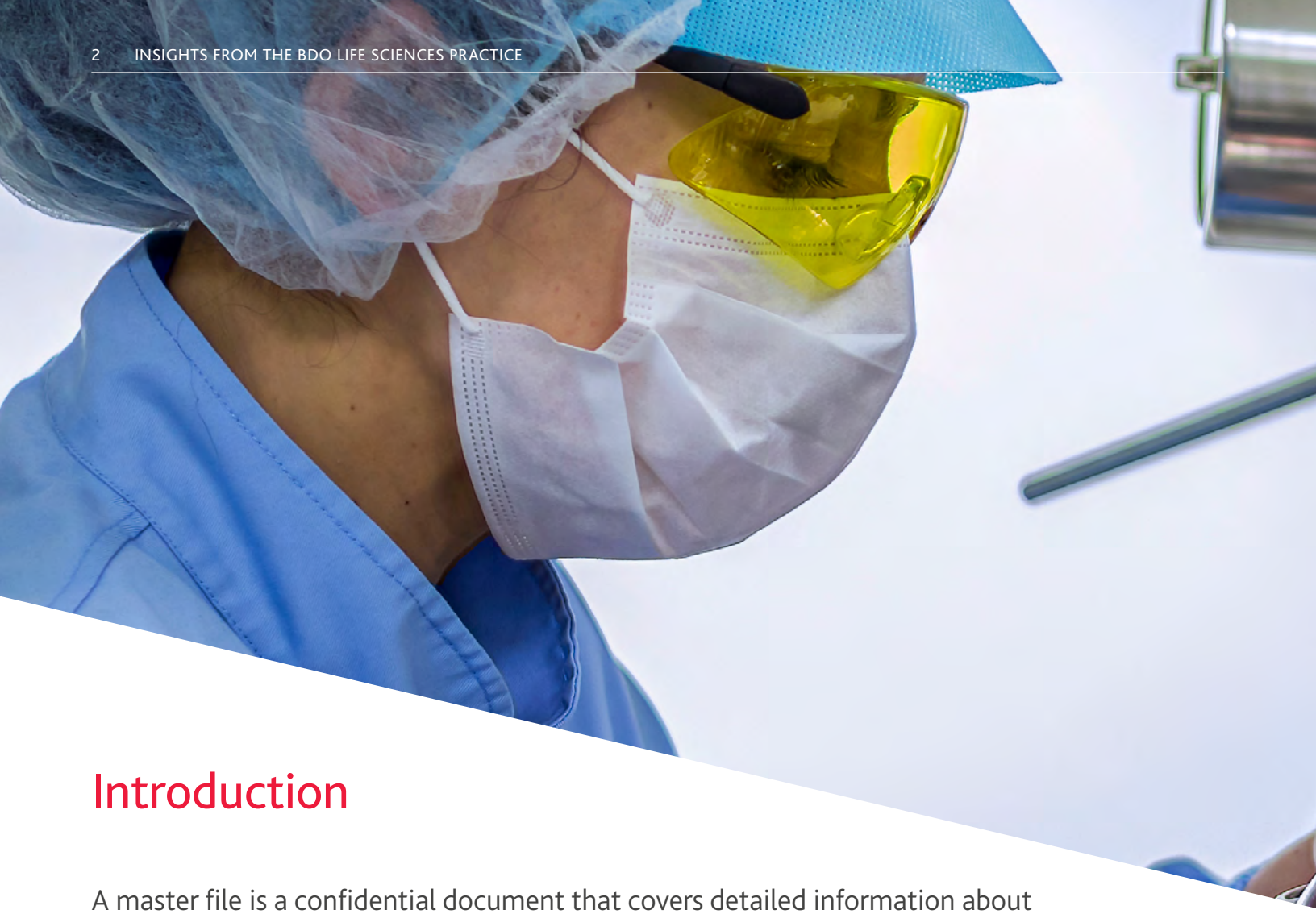
INSIGHTS FROM THE BDO LIFE SCIENCES PRACTICE

A GUIDE TO DRUG MASTER FILES

BDO



Introduction

A master file is a confidential document that covers detailed information about facilities, processes and articles used in the manufacturing, processing, packaging, and storing of biologic, drug, and device products. Master files may also cover other types of information including toxicology and shared system Risk Evaluation and Mitigation Strategies (REMS).

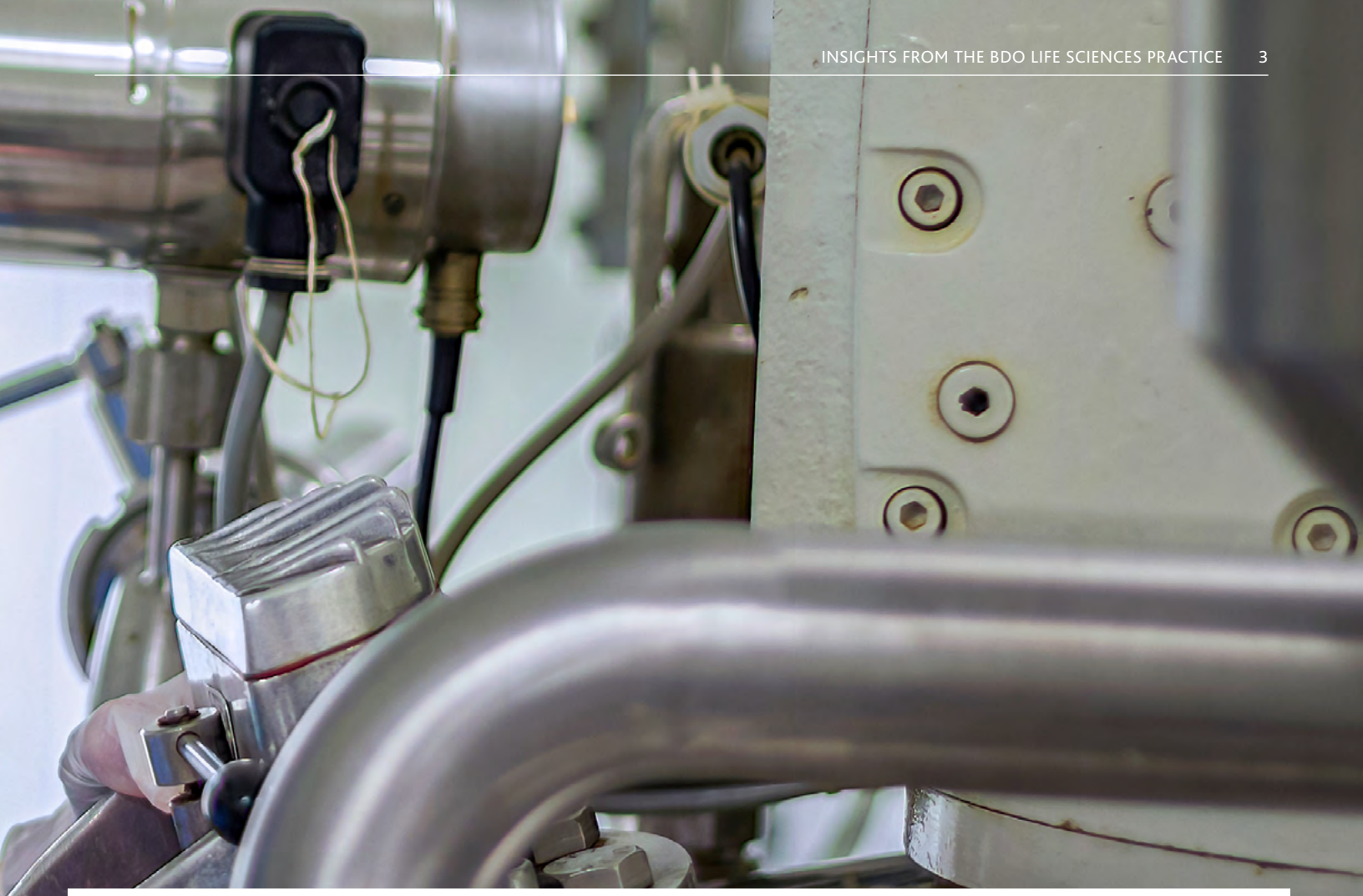
Master files are submitted directly to the Food and Drug and Administration (FDA) by a manufacturer and can subsequently be referenced in applicant or sponsor applications to the FDA. This allows the manufacturer to protect its intellectual information from disclosure to an applicant or sponsor while allowing the applicant or sponsor to comply with the regulatory requirements to provide the information as part of an application to the FDA. A Drug Master File (DMF) is not reviewed by the Agency until it is referenced in an applicant or sponsor submission.

Master files may be referenced in applications submitted for both drugs, biologics, and medical devices.

There are four types of master files:

- **Type II:** Drug substance, drug substance intermediates, and material used in their preparation, or drug product
- **Type III:** Packaging material
- **Type IV:** Excipients, colorant, flavor, essence, or material used in their preparation
- **Type V:** FDA-accepted reference information

In 2000, the Type I master file was discontinued but the numbering of the other types of master files remain same.



It is noteworthy that for Biologics License Applications (BLAs), the FDA has not generally accepted the inclusion of information about a drug substance, drug substance intermediate, or drug product by reference to a Type II DMF. The Agency expects such information to be submitted directly to the BLA [1,2]. However, an investigational new drug (IND) application for a biological product may incorporate by reference any information, including drug substance, drug substance intermediate, and drug product information, contained in a master file [3].

The terminology used for master file depends on the division of the FDA which will use the master file during a review of an application. Master file (MF) (21 CFR 601.51(a)) are reviewed by the Center for Biologics Evaluation and Research (CBER), DMFs (21 CFR 314.420) are reviewed by the Center for Drug Evaluation and Research (CDER), and Device Master Files (MAFs) (21CFR 814.20(c)) are reviewed by the Center for Devices and Radiological Health (CDRH). Throughout this document, the term DMF will be used to refer to master files, unless otherwise noted.

CDER maintains a database containing a publicly available list of DMFs filed with CDER [4]. The list contains information about the DMF number, activity status (active or inactive), type, holder name and subject (title). The list is updated on a quarterly basis.

This article is written to support and guide manufacturers that are interested in preparing and submitting DMFs to the FDA.

DMF FORMAT AND DELIVERY

The DMF submission must have a DMF number which is requested via the CDER NextGen Portal [5]. The DMF should typically be submitted in the standard electronic Common Technical Document (eCTD) format [6,7,8] through the FDA Electronic Submissions Gateway (ESG) [9]. The ESG allows the secure submission of regulatory information for review and is the FDA chosen method of transmission. At the time of submission through the ESG, the DMF holder should select the proper center at the FDA. The DMF might be submitted to the CDER, the CBER or multiple centers at the FDA.

For submission larger than 10 GB and for MF and MAF submissions, an electronic copy (e.g., on a compact disc or flash drive) or a paper copy may be mailed directly to the selected Agency center rather than submitting through the ESG.

DMF SUBMISSION CONTENT

DMF submissions must include the FDA form 3938 [1], a cover letter and administrative and technical information. Multiple templates are available on the FDA website to assist in the preparation of the administrative information contained in a DMF submission [10]. The original submission should contain complete administrative and technical information whereas subsequent submission should contain information pertaining to changes and updates. The relevant eCTD modules for a DMF submission are discussed below [2].

Module 1:

- **Cover letter:** this letter contains the submission type and the DMF holder's statement of commitment specifying that the DMF is current and the holder will fulfill statements made in DMF.
- **Administrative information:** this section should include information regarding the DMF holder's name and address, the contact/agent (if applicable), the manufacturer (name, site address, contact's name, telephone/fax number and email address) and debarment certification [11].
- **References:** The DMF holder should submit a Letter of Authorization (LOA) to the DMF to allow an applicant or sponsor (the "authorized party") to refer to the DMF as part of an application to the FDA. It should be noted that the FDA will not review a DMF unless the applicant or sponsor provides the copy of the LOA with their application. To withdraw an authorization, a letter of "Withdrawal of Authorization" should be submitted to the DMF and a copy should be sent to the authorized party. The FDA and the authorized party should be notified of any changes/additions/deletions to a DMF.
- **Application status:** See section "DMF Closure" for procedures for DMF closures.
- **Meetings:** A teleconference can be requested only by holders of Type II drug substance DMFs referenced in an ANDA in response to first cycle DMF deficiency letters.
- **Information amendments:** This section includes the information summary of changes to modules 2 through 5 or information that is not covered under modules 2 through 5.
- **Other correspondence:** An environmental assessment should not be submitted because the DMF is neither approved nor disapproved by the FDA [12]. Nevertheless, DMF holders should include a commitment to operate their facilities in agreement with applicable environmental laws.
- **Labeling:** A copy of the shipping label should be provided for Type II DMFs (drug substance, drug substance intermediates, and drug products) and excipients covered by Type IV DMFs.
- **REMS:** The REMS documents should be provided, if applicable [13, 14].

Module 2:

Module 2 recaps the applicable module 3 sections (and Modules 4 and 5, if applicable)

Module 3:

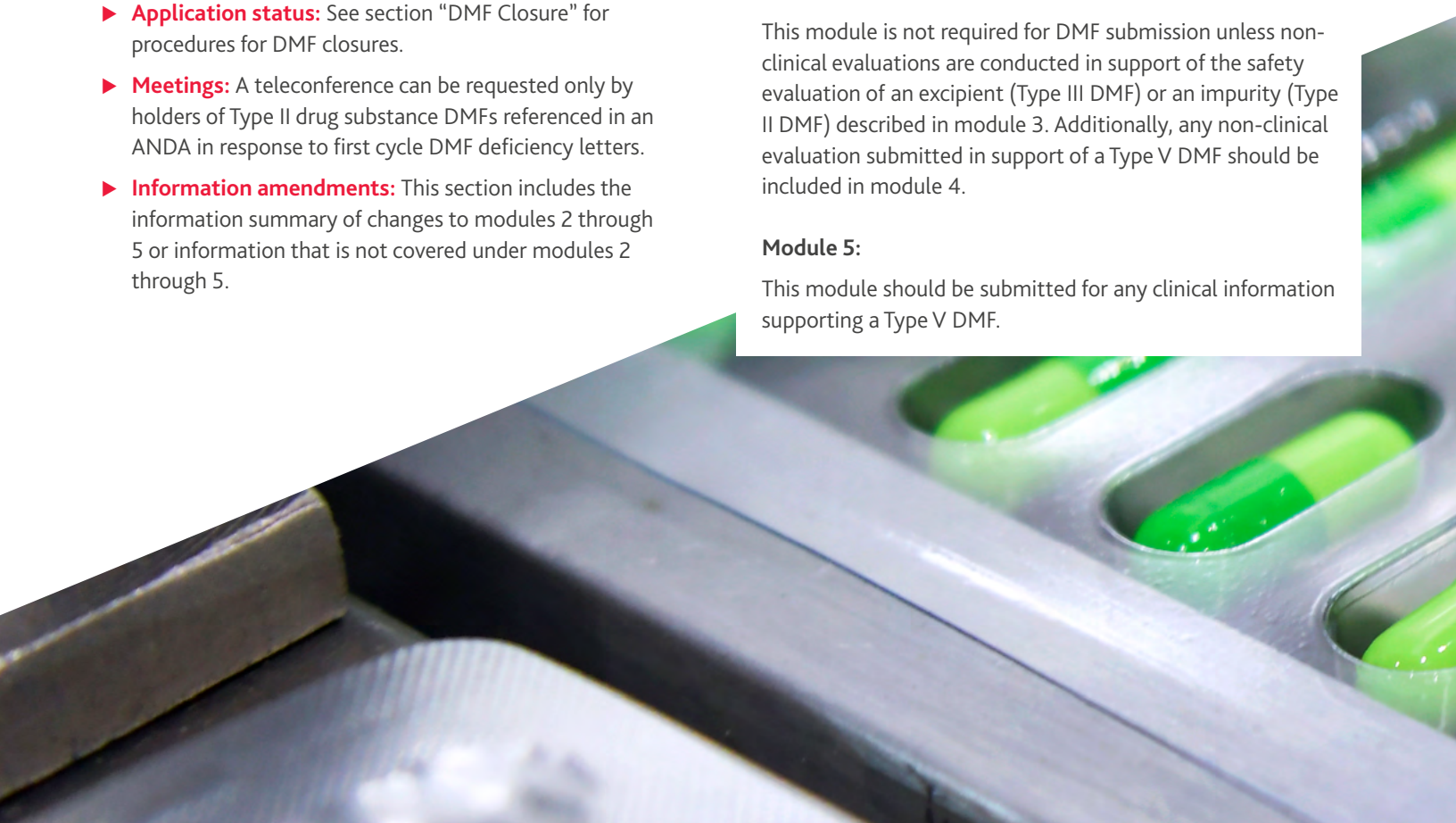
See "*Module 3 Content Recommended based on DMF Type*" in this article for information to include in this module.

Module 4:

This module is not required for DMF submission unless non-clinical evaluations are conducted in support of the safety evaluation of an excipient (Type III DMF) or an impurity (Type II DMF) described in module 3. Additionally, any non-clinical evaluation submitted in support of a Type V DMF should be included in module 4.

Module 5:

This module should be submitted for any clinical information supporting a Type V DMF.



MODULE 3 CONTENT RECOMMENDED BASED ON DMF TYPE

Type II: Drug Substance, Drug Substance Intermediate, and materials used in their preparation, or Drug product

There should be only a single drug substance, drug substance intermediate, type of material used in their preparation, drug product or drug product intermediate in each Type II DMF. For drug substances manufactured using different processes, separate DMFs should be submitted. The manufacturers of drug substance should collect stability data based on the stability protocol and continue to submit data from ongoing studies in a quality/stability amendment [15]. If a drug substance is sterilized in order to be used in sterile products, the same sterility assurance data should be submitted as for sterile products [16]. If a Type V DMF is not cross referenced for the facility and building information including floor plans, it can be submitted in the Type II DMF. If the Chemistry, Manufacturing and Control (CMC) information for material used in the preparation of a drug substance/drug substance intermediate (e.g., cell culture media) is required by the FDA, a Type II DMF may be submitted.

Type III: Packaging Material

The type (e.g., bottle) and Material of Construction (MOC) (e.g., high-density polyethylene) of packaging material(s) should be identified. The authorized party can be informed about the components of an MOC, including safety information, without filing a DMF. Safety and quality information for packaging material can be provided by referral to the appropriate Code of Federal Regulations and the United States Pharmacopeia-National Formulary (USP-NF). Type III DMFs can contain data regarding packaging material or container-closure system's components (e.g., a syringe barrel and a plunger), MOC, controls for release, intended use and the mixture of color additives and plastics used in manufacturing of plastic packaging components. If the packaging materials are sterilized and depyrogenated in order to be used in a sterile product, the same sterility assurance data should be submitted as for sterile products [17]. If a Type V DMF is not cross referenced for the facility and building information including floor plans, it can be submitted in the Type III DMF.

Type IV: Excipients, Colorant, Flavor, Essence, or material used in their preparation

Submission of a DMF is required for new excipients (including colorants, flavors, essences, and material used in their preparation) for which CMC and safety information is not accessible in appropriate regulations or in the USP-NF. Non-clinical safety evaluations [18] of a new excipient can be submitted in module 4 of the Type IV DMF or module 4 of a separate Type V DMF. For animal-derived excipients, the safety information with respect to contamination by infectious agents should be presented and can be reported directly to the authorized parties.

Type V: FDA-Accepted reference Information

The information that is not covered by Type II through Type IV, can be submitted by Type V DMF (e.g., non-clinical/clinical study data, shared system REMS, contract manufacturing facilities, sterilization processes and medical devices). Device master files may contain detailed information regarding specific manufacturing facilities, processes, methodologies, or components used in the manufacture, processing, or packaging of a medical device. They may also provide information regarding finished medical devices.

Specifically for shared system REMS, sterile processing facilities and toxicology studies, the DMF holder should first email a letter of intent to the FDA regarding a Type V DMF. After receiving the email, the FDA will contact the DMF holder to discuss the proposed DMF submission.

Additional recommendations regarding sharing, incorporating and referencing information in a DMF is provided in the FDA guidance document *Drug Master Files* [2]. The DMF holder can contact the FDA for all DMF-related submission questions at dmfquestion@fda.hhs.gov.

ANNUAL REPORTS

The annual report should be submitted on the anniversary date of the original DMF submission. The annual report should include Form 3938, a cover letter, a statement of commitment signed by the DMF holder, the appropriate administrative information, a tabulated summary of administrative and technical changes reported in amendments (including amendment number and date), a list of authorized parties and a list of withdrawn parties with the dates of withdrawal [19]. In the statement of commitment, it should be mentioned that the DMF is recent, and the holder will fulfill the contents of the DMF. It is noteworthy to mention that the annual report should not be used for any change of information. An amendment should be submitted to report changes.

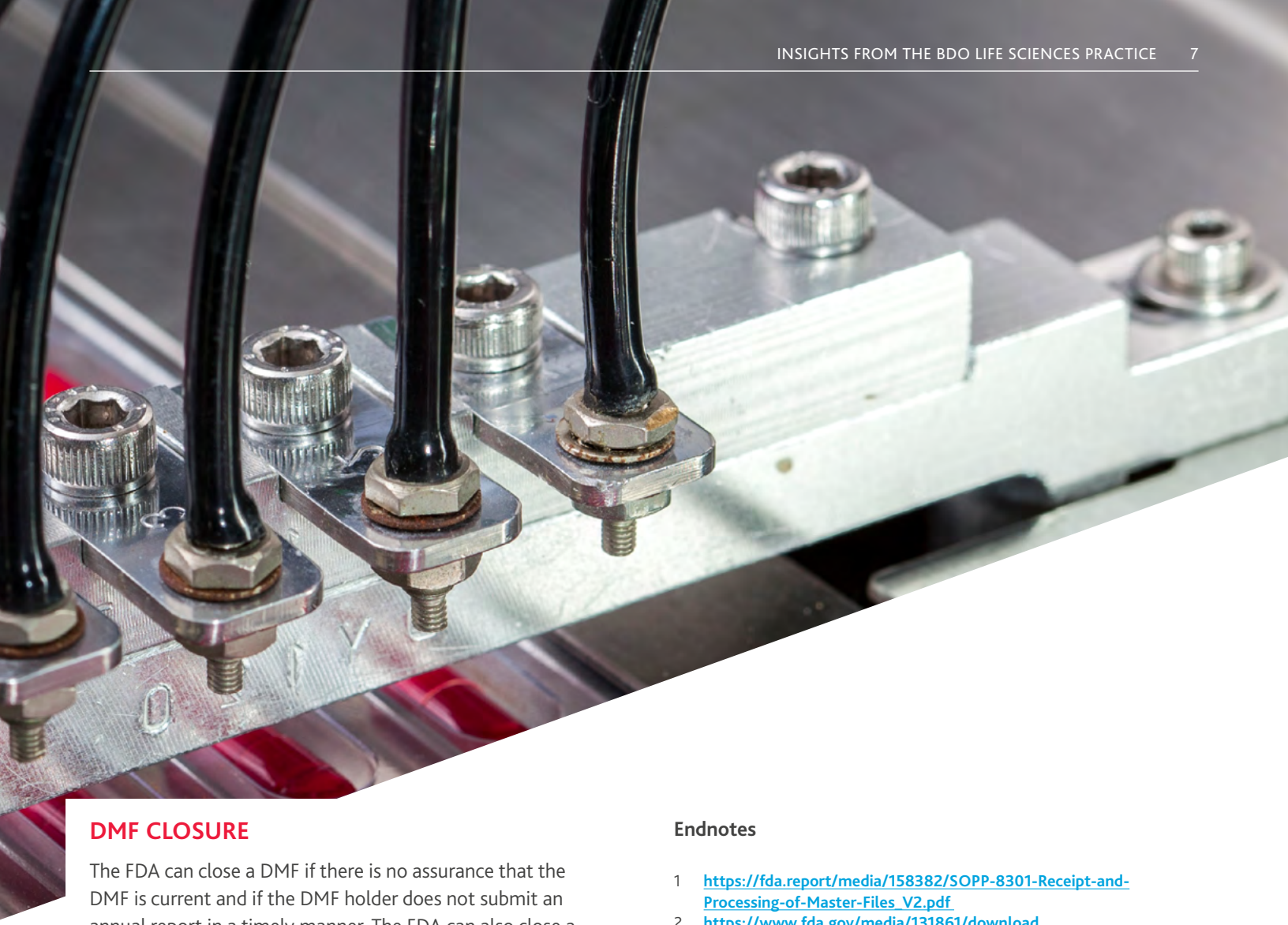
FDA PROCESSING AND REVIEWING

Administrative Review

Following the FDA's review and acceptance of the administrative information, an acknowledgment letter will be sent to the DMF holder. This letter includes the DMF number, subject (title), type and holder's name. In the case of missing information, the FDA will notify the DMF holder. The FDA will not start the technical review until the administrative issues have been resolved and the DMF has been referenced in an applicant or sponsor application or another DMF. The FDA assesses subsequent submissions (e.g., amendment, LOA) to make sure that the administrative content matches that of the DMF on file at the FDA. No acknowledgment letter is sent to the DMF holder for subsequent submissions.

Technical Review

The FDA does not independently review or approve a DMF and only reviews a DMF as part of an applicant or sponsor application. Hence, the technical information of a DMF is reviewed by the FDA once an authorized party submits a copy of the DMF holder's LOA in its related application or in another DMF. The FDA will notify the DMF holder if additional information is required to support approval of an application. If the FDA has recommendations for additional information to include in a DMF, an Advice/Information Request letter may be sent to the DMF holder. Within the FDA, the center that the DMF is allocated to is determined on a case-by-case basis, depending on the DMF topic and the jurisdiction of any of the regulatory submissions authorized to reference the DMF when receiving the original DMF [1].



DMF CLOSURE

The FDA can close a DMF if there is no assurance that the DMF is current and if the DMF holder does not submit an annual report in a timely manner. The FDA can also close a DMF following a request for closure by the DMF holder. The DMF holder should submit an administrative amendment for the closure and inform all authorized parties. A new DMF can be submitted to the FDA to replace a closed one if the DMF holder wishes to re-establish the DMF.

Summary

This article provides information pertaining to the lifecycle management of DMFs which is relevant for manufacturers interested in protecting confidential information while allowing applicants or sponsors to comply with regulatory requirements for biologics, drugs and medical device applications. BDO has the technical and regulatory expertise to support your company should questions arise or support be needed during the DMF preparation, review and submission process.

Endnotes

1 https://fda.report/media/158382/SOPP-8301-Receipt-and-Processing-of-Master-Files_V2.pdf
2 https://www.fda.gov/media/131861/download
3 https://www.federalregister.gov/documents/2019/06/28/2019-13753/biologics-license-applications-and-master-files
4 https://www.fda.gov/drugs/drug-master-files-dmfs/list-drug-master-files-dmfs
5 https://www.fda.gov/drugs/electronic-regulatory-submission-and-review/requesting-pre-assigned-application-number
6 https://www.fda.gov/media/135373/download
7 https://www.fda.gov/media/71551/download
8 https://www.fda.gov/media/71581/download
9 https://www.fda.gov/industry/electronic-submissions-gateway
10 https://www.fda.gov/drugs/drug-master-files-dmfs/drug-master-file-dmf-templates
11 https://www.fda.gov/media/72557/download
12 https://www.fda.gov/media/70809/download
13 https://www.fda.gov/media/109124/download
14 https://fda.report/media/108715/Technical-Conformance-Guide-for-Shared-System-REMS-Drug-Master-File-Submissions.pdf
15 https://www.fda.gov/media/71707/download
16 https://www.fda.gov/media/71442/download
17 https://www.fda.gov/media/71442/download
18 https://www.fda.gov/media/72260/download
19 https://www.fda.gov/drugs/forms-submission-requirements/drug-master-files-dmfs

People who know Life Sciences, know BDO.

www.bdo.com/**bptg**

HAVE QUESTIONS OR WANT TO LEARN MORE? CONTACT US!

BDO wishes to acknowledge the authors:

Sanaz Momben Abolfath, Ph.D., Manager, BioProcess Technology Group
Lotte McNamara, Ph.D., Managing Director, BioProcess Technology Group