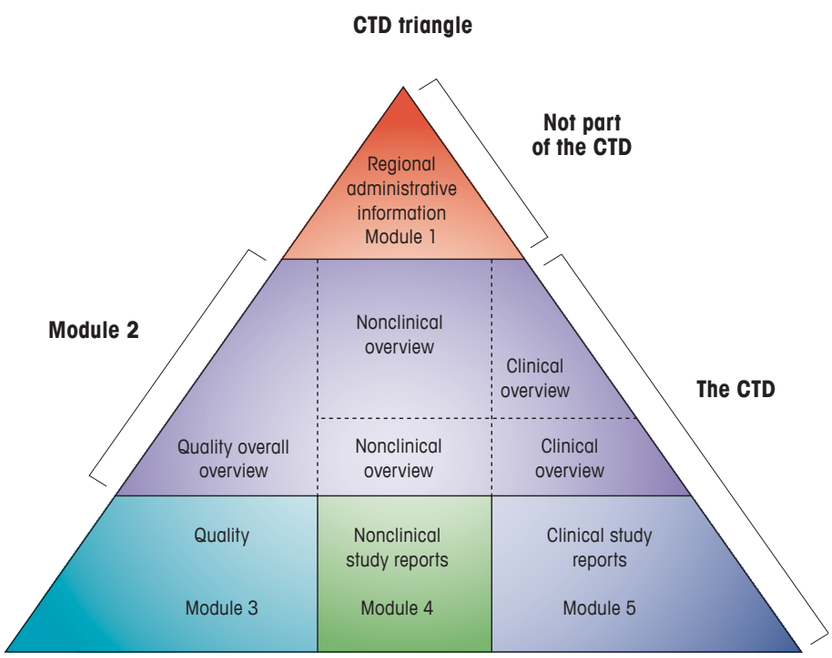

Fig. 1 CTD triangle [1]. Drug substance documentation is part of Module 3: Quality.

For authorization in Europe, the drug product dossier to be submitted by the applicant must be presented in the Common Technical Document (CTD) format. The dossier consists of Modules 1 to 5 (see Fig. 1) and documents the drug product's efficacy, safety and pharmaceutical quality. The pharmaceutical quality of the drug product is documented in Module 3 (Quality) of the CTD dossier, which is subdivided into sections for the drug substance(s) (Module 3.2.S Drug Substance) and the drug product itself (Module 3.2.P Drug Product).

Drug substances

Only rarely is the manufacturer of the drug substance (or active substance) the same as the drug product manufacturer or marketing authorisation holder. This may be true for new drug substances from major research-focused pharmaceutical companies, but in most cases, where the application involves known drug substances, the substances for a drug product are sourced from specialized drug substancwe manufacturers. Today, most of the drug substances that are used in drug products in Europe are no longer manufactured within Europe but are made in India and China [2].

When manufacturing drug products, all of the drug substances used in the product must have been manufactured in accordance with Good Manufacturing Practice (GMP) principles. If the drug substance is to be sourced from a third party, GMP compliance must be assured by the EEA-based drug product manufacturer or importer by means of a drug substance supplier qualification and audit.

Drug substance quality documentation

There are three options available for documenting the pharmaceutical quality of the drug substance in the European drug product dossier: submission of a full set of drug substance documentation in Module 3.2.S, submission of an Active Substance Master File (ASMF) or submission of a Certificate of Suitability to the Monographs of the European Pharmacopoeia (CEP) [3]. The sections below provide details and a discussion of these three options for drug substance documentation.

Option 1: Full set of drug substance documentation

A full set of drug substance documentation must be submitted if standardized documentation in the shape of an ASMF or CEP is unavailable or not acceptable for regulatory reasons – as is the case with biotechnology-derived substances, for example. The documentation includes data on the structure and physical properties of the drug substance, detailed information about the manufacturer and manufacturing process, information about substance characterization and potential impurities, drug substance specification (including analytical methods to be used and information about their validation), batch results, information on reference substances, and statements on drug substance stability, as derived from the results of suitable studies [4–7]. All data must be submitted in the form prescribed by the CTD format [see tab. 1). A Quality Overall Summary (QOS, Module 2.3) is also required. The QOS provides a summary, discussion and critical assessment of the properties, manufacturing process, specification, analysis and stability of the drug substance. The QOS must be authored by a suitably-qualified expert in the field, whose curriculum vitae, together with a signed declaration that the preparation of the QOS has been completed in compliance with the relevant legal regulations, must be included in Module 1 of the drug product dossier.

Tab. 1: Overview of Module 3.2.S Drug substance as per CTD standards [4]

CTD Module 3.2.S Drug Substance
3.2.S.1 General Information
3.2.S.1.1 Nomenclature
3.2.S.1.2 Structure
3.2.S.1.3 General Properties
3.2.S.2 Manufacture
3.2.S.2.1 Manufacturer(s)
3.2.S.2.2 Description of Manufacturing Process and Process Controls
3.2.S.2.3 Control of Materials
3.2.S.2.4 Controls of Critical Steps and Intermediates
3.2.S.2.5 Process Validation and/or Evaluation
3.2.S.2.6 Manufacturing Process Development
3.2.S.3 Characterisation
3.2.S.3.1 Elucidation of Structure and other Characteristics
3.2.S.3.2 Impurities
3.2.S.4 Control of Drug Substance
3.2.S.4.1 Specification
3.2.S.4.2 Analytical Procedures
3.2.S.4.3 Validation of Analytical Procedures
3.2.S.4.4 Batch Analyses
3.2.S.4.5 Justification of Specification
3.2.S.5 Reference Standards or Materials
3.2.S.6 Container Closure System
3.2.S.7 Stability
3.2.S.7.1 Stability Summary and Conclusions
3.2.S.7.2 Post-approval Stability Protocol and Stability Commitment
3.2.S.7.3 Stability Data

Starting material documentation

One hot topic in the context of drug substance dossier preparation concerns the documentation that is provided for the starting materials used in drug substance synthesis. According to the Q11 guideline from the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) [8], the starting materials must be defined during drug substance synthesis development and their selection adequately justified. Drug substance synthesis must be performed under GMP conditions from the very first use of a defined starting material. Since various interpretations of the above from both applicants and regulatory agency assessors has been encountered on regular occasions, the EMA saw itself duty-bound to publish an explanatory document [9]. The document was intended to aid applicants in selecting starting materials acceptable to regulators and presenting a plausible justification for this selection. The manufacturers of the starting materials must be named in the dossier. As a rule, the synthesis pathway specified in the drug substance dossier must contain as many steps as are necessary to unambiguously clarify the formation of the relevant structural core elements and the origin of potential impurities. Where synthesis steps in the specified pathway are critical for quality, these must be named and controlled appropriately. The ICH is also working on the preparation of a Q&A document on starting materials, although the publication of an initial draft of the document is not expected until late 2015 at the earliest [10].

Option 2: Active Substance Master File (ASMF)

For both new and known drug substances, an Active Substance Master File (ASMF) (formerly: Drug Master File (DMF) or European Drug Master File (EDMF)) can be included as part of the drug product dossier as an alternative to a full set of drug substance documentation. This alternative is typically chosen if the drug substance manufacturer and the drug product manufacturer or applicant/marketing authorization holder are not one and the same company. In such cases, the use of an ASMF permits the drug substance manufacturer to avoid disclosing confidential information about the drug substance manufacturing process to business partners.

The ASMF consists of two parts: a non-confidential part, the Applicant's Part (AP, formerly: Open Part), and a confidential part, the Restricted Part (RP, formerly: Closed Part). The non-confidential part, which must be provided to the applicant or marketing authorization holder, documents key details of the drug substance in terms of analysis and quality control: the marketing authorization holder needs these data to fulfil its various obligations. The confidential part, on the other hand, in which the drug substance manufacturer precisely documents the synthesis pathway and process development for the substance, is received only by regulators, so as to honor the protection of trade secrets [11].

ASMF assessment

As things currently stand in Europe, an ASMF is not assessed as a standalone document but only in conjunction with an application for drug product marketing authorization by the responsible regulator. Since the same ASMF can be used for separate drug product marketing authorizations, this repeatedly results in multiple assessments of the same ASMF by multiple regulatory authorities – with occasionally varying results. This state of affairs is unsatisfactory both for regulators and for applicants. Accordingly, efforts are being made to bring about changes here, and an EU-wide "ASMF Assessment Worksharing Procedure" is now being piloted [12]. The aim is for an ASMF to be assessed by just one European regulatory agency: other European regulators can then use this assessment if the ASMF is again submitted as part of an authorization request.

Both parts of the document are prepared and maintained by the drug substance manufacturer and reviewed by regulators. An ASMF for a drug product for human use must be presented in CTD format. A QOS must be submitted for both the confidential and non-confidential ASMF part. Key challenges in the ASMF process include ensuring the exchange of information between the drug substance manufacturer and the marketing authorization holder in the event of changes to the ASMF, and, in the case of the submission of the drug product dossier to regulators, the successful coordination of non-confidential ASMF part submission by the applicant or marketing authorization holder and confidential part submission by the drug substance manufacturer.

Option 3: Certificate of Suitability (CEP)

Another commonly-used alternative for drug substances monographed in the European Pharmacopoeia is to submit a Certificate of Suitability to the Monographs of the European Pharmacopoeia (CEP) for the drug substance. Typically, drug substance manufacturers will submit the CEP application to the European Directorate for the Quality of Medicines & HealthCare (EDQM) in Strasbourg. The applicant must submit a full set of drug substance documentation to the EDQM, including a detailed description of the manufacturing process and an impurity profile. All of the impurities that can potentially occur during manufacturing must be detectable using the analytical methods as described in the drug substance monograph from the European Pharmacopoeia. If this is not the case, then the applicant must submit in-house analytical methods that satisfy this requirement. The description of these analytical methods, with a corresponding specification of the impurities, is then included as an annex to the CEP. If a CEP is issued, this can be used by the CEP holder as evidence that the drug substance is sufficiently controlled by the corresponding monograph of the European Pharmacopoeia (and by analytical methods as described in the annex, as applicable). CEPs are recognized by the European Union and all signatory states to the European Pharmacopoeia Convention. A database of all available and valid CEPs can be found on the EDQM website.

If the drug substance manufacturer can provide the drug product manufacturer with a CEP, this considerably simplifies the compilation of the drug substance documentation to be submitted to regulators, since the CEP

essentially replaces a detailed drug substance dossier. Supplementing the CEP itself, the drug substance specification and analytical methods applied by the applicant or marketing authorization holder should also be submitted, as should any documentation on drug substance packaging and stability, if these details are not already to be found in the CEP. With a CEP, subsequent dossier maintenance is also comparatively simple. When the CEP is updated, the drug substance manufacturer must inform the drug product manufacturer or marketing authorization holder appropriately. The drug substance dossier update required within specific periods as set by regulators is then typically limited to simply exchanging the corresponding versions of the CEP.

One factor to bear in mind, however, is that a CEP offers the drug product manufacturer far less information than is the case with an ASMF or a full set of drug substance documentation (such as data about the drug substance's impurity profile) – even though the former must nonetheless bear overall responsibility for drug product quality. And if regulators choose to raise queries about the impurity profile, it must still be possible to source the appropriate extra information from the drug substance manufacturer.

Summary

The drug substance documentation forms a key part of the drug product dossier: it is relevant for marketing authorization and is critically reviewed by the regulators. For successful marketing authorization, care must be taken when preparing the dossier or selecting a supplier for the drug substance(s), so as to ensure that the drug substance documentation meets the latest standards set by European regulators. Use of an ASMF or CEP simplifies the dossier creation and maintenance process for the applicant or marketing authorization holder while simultaneously allowing the drug substance manufacturer to limit disclosure of confidential data about substance manufacture to regulators only.

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