Chapter 1: United States

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Introduction

Globally, the term "marketing application" (MA) is applied to the collection of data, analyses, and summary reports ("the dossier") pharmaceutical applicants submit to regulators to support a formal request for commercial distribution of medicinal products. MAs contain evidence intended to demonstrate a medicinal product's safety, effectiveness, and quality and are subject to many technical, discipline-specific, and administrative regulatory requirements as a condition of approval.

Even after an MA is approved, there are regulatory requirements that continue to apply, e.g., when an MA is transferred from one applicant to another; annual updates; and other administrative changes in the elements that comprise the MA or that impact the MA overall. While it may be tempting to deprioritize or overlook compliance with the regulatory requirements that govern these changes, they serve an important function: facilitating the continuous medicinal product surveillance through which regulators support and maintain public health. Further, in some cases, noncompliance can be associated with significant adverse consequences, including proposed withdrawal of the MA or financial penalties.

This chapter reviews applicable US regulatory requirements for MA transfers and other administrative changes. The requirements that govern administrative changes to drug master files (DMFs) are also reviewed.

Key Terms

The US Food and Drug Administration (FDA) recognizes three broad categories of MAs for human drug/biologic products: the new drug application (NDA), the biologics license application (BLA), and the abbreviated new drug application (ANDA).

The term NDA describes the dossier applicants use to propose marketing of a new drug, i.e., one not generally recognized, among experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, as safe and effective for use under the condition prescribed, recommended, or suggested in the labeling.[1] The regulations having to do with NDAs are found in 21 CFR Part 314. The applicable statute is Section 505 of the Federal Food, Drug, and Cosmetic Act (FD&C Act).

Similarly, a BLA is a request for permission to introduce, or deliver for introduction, a biologic product into interstate commerce. The BLA is regulated under 21 CFR Parts 600–680.[2] Biologics are regulated under Section 262 of the Public Health Service Act.

An ANDA contains data submitted to FDA for the review and potential approval of a generic drug product. A generic drug product is one that is comparable to an innovator drug product in dosage form, strength, route of administration, quality, performance characteristics, and intended use. Applicable regulations are in 21 CFR Parts 314 and 320.[3] Generic drugs are regulated under section 505(j) of the FD&C Act.

Applicable Regulatory Requirements

Where application type-specific regulations, guidances, or other policy documents apply, they are noted below. Otherwise, general recommended best practices are provided, and the term "MA" will be used to encompass all three application types.

MA Transfer

There are several circumstances that can cause ownership of an MA to be transferred, including by sale, from one applicant to another. For example, pharmaceutical companies can decide to cease all development and commercialization in a particular therapeutic area for business reasons. As previously indicated, a key regulatory principle is maintaining an accurate MA, which would include accurate contact information, at all times.

For an NDA or an ANDA, the regulations at 21 CFR 314.72 require submission of the following information to FDA at the time an MA is transferred:[4]

- The former owner must submit a letter or other document indicating that all rights to the MA have been transferred to the new owner.
- The new owner must submit an updated form FDA 356h, signed by the new owner, along with a letter or other document that contains the new owner's commitment to the agreements made by the former owner and contained in the MA, the date that the change in ownership goes into effect, and a statement that the new owner has a complete copy of the approved MA, including any supplements and records required to be maintained according to 21 CFR 314.81. (These reports include field alerts and annual reports, discussed elsewhere in this book.)

The range of products regulated under a BLA is very broad, including cell and gene therapy, therapeutic proteins, vaccines, and blood products. While, in theory, a BLA can change ownership for the same reasons that an NDA applicant decides to transfer ownership, the complexity of many biologics makes such a transfer unlikely. However, if such a transfer is planned, while there are no applicable regulations, the same principles apply to this situation as for the transfer of ownership of an NDA. Specifically, the Center for Biologics Research and Evaluation (CBER) has a Standard Operating Procedures and Policies (SOPP) document that recommends the following:[5]

- Changes to a US license that are required due to changes to the applicant's or the product's ownership will be handled as administrative actions through product correspondence. The information regarding the new applicant, including changes to the labeling, will be reviewed by the responsible product office.
- The submission for a change in applicant or product ownership should include the following in the cover letter: the new applicant's name, any changes in personnel, manufacturing, standard operating procedures, and manufacturing facilities.
- If the name change is due to a corporate buy out, two submissions are needed.
- One submission should be from the applicant being bought. The cover letter should include information (e.g., name, address, existing license number, if applicable) on who is buying the applicant.
- The other submission should be from the firm buying the applicant. The cover letter should include information (e.g., name, address, license number, if applicable) on the applicant they are buying and the products that are being bought. (Ideally, the submissions should be coordinated, so they can be processed at the same time.)

Change in Applicant Name/Address

Changes to an applicant's name in the absence of a change of ownership are rare. However, if such changes do occur or if the address of record changes, they would not be expected to have an adverse impact on product identity, purity, safety, efficacy, or quality. As such, applicants can notify FDA of these changes via the MA annual report. See the NDA/ANDA and BLA annual report regulations at 21 CFR 314.70(d), 314.81(b)(2), and 601.12(d) for the applicable content/format requirements for an MA annual report. As noted, detailed information about the content and format requirements for MA annual reports is provided elsewhere in this book.

Note: Changes to an applicant's name or address would likely provoke changes to the labeling. The regulatory requirements for postapproval labeling changes are addressed elsewhere in this book. Changes to an applicant's name or address should also prompt notification of the change to FDA's drug registration and listing system, in accordance with Section 521 of the FD&C Act, as well as 21 CFR Part 207.

Change in Drug Master File (DMF) Holder[6]

If circumstances prompt a change in the holder of a DMF, the current holder should notify FDA (along with the people authorized to reference the DMF) in writing. This notification should include:

- Name of transferee
- Address of transferee
- Name of responsible official of transferee
- Effective date of transfer
- Signature of the transferring official
- Typewritten name and title of the transferring official

The new holder should submit a letter of acceptance of the transfer and an update of the information contained in the DMF, where appropriate. This submission also should include a description of any changes relating to the new ownership (e.g., plant location and methods). The new DMF holder shall issue an updated letter of access to the MAH.

Administrative Changes Impacting Multiple MAs

It is not uncommon for an administrative change to impact multiple MAs. For example, in the event of a corporate merger or acquisition, there would likely be multiple products with revised labeling (i.e., to reflect the new corporate branding and company name) described in subsequent annual reports as a result. FDA has processes and recommendations that describe how applicants are to notify FDA of grouped product quality changes.[7] In essence, these processes and recommendations also can be applied to grouped administrative changes, i.e., submissions should clearly describe the change and cross-reference all related submissions to other MAs. Consider contacting the appropriate review division for situation-specific advice before submitting any grouped set of administrative changes.

Other Administrative Changes

MA Withdrawal—Applicant-Initiated

If an applicant elects to withdraw one or more of its MAs voluntarily, usually in cases where marketing of the associated product(s) has been permanently discontinued (e.g., for commercial reasons) but sometimes in response to an FDA request or in anticipation of an adverse regulatory action, this process can be initiated with correspondence to the relevant FDA review division. A correspondence requesting withdrawal of an MA is considered to have been submitted voluntarily, and the applicant waives its right to a hearing.

- As noted in 21 CFR 314.150(c),[8] FDA will withdraw approval of an NDA or ANDA at the applicant's request because the drug subject to the application or abbreviated application is no longer being marketed, provided none of the listed situations described in 21 CFR 314.150 (a) or (b) apply.
- Similarly, 21 CFR 601.5[9] provides for FDA to revoke a biologics license if the manufacturer gives notice of the intent to discontinue manufacture of all products manufactured under that license or to discontinue the manufacture of a particular product for which a license is held.

MA Withdrawal—FDA-Initiated

FDA-initiated withdrawals without the applicant's cooperation are relatively rare.

21 CFR 314.150(a), (b), and 21 CFR 314.151 describe the circumstances that can prompt FDA to propose withdrawal of an NDA or ANDA. Typically, FDA proposes this action in the face of significant, serious situations, such as a finding of imminent hazard to public health, a new serious safety problem that cannot be mitigated with labeling or other risk management tools, new information that indicates a lack of substantial evidence of effectiveness from adequate and well-controlled studies, or a finding that the NDA or ANDA contains an untrue statement of material fact. An applicant will be offered the opportunity for a public hearing to discuss the issues prompting the proposal for withdrawal before the withdrawal becomes effective.

The regulations at 21 CFR 601.5 are analogous to those at 21 CFR 314.150(a) and (b) and describe the circumstances under which FDA will initiate revocation of a BLA.

The regulations at 21 CFR 314.530 and 601.43 describes specific, expedited withdrawal procedures and criteria for new drugs and biologics, respectively, approved based on surrogate endpoints and/or with restrictions to ensure safe use (i.e., drugs or biologics approved under "accelerated approval"). Withdrawal under 21 CFR 314.530 or 601.43 is most likely to occur when confirmatory studies fail to demonstrate clinical benefit.

In accordance with 21 CFR 314.152 and 601.8, NDA, ANDA, and BLA withdrawals and revocations are published in the US *Federal Register.* See, for example, https://www.federalregister.gov/documents/2020/05/14/2020-10367/janssen-pharmaceuticals-inc-et-al-withdrawal-of-approval-of-16-new-drug-applications.

Conclusion

This chapter reviewed the applicable US regulations and guidances that address MA transfers and other administrative (i.e., non-scientific, clinical, or technical) postapproval changes. To ensure continued compliance with all applicable regulations after approval, US MA applicants must make timely notification to FDA of these administrative changes, as appropriate, consistent with these regulations and guidances. While the letter of these requirements varies from country to country, as will be seen throughout this book, certain principles apply regardless of the country or regulator, namely applicants' obligations to keep regulators aware of dossier content as it evolves after initial approval, regardless of how minor the change is perceived to be.

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All URLs were accessed on 9 May 2022.

Chapter 2: Argentina, Brazil, Canada, Chile, and Mexico

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Introduction

This chapter reviews the applicable regulatory requirements for marketing authorization (MA) transfers, renewals, and other administrative changes for each of the listed countries.

Argentina (Latin America)

National Administration of Medicines, Food, and Medical Devices (ANMAT)

ANMAT recognizes two categories of MAs: 1) drug product registration and 2) biological drug product registration. The drug product registration process is described in disposition 680/2013. ANMAT has implemented two regulations for biologic product registration, namely Regulation No. 7075/2011 (14 October 2011)[1] and Regulation No. 7729/2011 (14 November 2011).[2] Most of the requirements are aligned with the EU regulations for registration.[3]

Brazil

Agencia Nacional de Vigilancia Sanitaria (ANVISA)

Various ANVISA standards characterize the registration process for new drugs, branded generics, non-branded generics, and biological drug products, including the following:

- The ANVISA standard, RDC No. 200/2017 innovative drug products, provides the registration of new, generic, and similar drug products.
- The ANVISA standard, RDC No. 55/2010, provides for the registration of biological products.
- The ANVISA standard, RDC No. 49/2011, covers postapproval changes.

Canada

Health Canada (Therapeutic Products Directorate [TPD])

The TPD recognizes three broad categories of MAs, i.e., new drug application (NDS), the abbreviated new drug submission (ANDS), and generic applications. The regulations governing generic applications are covered in Food and Drug Regulations Section C.08.002.1.[4]

The Centre for Biologics Evaluation (CBE) is responsible for the regulatory and scientific evaluation of vaccines, allergenic extracts, albumins, immunoglobulins, coagulation factors and their inhibitors from human plasma or from