Version 4.1 of the AMCP Format: Introducing a Trio of Dossiers to Support a Product Throughout its Lifecycle

Introduction

On December 23, 2019, the Academy of Managed Care Pharmacy (AMCP) released **Version 4.1 of the AMCP Format for Formulary Submissions**.[1] This new version of the AMCP Format describes three types of dossiers that manufacturers may choose to develop:

1. Unapproved Product Dossiers,
2. Approved Product Dossiers, and
3. Unapproved Use Dossiers.[2]

Dossier Types

UNAPPROVED PRODUCT DOSSIERS provide information about a product that is not currently approved by the United States (US) Food and Drug Administration (FDA).[2] Manufacturers may use these dossiers to provide information about a product to healthcare decision makers (HCDMs) prior to FDA approval.[2]

APPROVED PRODUCT DOSSIERS present information about a product that has been approved by the FDA.[2] Manufacturers may use these dossiers to reactively provide information about a product to HCDMs in response to an unsolicited request after FDA approval.[2]

UNAPPROVED USE DOSSIERS contain information about a product that is currently approved by the FDA.[1] However, this information focuses on a currently unapproved indication of the approved product.[1] Manufacturers may use these dossiers to inform HCDMs about an unapproved use of an approved product prior to FDA approval of the unapproved use.[2]

While developing Version 4.1 of the AMCP Format, the AMCP Format Executive Committee decided to focus their updated recommendations on Unapproved Product Dossiers and Unapproved Use Dossiers, and made minimal changes to the section on Approved Product Dossiers.[2] Therefore, a piece of good news for manufacturers is that converting an existing Post-Approval Dossier that follows Version 4.0 of the AMCP Format into an Approved Product Dossier that follows Version 4.1 of the AMCP Format is a straightforward process.

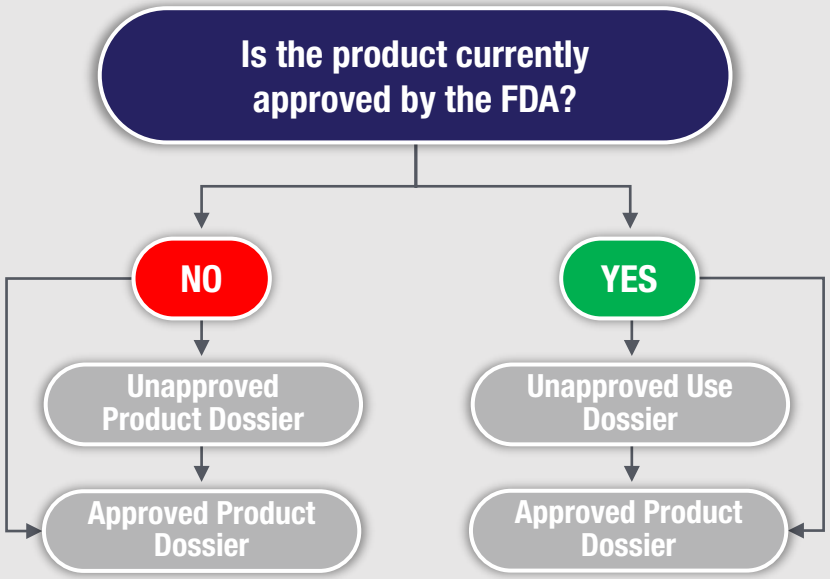
Why Develop an Unapproved Product Dossier or Unapproved Use Dossier?

Even though manufacturers are not required to develop Unapproved Product Dossiers or Unapproved Use Dossiers,[2] they can be very useful tools and may be helpful if:

- The manufacturer is **entering a new field** and is not familiar with the disease and/or its key treatments.
- The manufacturer wants to start work on an AMCP dossier for internal needs, but feels that it is **too early to start work on an Approved Product Dossier**.
- The manufacturer wants to understand how the **available literature supports** their early, and often aspirational, **value story** and what evidence gaps exist.
- The product will have an **orphan or fast-track designation**
- The product is **not being launched outside of the US**, and therefore there is **no global value dossier**.
- The clinical development plan for a product includes **multiple indications or disease populations**.
- The manufacturer wants to **share information with HCDMs prior to FDA approval** of the unapproved product or the unapproved use.

> *HCDMs need and are interested in receiving information from manufacturers about unapproved products and about unapproved uses of approved products for which FDA approval is being sought.*[2]
>
> Version 4.1 of the AMCP Format for Formulary Submissions

Figure 1. Dossier Types That Can Be Developed Based on a Product's Approval Status



An Important Question

When deciding which new dossier type(s) to develop, it is important to ask whether the product of interest is currently approved by the FDA.

- If the product is not currently approved by the FDA, the manufacturer may develop an Unapproved Product Dossier and/or an Approved Product Dossier (See Figure 1). The manufacturer is not obligated to develop an Unapproved Product Dossier prior to developing an Approved Product Dossier.[2]
- If the product is currently approved by the FDA, the manufacturer may develop an Unapproved Use Dossier and/or an Approved Product Dossier (See Figure 1). There is no requirement for a manufacturer to develop both an Unapproved Use Dossier and an Approved Product Dossier.[2]

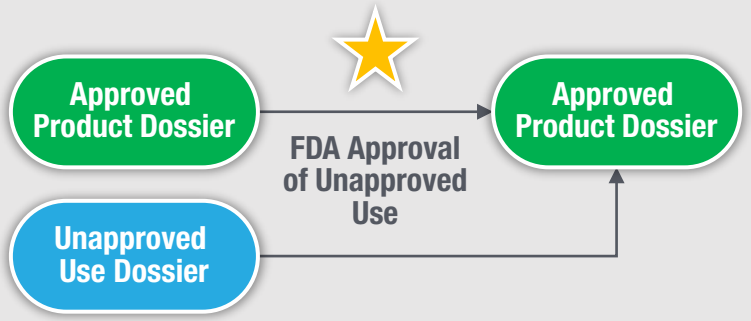
Unapproved Product Dossiers and Unapproved Use Dossiers

As shown in Figure 2, an Unapproved Product Dossier should be converted into an Approved Product Dossier when the unapproved product receives approval from the FDA. An Unapproved Product Dossier and an Approved Product Dossier for the same product never exist simultaneously; a product is either approved by the FDA or it is not.[2]

In contrast, an Unapproved Use Dossier and an Approved Product Dossier may exist simultaneously; this depends upon the product and the goals of the manufacturer (See Figure 3). However, the information in the Unapproved Use Dossier should be incorporated into the existing Approved Product Dossier after FDA approval. Alternatively, an Unapproved Use Dossier could become its own Approved Product Dossier, and the manufacturer could ultimately have multiple Approved Product Dossiers for a single product.[2]

Figure 2. Unapproved Product Dossier Flow Chart

Figure 3. Unapproved Use Dossier Flow Chart



Per Version 4.1 of the AMCP Format, Unapproved Product Dossiers and Unapproved Use Dossiers should contain the same four main sections.[2]

SECTION 1: HIGHLIGHTS AND OVERVIEW

Consists primarily of a table and outlines some of the important general information about a product, such as its name, expected approval date, clinical trials, and expected indication.[2]

SECTION 2: PRODUCT INFORMATION AND DISEASE DESCRIPTION

Includes general information about the unapproved product, such as its mechanism of action, the patient population being examined, projections related to patient utilization, and patient support programs. It also describes the disease, including information on epidemiology, clinical presentation, and disease burden.[2]

SECTION 3: CLINICAL EVIDENCE

Discusses the clinical trial program that supports the unapproved product or unapproved use of interest. Information that may be included in this section includes publicly available information describing the design, patient population, and results of the studies.[2]

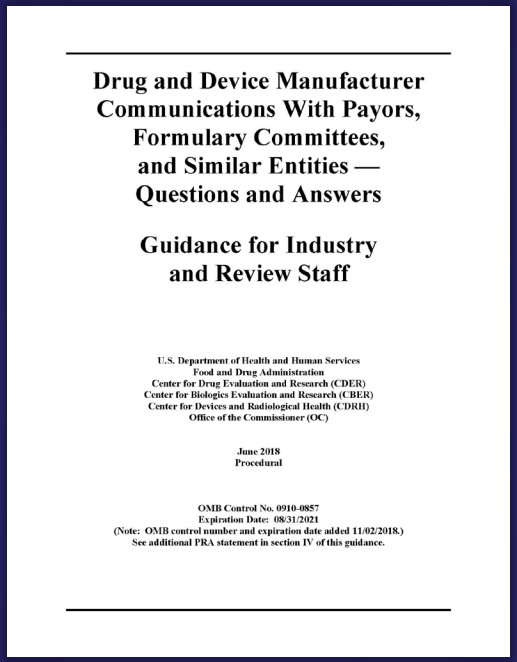
SECTION 4: ECONOMIC INFORMATION

For Unapproved Product Dossiers, the intent of this section is to provide HCDMs with information on pricing before FDA approval so that they can plan for future reimbursement decisions in a more informed manner. For Unapproved Use Dossiers, this section should include the known price of the approved product.[2]

Relationship to FDA Guidance

Version 4.1 of the AMCP Format was created in response to the **Final FDA Guidance on Drug and Device Manufacturer Communications With Payors, Formulary Committees, and Similar Entities** that was published in June 2018[2-4]. In fact, in the sections of the AMCP Format that describe Unapproved Product Dossiers and Unapproved Use Dossiers, the AMCP Format specifies which sections of the dossiers arise from the aforementioned FDA Guidance and which ones are AMCP Format recommendations.[2]

While the FDA Guidance does not specifically mention unmet need, treatment guidelines, or economic models, it does mention information on product pricing and the manufacturer's ability to provide a "factual presentation of results" related to both placebo and active controls included in trials examining the unapproved product or unapproved use of interest.[3] The FDA Guidance also provides some useful examples that highlight some of the differences between providing a "factual presentation of results" from a clinical trial and making a characterization or conclusion about the safety or effectiveness of an unapproved product or an unapproved use.[3]



Drug and Device Manufacturer Communications With Payors, Formulary Committees, and Similar Entities — Questions and Answers

Guidance for Industry and Review Staff

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Devices and Radiological Health (CDRH)
Office of the Commissioner (OC)

June 2018
Procedural

OMB Control No. 0910-0857
Expiration Date: 08/31/2021
(Note: OMB control number and expiration date added 11/02/2018.)
See additional PRA statement in section IV of this guidance.

Other Considerations for Manufacturers

TIME NEEDED FOR REVIEW AND APPROVAL

Information in these dossiers is often desired by HCDMs 6 to 24 months prior to FDA approval.[2]

WHEN TO UPDATE THE DOSSIER

If the initial version of an Unapproved Product Dossier or an Unapproved Use Dossier is completed far ahead of FDA approval, it may be valuable to update the dossier again prior to approval if data from an ongoing clinical trial are published, there is a change in the FDA review time, or information on patient support programs becomes available.

We recommend that manufacturers review the options offered by Version 4.1 of the AMCP Format and consider which type of dossier will best meet their needs. Developing an Unapproved Product Dossier or Unapproved Use Dossier not only provides the manufacturer with an opportunity to prepare for the launch of new products and new indications, but also helps HCDMs plan for future FDA approvals.

Unapproved Product Dossiers and Unapproved Use Dossiers: Lessons Learned in 2020

Below we present some of the key lessons learned from our experiences working on Unapproved Product Dossiers and Unapproved Use Dossiers during 2020.

FLEXIBILITY IN DOSSIER TERMINOLOGY

MANUFACTURERS PREFER INCLUDING ONLY PUBLICLY AVAILABLE INFORMATION

TREATMENT GUIDELINES ARE IMPORTANT

LEAVE TIME FOR DOSSIER REVIEW AND APPROVAL

Flexibility in Dossier Terminology

Some manufacturers have decided not to use the terms "Unapproved Product Dossier" and "Unapproved Use Dossier." Instead, they have chosen to go with terminology such as "Pre-Launch Dossier" or "Pre-Approval Dossier." Given the flexibility of the AMCP Format, this is fine as long as the definitions of these terms are clear in the dossier since, for example, the term "Pre-Approval Dossier" could technically refer to either a product or an indication. Similarly, some manufacturers have replaced the term "Unapproved Product" with either "Investigational Indication" or "Indication Being Sought." Again, manufacturer verbiage preferences are fine as long as it is clear whether the product

1. Has never been approved by the FDA, or
2. Has been approved by the FDA for other indication(s) but is not yet approved for the use discussed in the dossier.

Manufacturers Prefer Including Only Publicly Available Information

The majority of manufacturers have decided to limit the information presented in these dossiers to information that is publicly available, though data on file may be included in Unapproved Product Dossiers and Unapproved Use Dossiers. This is not a surprise, but it does serve as a reminder as to how many publicly available sources of information there are beyond published manuscripts. Indeed, information from ClinicalTrials.gov; press releases; study protocols; and conference abstracts, posters, and oral presentations have all found their way into Unapproved Product Dossiers and Unapproved Use Dossiers during 2020.

Treatment Guidelines are Important

Despite the fact that including information on treatment guidelines in Unapproved Product Dossiers and Unapproved Use Dossiers is not specifically mentioned in Version 4.1 of the AMCP Format, such information may be included at the manufacturer's discretion as long as it is presented in a factual and unbiased manner. Discussions about whether or not to include information on treatment guidelines and where to place it have resulted in most manufacturers deciding to include this information in Section 2 (Product Information and Disease Description). This approach makes sense since a summary of treatment guidelines is also included in Section 2 in Approved Product Dossiers. An alternative approach is to add a Section 5 (Additional Supporting Evidence) as a way to include treatment guidelines. Unapproved Product Dossiers and Unapproved Use Dossiers do not require the addition of a Section 5; however, it is part of the guidance for Approved Product Dossiers. Therefore, adding a Section 5 to house the treatment guidelines makes sense and is acceptable since manufacturers have the final say on how they communicate and present information in Unapproved Product Dossiers and Unapproved Use Dossiers.

Leave Time for Dossier Review and Approval

Due to a high level of scrutiny from medical, legal, and regulatory review teams, Unapproved Product Dossiers and Unapproved Use Dossiers have required unexpected rounds of review prior to approval. Some of this seems to be due to the fact that the information in these dossiers will be shared with payers prior to product approval. In other cases, the publication or release of important new data has necessitated updates to the dossier. Finally, there have also been times when a lack of experience with Version 4.1 of the AMCP Format has led manufactures to verify exactly what can and cannot be included in these types of dossiers. Review times have varied, but our recommendation is that a protracted review period should be a consideration when planning for an Unapproved Product Dossier or Unapproved Use Dossier to ensure the dossier will be reviewed and ready for distribution at least six months prior to the expected product approval. A planning meeting to discuss when to "lock" the dossier and no longer add new information can help ensure that the dossier can be finalized and released in a timely fashion.

Conclusion

Version 4.1 of the AMCP Format provides manufactures with guidance on generating a trio of dossiers that can help support a product throughout its lifecycle.[2] Even though manufacturers are not required to develop Unapproved Product Dossiers or Unapproved Use Dossiers, they can be useful tools for facilitating communications with HCDMs. We recommend that manufacturers review the options offered by Version 4.1 of the AMCP Format and consider which type of dossier will best meet their needs. Developing an Unapproved Product Dossier or Unapproved Use Dossier not only provides the manufacturer with an opportunity to prepare for the launch of new products and new indications, but also helps HCDMs plan for future FDA approvals.

Helpful References

Please visit the references listed below to further educate yourself on related AMCP and FDA frameworks and guidances:

1. AMCP. AMCP Format for Formulary Submissions – Guidance on Submission of Pre-approval and Post-approval Clinical and Economic Information and Evidence, Version 4.1. December 23, 2019. Available at: https://www.amcp.org/Resource-Center/format-formulary-submissions/AMCP-Format-for-Formulary-Submissions-4.1. Accessed January 29, 2020.

2. AMCP. The AMCP Format for formulary submissions (version 4.1). Guidance on Submission of Pre-approval and Post-approval Clinical and Economic Information and Evidence. December 23, 2019. Available at: https://www.amcp.org/sites/default/files/2019-12/AMCP_Format%204.1_1219_final.pdf. Accessed December 26, 2019.

3. FDA. Drug and Device Manufacturer Communications With Payors, Formulary Committees, and Similar Entities — Questions and Answers Guidance for Industry and Review Staff. June 2018. Available at: https://www.fda.gov/media/102683/download. Accessed January 29, 2020.

4. AMCP. AMCP Format v4.1: New Guidance on Evidence Requirements for Unapproved Products and Unapproved Uses. January 23, 2020. Available at: https://www.amcp.org/Resource-Center/formulary-utilization-management/amcp-format-v41-new-guidance-evidence-requirements. Accessed January 29, 2020.

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