ReciBio Pharm

Streamlining Regulatory Compliance with Advanced Therapeutics CDMOs Through Drug Master Files

The Food and Drug Administration (FDA) regulates products that account for about 21 cents per every dollar spent by the United States consumer[1]. In terms of applications[2], the agency receives about 1500 initial Investigational New Drug (IND) applications, and in 2024, they have also approved 35 commercial 'novel' therapies (NDA, BLA).[3] The Drug Master File (DMF) accelerates the regulatory process by simplifying the communication between the Sponsor of the drug, the vendor used to fully manufacture the drug or a component of the drug, and the health authority. In the Advanced Therapeutics (ATMP) industry, Contract Development and Manufacturing Organizations (CDMOs) are commonly used by many Sponsors to manufacture advanced therapy drug candidates due to manufacturing complexity and lack of existing manufacturing infrastructure. By using a DMF to relay important manufacturing information, CDMOs can ensure regulatory compliance by providing information required for applications and reduce redundancy.

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DMF AND ITS VALUE TO A SPONSOR COMPANY

A DMF is a submission to a health authority (e.g., US Food and Drug Administration, Health Canada) that is used to provide confidential information in support of an IND, NDA, BLA, Clinical Trial Application [ex-US] (CTA), New Drug Submission [Canada] (NDS), New Drug Application (NDA), Abbreviated New Drug Application [generics] (ANDA), export application, or application amendments. While DMFs are not required to be submitted by regulation and are submitted solely at the discretion of the holder, the application itself is a regulated by 21 CFR 314.420 (US only).

When a holder submits a DMF application, it is neither approved nor disapproved from the perspective of the holder or health authority. However, health authorities expect that the application is kept up to date while it is active and removed when the DMF is no longer needed. The technical components of the DMF are reviewed in connection with the review of sponsor applications and are not evaluated independently.

Information in a DMF is used to convey confidential technical aspects to the applicable health authorities. This includes, among others, manufacturing facilities, processes, or articles used in the manufacturing, processing, packaging, and storing of drugs. Each country that uses a DMF system breaks the DMF down by type that can be found in Table 1.

Table 1. DMF Types per Country.

Country	Nomenclature	Type of DMFs
United States of America – Food and Drug Administration (FDA)	Drug Master Files	• **Type I:** Manufacturing site, facilities, operating procedures and staff not specific to a drug substance. Type I DMFs are no longer accepted by FDA, but old ones remain on file • **Type II:** The most common form of a DMF, Type II covers drug substances, substance intermediates, and materials used in their preparation, or a drug product • **Type III:** packaging material; from bottles and caps to PVC resin • **Type IV:** excipient, colorant, flavor, essence; excipients, which are chemically inactive substances • **Type V:** FDA-accepted reference material[4]
Canada – Health Canada (HC) Master Files	Master Files	• **Type I Active Substance Master Files (ASMFs):** For biologics/ATMPs: Drug substances can include bulk process intermediates, vaccine antigens, adjuvants (except for alum), albumin (except when used as an excipient) and critical raw materials for radiopharmaceuticals or vectors for gene therapy • **Type II Container Closure System Master Files:** Container closure systems (CCS) or CCS components • **Type III Excipient Master Files:** All excipients including those of biological origin (such as albumin), capsule shells, coating ingredients, colorants, flavors and other additives (such as gelatin, alum and growth media) • **Type IV Dosage Form Master Files:** Dosage forms and drug product intermediates • **Type V Facilities and Equipment Master Files:** Diagrams illustrating manufacturing flows (including movement of raw materials, personnel, waste and intermediate(s) in and out of the manufacturing areas, for example)[5]
Europe – European Medicines Agency (EMA)	Active Substance Master Files (ASMF)	• Only allows for the active substance manufacturers to keep know-how information about their manufacturing processes confidential
Australia – Therapeutics Goods Administration (TGA)	Drug Master Files	• DMFs are generally utilized as part of the initial registration process (Category 1 commercial marketing applications) to TGA • Clinical Trial Applications (CTA) are scarce in Australia, many are Clinical Trial Notifications (CTN), which rely on minimal CMC information initially upon submission. DMFs can be used for CTA, but it is not common and not needed for CTNs
Japan – Pharmaceutical and Medical Device Agency	Master Files	• Only allows for the active substance manufacturers to keep know-how information about their manufacturing processes confidential

The Sponsor will need authorization from the DMF holder so the health authority can review the DMF application in connection with its application. This authorization is provided as a Letter of Authorization (LOA) signed by the DMF holder's authorized representative and must occur prior to filing of the application. For congruency, both the Sponsor and the DMF holder will submit copies to their respective applications. The DMF holder needs to submit this LOA before the Sponsor files their application. FDA and Health Canada provide the templates with the information required on their websites and the DMF holder fills in the pertinent information specific to the sponsor. The relationship between the DMF holder, Sponsor, and the health authority is directional as shown in figure 1,

CDMOS AND DMFS

CMDOs, like ReciBioPharm, may elect to hold DMFs to simplify the process and make it easier for the sponsor company. As stated in our whitepaper "Product Quality in Advanced Therapies Manufacturing", the ICH CTD is a series of modules that details specific CMC, clinical, non-clinical, and labeling information required for health authority review of advanced therapy applications. The benefits of this type of application format include:

Standardization: ICH CTD formatting is used for the Sponsor drug application as well as for the DMF application, so in terms of format, they are aligned from what the agencies are expecting.

Efficiency and Systematic Review: the CTD application framework streamlines the application review and approval process for regulators and industry by improving communication.

Lifecycle Management: CTD format can help ensure that changes made to the DMF are consistenty updated and tracked contemporaneously.

Confidentiality: DMFs provide only the need-to-know information: authorization for the specific sections that the sponsor is allowed/ needs to reference.

Market Access: Since the US, Canada, Europe, Australia, and Japan are lucrative markets to enter and are ICH members with mature regulatory health authorities, having a DMF in CTD format to reference in these markets can facilitate market access for Sponsors.

Since DMFs are submitted at the discretion of the DMF holder, they may need to include all sections of a Module or only include one or two pertinent sections based on their purpose. For example, the FDA requires that the Sponsor provide Facilities and Equipment (eCTD section 3.2.A.1) information for early phase through commercial. This section contains unique and confidential information about the facility related to the product that is being manufactured. A CDMO may only maintain a DMF that contains the 3.2.A.1 section as this is the pertinent information of the facility that can and will change over time and is usually the only section that is shared among all clients. In contrast, a DMF holder that is sharing complex manufacturing steps in the terms of proprietary API manufacture will have more sections submitted in their DMF.

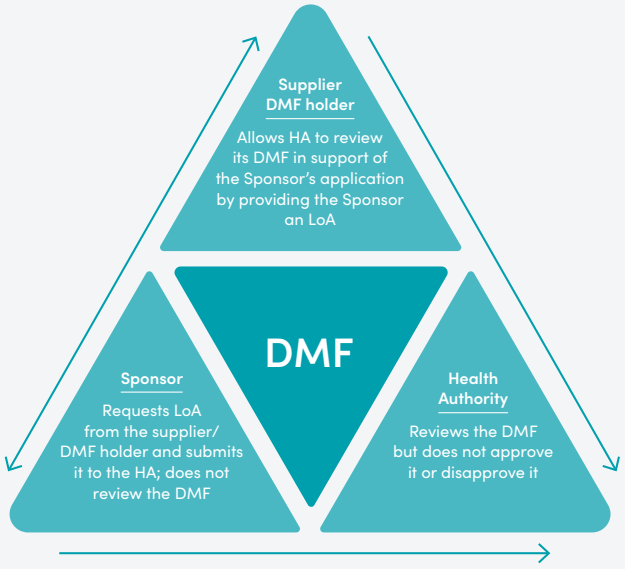

Figure 1: DMF Relationship between holder, sponsor, and health authority.

It is in the best interest of both the Sponsor and the DMF holder to use a DMF system in a CDMO/Sponsor relationship because:

1) When the DMF materially changes, the DMF holder will submit the updated information, so it is always up to date.
2) The Sponsor does not need to summarize the information in the section, only reference the DMF number and direct the reviewers to the LoA.
3) The Sponsor does not need to submit amendments to their application each time the DMF holder makes a change (the sponsor will be notified of changes to check for regulatory impact).

At ReciBioPharm, our facility is capable of manufacturing investigational and commercial ATMPs or portions there of. ReciBioPharm maintains DMFs in both the United States and Canada to ensure our clients will have what they need for their investigational and/or commercial applications. In our DMFs, our 3.2.A.1 Facilities and Equipment section is mature and follows FDA and HC recommendations on current Good Manufacturing Practices (cGMPs) for sterile drug products. In addition to the facility maps for airflow, flow of personnel, materials, waste, and other utilities, we include robust description of our overall facility contamination control strategy. This includes our aseptic process simulations conducted to date, environmental monitoring program, and details of our in-house VHP system. ReciBioPharm have held two Type C meetings with the FDA to ensure our facility meets high standards of quality and inspectional readiness. Furthermore, ReciBioPharm offers CTD Module 3 writing services, briefing book writing support, and ReciBioPharm has a Regulatory CMC employee available for regulatory support as needed. ReciBioPharm's DMF system, regulatory writing support, and mature GMP manufacturing facility add a great value to client programs. This is all part of its greater effort to support customers in their journey to develop live saving advanced therapies.

References

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About us

ReciBioPharm, a division of Recipharm, is a contract development and manufacturing organization (CDMO) specifically established to focus on serving companies seeking to develop and commercialize advanced therapy medicinal products (ATMPs). ReciBioPharm's specialized CDMO capabilities include pre-clinical to clinical and commercial development and manufacture for new biological modalities encompassing technologies based on live viruses and viral vectors, live-microbial biopharmaceutical products, nucleic acid-based mRNA and plasmid DNA production. Led by a management team and technical experts with a proven track record in both process development and contract manufacturing, ReciBioPharm offers the knowledge and resources necessary to help customers develop and manufacture promising new therapies to meet the needs of patients across the world.

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