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## Master Files

### Context

Drug Master Files (DMFs), Biologic Master Files (BMFs), and Master Files for Devices (MAFs), collectively referred to as master files, are U.S. Food and Drug Administration (FDA) submissions that provide confidential and detailed information about facilities, processes, or articles used in the manufacturing, processing, packaging, and storing of human drug products and devices. Master files are critical regulatory documents manufacturers use to confidentially disclose comprehensive information about their processes, components, and facilities. They also allow FDA access to information supporting collaborations with third-party entities without the original innovator disclosing confidential/ proprietary information to those collaborators.

The primary purpose of master files is to support applications for marketing approval or clearance submitted to regulatory agencies. For instance, the FDA, the European Medicines Agency (EMA), and other regulatory agencies rely heavily on the information in these files when reviewing applications. These files facilitate the approval or clearance process by offering a detailed insight into manufacturing processes and facilities, ensuring the products described meet necessary safety and efficacy standards.

Master files are not required by statute or regulation and are neither approved nor disapproved. Instead, the FDA reviews the technical contents of DMFs and MAFs in connection with the review of applications that reference them (e.g., New Drug Applications [NDAs], Investigational New Drugs [INDs], Biologics License Applications [BLAs]).

Information contained within DMFs, BMFs, and MAFs is confidential. This allows manufacturers to protect their proprietary information while complying with regulatory requirements.

### Types of Master Files

DMFs, BMFs, and MAFs are pivotal in the regulatory landscape for drugs, biological products, and medical devices. They bridge the gap between manufacturers and regulatory bodies, fostering transparency and compliance while safeguarding proprietary information.

#### DMFs – The Pharmaceutical Blueprint

DMFs provide a comprehensive pharmaceutical manufacturing, processing, packaging, and storage blueprint. They include intricate details of Active Pharmaceutical Ingredients (APIs), excipients, and packaging materials. Regulatory agencies like the Center for Drug Evaluation and Research (CDER) review DMFs during drug application evaluations, such as NDAs and Abbreviated New Drug Applications (ANDAs), to ensure compliance with regulatory standards. Manufacturers compile and regularly update these files to reflect changes in manufacturing processes or quality control procedures, maintaining a balance between comprehensive disclosure and confidentiality.

## BMFs – The Biological Product Dossier

BMFs are confidential dossiers for biological products detailing the manufacturing, processing, and testing of products such as vaccines and gene therapies. The Center for Biologics Evaluation and Research (CBER) reviews BMFs during evaluations for BLAs or IND applications. These files contain specific information on biologics, including cell culture, purification techniques, and cleanroom operations, and are updated as necessary to reflect process or quality control revisions.

## MAFs- The Medical Device File

MAFs detail medical device design, manufacturing, materials, and components, ranging from implantable devices to surgical instruments. The Center for Devices and Radiological Health (CDRH) uses MAFs in reviews of medical device applications such as Premarket Approval (PMA) or 510(k) submissions. These files include device design specifications and manufacturing process details, and like DMFs and BMFs, are updated to include any design or manufacturing changes.

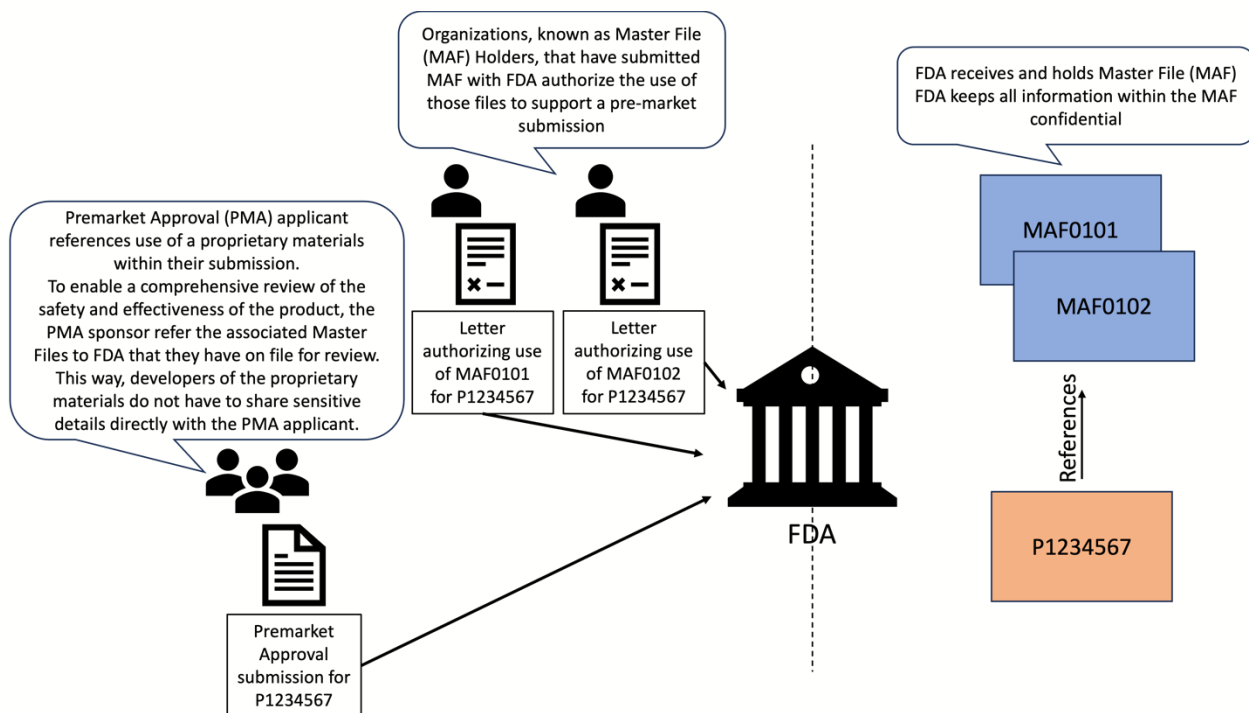
## Key Differences & Regulatory Focus

While DMFs focus on drug manufacturing, BMFs on biologics, and MAFs on medical device design and manufacturing, all share the common goal of ensuring products meet stringent regulatory requirements. Each master file type has a specific content focus and adheres to regulatory guidelines tailored to the product type, playing a strategic role in the approval process and ongoing market presence. The meticulous management of these files is crucial for successful regulatory navigation and maintaining a competitive edge in the healthcare industry. The narrative weaves together the purpose, creation, challenges, and examples of content for each type of master file, highlighting their unique roles and the importance of their maintenance and updating.

## Using Master Files

Submitting a master file directly to a regulatory authority (e.g., FDA) is an option for manufacturers, innovators, and sponsors. Once accepted, a master file becomes a reference document for the FDA in subsequent applicant or sponsor applications. These applicants or sponsors can then cite the master file in their applications, such as New Drug Applications, Biologics License Applications, or 510(k) submissions, when provided with a letter of authorization (LOA) by the master file holder. The regulatory authority evaluates the master file alongside the application.

For manufacturers, master files serve various critical purposes: safeguarding proprietary information, supporting regulatory submissions, expediting reviews, ensuring compliance, and facilitating communication with regulatory agencies. Innovators use master files to provide detailed information about the sourcing, quality, and handling of raw materials or components in their products. This detailed information can demonstrate the integrity and compliance of these materials with regulatory standards. Information included in master files provides FDA with information about the adequacy of product manufacturing and quality control processes without revealing proprietary information. Referencing a master file, however, does not guarantee that FDA will clear or approve a product.



The FDA has established the device master file system to help preserve the trade secrets of the ancillary medical device industry while facilitating the sound scientific evaluation of medical devices. In the example illustrated above, a product manufacturer of submission P1234567 can reference MAF0101 and MAF0102 to support their PMA submission, leveraging other innovations without seeing proprietary information in those materials. Other PMA applicants may also use these master files in the future.

Master files play multiple roles in FDA processes. They serve as confidential repositories for detailed manufacturing and quality control information and may support regulatory submissions by demonstrating compliance without divulging proprietary details. They aid regulatory review by providing comprehensive information to assess product safety, efficacy, and quality, ensuring that manufacturing processes adhere to regulatory standards like Good Manufacturing Practices (GMP). Additionally, they allow manufacturers to communicate changes to regulators.

It's crucial to note that incomplete or inaccurate master files can cause significant delays in the review process, impacting product approval or clearance timelines. Failure to provide complete and accurate information may lead to compliance actions from regulatory bodies, including audits, fines, or even product recalls. These delays or compliance failures can negatively affect a company's market presence and financial performance, influencing investor confidence and market competitiveness. Proper use and management of master files are essential for navigating regulatory processes, ensuring product integrity, and maintaining a competitive edge in the market.

## Regulatory Resources

The FDA emphasizes using master files to facilitate the sound scientific evaluation of medical devices and drugs. The FDA also provides guidance for the industry on preparing and submitting DMFs.

- Guidance documents
  - [Drug Master Files \(DMFs\)](#) – This provides an overview of DMFs, including types, submission resources, and templates. It also includes detailed information about facilities, processes, or articles used in the manufacturing, processing, packaging, and storing of human drug products.
  - [Drug Master Files Guidance for Industry](#) – This contains FDA’s current thinking on DMFs, including submission procedures and required information types.
  - [Device Master Files](#) – This outlines the process for submitting and appropriately using device master files.
  - [Master Files for CBER-Regulated Products](#) – This details the submission of master files for biologics, including the types of information and submission procedures.
  - [Drug Master Files: Guidelines](#) – This offers guidance on preparing and submitting DMFs, including types and content requirements.
  - [Active Substance Master File Procedure: Scientific Guideline](#) – This outlines the procedure for submitting active substance master files to protect intellectual property while ensuring regulatory compliance.
  - [Biologics: Active Substance](#) – This provides guidelines for manufacturing, characterizing, and controlling biological drug substances.
- Additional external resources
  - [Registrar Corp. Master Files](#) – This describes submitting master files to regulatory bodies to protect proprietary product data.
  - [A Guide to Drug Master Files](#) – This offers insights on preparing and submitting DMFs to the FDA, covering types, formats, and delivery.
- Public FDA databases
  - FDA’s [List of Drug Master](#) Files
  - FDA does not maintain a publicly accessible list of BMFs similar to the list of DMFs. However, FDA provides information about BMFs at [Master Files for CBER-regulated products](#).
  - [Device Product Classification](#) – access to regulatory information such as product descriptions, codes, and CDRH review panels
    - Tip: Include information on related product codes and regulations in the background information section to support that the De Novo pathway is appropriate for the proposed device
  - [PMA, De Novo, 510\(k\)](#) – access to decision summaries for related devices
    - Tip: Read and review decision summaries for clinical and non-clinical testing overviews, Instructions for Use statements, and any relevant general/special controls for similar devices
- National Institutes of Health network
  - Work with program officers and obtain regulatory feedback within the NIH
  - NIH awardees can request a meeting with the [NIH Small Business Education and Entrepreneurial Development \(SEED\)](#) Innovator Support Team to ask questions about this process and request a discussion related to the draft cover letter and overall approach. The SEED office does not review or comment on the submission’s scientific validity or data elements.

- Submission procedures
  - For DMFs:
    - FDA: [Drug Master Files \(DMFs\)](#)
    - FDA: [Drug Master File \(DMF\) Submission Resources](#)
  - For BMFs:
    - FDA: [Master Files for CBER-Regulated Products](#)
    - FDA: [Electronic Regulatory Submission and Review](#)
  - For MAFs:
    - FDA: [eCopy Medical Device Submissions](#) The eCopy is a format for submitting an electronic copy to FDA. This is a recently updated process, so obtain the most up-to-date information from FDA.
    - FDA: [Send and Track Medical Device Premarket Submissions Online: CDRH Portal](#) This webpage explains how to submit medical device submission eCopies to FDA online.

## What to Expect

### Timeline

The timeframe for FDA to review these master files varies depending on their complexity. However, FDA will generally only conduct an administrative review of the submission and notify the master file holder with an acknowledgment letter. The FDA does not provide a specified timeframe for this administrative review; however, its scope is limited to administrative information included in the file.

After the master file holder provides an LOA, FDA reviews the technical information referenced to assess whether the master file supports the referenced product.

### General Tips

- Sponsors can reference master files in FDA applications. This allows them to use another party's product (e.g., ingredient, subassembly, or accessory) or facility to manufacture a device or drug without direct access to confidential information.
- Master file holders should identify the specific information in their files that they consider trade secrets or confidential commercial/financial information. This will unambiguously inform FDA of information to omit during Freedom of Information Act (FOIA) inquiries or when referring to the master files.