THE AMCP FORMAT FOR FORMULARY SUBMISSIONS

VERSION 4.1

Guidance on Submission of Post-approval and Pre-approval Clinical and Economic Information and Evidence

Select Provisions for Public Comment

Intended for Release in 2019

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Please provide feedback on whether the role of the Format is accurately conveyed based on current Food and Drug Administration guidance and the current state of communications between manufacturers and payers.

**THE ROLE OF THE AMCP FORMAT**

The evidence requirements and guidelines outlined in the AMCP Format are intended for use by manufacturers to provide clinical and economic evidence and information to HCDMs and which are consistent and aligned with current legal, regulatory, and compliance requirements. These communications are designed to provide evidence and information to support coverage, reimbursement, formulary placement, and to develop utilization strategies for new and existing pharmaceuticals, tests, or medical devices.

The Format supports the informed selection of pharmaceuticals, tests, and devices by:

- Identifying the evidence required for evaluating the clinical and economic value of pharmaceutical products, companion diagnostic tests, and devices.
- Standardizing the synthesis and organization of the evidence in a concise document also known as an “AMCP dossier” or “product dossier” used to communicate pre-approval information, post-approval information, or information about new indications of existing products under consideration.
- Providing manufacturers with the opportunity to communicate the value of a product that is grounded in evidence-based medicine principles.
- Supporting the current legal, regulatory, and compliance framework that manufacturers must follow to provide evidence and information to HCDMs.
- Including economic models and projections of product impact on the organization and its enrolled population.
- Encouraging a clear and transparent, bi-directional communications and sharing process between manufacturers and HCDMs.

The AMCP Format is designed to encourage sharing of objective and credible information on pharmaceuticals, tests, and medical devices. Specifically, the Format seeks to meet two important goals:

- Improve the timeliness, scope, quality, and relevance of clinical evidence and economic information provided by manufacturers to HCDMs. This evidence may improve the HCDM’s ability to compare the effects of formulary alternatives on clinical outcomes, value, and economic consequences for the entire health care system.
- Streamline the evidence acquisition and review process for HCDMs. By clearly specifying the standards of evidence implicit in the existing formulary process, the Format furnishes manufacturers with consistent direction concerning the nature and presentation of information expected. In addition, the standardized presentation allows HCDMs to formally evaluate the completeness of submissions received and to easily add the results of their own systematic literature reviews and analysis.

Submission of information by manufacturers to HCDMs according to Format does not guarantee approval of products for formulary listing or product selection. Manufacturers and HCDMs should view discussions about evidence and information in dossiers as a process to improve the quality and layout of information provided, but not as a formula for approval. The Format offers a clear, shared vision of the requirements to facilitate the bi-directional communication necessary between HCDMs and manufacturers to support appropriate and evidence-based product evaluation. The Format also describes
the information requirements necessary to support a comprehensive assessment of a proposed product, test or medical device.

AMCP developed the *Format* as a template or and guidance that has become among the most widely recognized standard in requesting and receiving clinical and economic evidence from manufacturers for evaluating the value of pharmaceutical products, tests, and medical devices. Individual HCDMs make determinations about the use of the information in dossiers for the formulary review process and other population health care decision-making. AMCP encourages manufacturers to develop dossiers according to the *Format* and for HCDMs to request product dossiers in the AMCP *Format*. The aim of the *Format* is to provide comprehensive evidence and information requirements that meet the evidence needs of HCDM. AMCP recognizes that while other organizations may release formats, guidelines, and value frameworks, it regards the adoption and use of *Format* as a best practice for the formulary review process by individual organizations.

In some areas, the *Format* provides examples of methods for assessing clinical benefit and economic impact tables for consideration, but these are meant to provide general guidance and not intended to limit the type of assessments used. Information and evidence presented about clinical benefit, harms, or economic impact, should meet current accepted standards of evidence-based medicine and health technology assessment. It is the manufacturer’s responsibility to utilize appropriate study designs, analytic techniques, and data sources. Likewise, it is the HCDM’s responsibility to critically evaluate the evidence supplied according to currently accepted and published approaches to Pharmacy and Therapeutics (P&T) Committee processes and formulary decision-making reported in the literature.5-7
AMCP has updated definitions upon new FDA guidance. This section also outlines the communication process between manufacturers and HCDMs. Do these definitions properly convey the current state of communications based upon the FDA guidance? In particular, please provide feedback on whether Table 1 is helpful in conveying requirements in a concise manner. In addition, are the terms pre-approval information dossier, post-approval dossier and new indication dossier helpful in being able to convey this information?

**GENERAL DEFINITIONS AND CONSIDERATIONS**

This section provides the key terms used throughout this document that are directly relevant to creation of dossiers based on the *Format*. Appendix A also includes additional terms used in the document.

**DOSSIER**

A detailed report for products submitted by a manufacturer to HCDMs for consideration related to formulary coverage and other population-health decision making that contains (1) clinical and economic data from published and unpublished studies and (2) a disease-based economic model to project the potential impact that introducing the product would have on health and economic consequences occurring across the entire system. Dossiers may contain information and data for products and indications under consideration by FDA (pre-approval) and for products that have been approved by FDA (post-approval). Creation and submission of dossiers by manufacturers must comply with all current FDA laws, regulations, and guidance related to communication of such information.

**HEALTH CARE DECISION MAKERS (HCDMS) AND MANUFACTURERS**

The term “health care decision maker” (HCDM) is used throughout this document to refer to ANY health care personnel, committee, or organization that uses an evidence-based process for making health care coverage and reimbursement decisions for patient populations, including, but not limited to payers, health plans, integrated delivery systems, pharmacy benefit management companies, specialty pharmacies, health insurance companies, medical groups, hospitals, hospital systems, (P&T) Committees, health technology assessment (HTA) organizations, clinical practice guideline bodies, and other organized health care systems that make or influence population-based health care decisions.

- Furthermore, the 2018 final FDA guidance defined “payor” (spelled payer in the *Format*) collectively as “a payor, formulary committee, or other similar entity with knowledge and expertise in the area of health care economic analysis, carrying out its responsibilities for the selection of drugs for coverage or reimbursement… or …public and private sector payors, formulary committees (e.g., P&T committee), drug information centers, technology assessment committees, pharmacy benefit managers, third party administrators, and other multidisciplinary entities that, on behalf of health care organizations, review scientific and/or technology assessments to make drug or device selection or acquisition, formulary management, and/or coverage and reimbursement decisions on a population basis.”

Given this definition, eligible recipients of pre-approval and post-approval dossiers created according the AMCP *Format* include HCDMs, payers, and any entity that makes or influences formulary, coverage, policy, and reimbursement decisions. Neither the FDA final guidance nor the *Format* applies to other audiences, such as healthcare providers who are making individual patient prescribing decisions or consumers (including patients and caregivers).

The term “manufacturer” is used throughout this document to refer to ANY company that develops, manufactures, or markets drugs (brand, generic, biologics, biosimilars, vaccines), tests (companion diagnostic tests), or related medical devices (e.g., syringes, glucometer, wearable technology, digital applications/apps, etc.).
PRODUCT

The term product used throughout includes pharmaceuticals, test, or medical devices. The Format was originally developed to address evidence for pharmaceutical products (pharmaceuticals, biologics, and vaccines), however, today, the Format aims to also provide guidance for developing dossiers for non-pharmaceutical products (e.g., tests and devices) that may be relevant to formulary and medical policy decisions.

COMMUNICATIONS BETWEEN HCDMS AND MANUFACTURERS

Communications between HCDMs and manufacturers are strictly regulated by the FDA. In addition, the FDAMA of 1997, Section 114 allows proactive, solicited communications by drug manufacturers about health care economic information (HCEI) to a limited audience of “formulary committees and similar entities”. In 2016, the 21st Century Cures Act (Pub. L 114-255) Section 3037 expands and modernizes FDAMA Section 114 relating to communication of HCEI. In June 2018, the FDA published the final guidance named Drug and Device Manufacturer Communications with Payors, Formulary Committees, and Similar Entities (“FDA Final Guidance”) which clarifies common questions regarding manufacturers’ communication of HCEI regarding drugs and devices to payers, formulary committees, or other similar entities. HCEI as defined by FDAMA Section 114 and further clarified by 21st Century Cures and the FDA Final Guidance is intended for proactive communication of competent and reliable scientific evidence. In reviewing the FDA Final Guidance, AMCP considered the potential impact on economic evidence that is presented in an FDA-approved product dossier based on the AMCP Format and added additional suggestions to Section 4 on economic value for such dossiers.

While the FDA Final Guidance does not impact or change manufacturers’ communication of post-approval information based on an unsolicited request, it has established drug and device manufacturers’ ability to provide proactive communications about unapproved products and unapproved uses of approved products. Thus, a second and separate topic covered by the June 2018 FDA Final Guidance describes the FDA’s current thinking on manufacturer’s communications to payers about unapproved drugs/devices (unapproved products) and about unapproved uses of approved/cleared products (unapproved indication) and is a key focus area for the Format updates from Version 4.0 to 4.1. As such, Format 4.1 includes guidance on the development and communication of pre-approval dossiers that can be communicated in a proactive fashion to appropriate audiences (payers, formulary committees, or similar entities) by appropriate manufacturer personnel who have the appropriate medical, scientific, and clinical training, credentials, and expertise. Format 4.1 is intended to align with the FDA Final Guidance as well as provide helpful recommendations for best practices where the Final Guidance is silent.

In addition to proactive, solicited communications, the FDA also allows manufacturers to reactively respond to unsolicited requests for information from HCDMs. The unsolicited request process has historically been used for the communication and provision of FDA-approved (post-approval) dossiers developed according to the AMCP Format. This unsolicited process continues to be the mechanism through which the traditional post-approval product dossiers be communicated and provided to HCDMs.

POST-APPROVAL AND PRE-APPROVAL DOSSIERS

Based on input from the Format Executive Committee and comments received by stakeholders, AMCP determined that proper definitions and terminology must be established and used to avoid confusion between 1) pre-approval product dossiers, 2) post-approval product dossiers, and 3) unapproved indication dossiers. Table 1 below summarizes key elements of each type of dossiers. Readers should refer to the more detailed information about each type within this document. While these distinctions are made among the types of dossiers, communications between manufacturers and HCDMs should be considered a continuous and evolving process from pre-approval to post-approval and new indications.
Table 1. High-Level Comparison of Dossiers for Pre-approval Products, Post-approval Products, and Unapproved Indications

<table>
<thead>
<tr>
<th>What is it?</th>
<th>Pre-approval Information Dossier</th>
<th>Post-approval Product Dossier</th>
<th>Unapproved Indication Dossier</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A document containing as much clinical and economic information as feasible at the time of communication about an unapproved product</td>
<td>Comprehensive document containing clinical and economic information about an FDA-approved product</td>
<td>A document containing as much clinical and economic information as feasible at the time of communication about an unapproved indication or use of an FDA-approved product</td>
</tr>
<tr>
<td>Why do HCDMs need dossier?</td>
<td>To plan and budget for future coverage and/or reimbursement decisions prior to the product’s FDA approval</td>
<td>To evaluate an FDA-approved product for formulary, policy, coverage, or reimbursement decisions</td>
<td>To plan and budget for coverage and/or reimbursement decisions about an unapproved indication or use of an FDA-approved product prior to the indication’s FDA approval</td>
</tr>
<tr>
<td>How should manufacturers provide dossier?</td>
<td>Proactive communication Reactive communication permitted</td>
<td>Reactive communication upon an unsolicited request only</td>
<td>Proactive communication Reactive communication permitted</td>
</tr>
<tr>
<td>Who from the manufacturer should communicate or provide dossier?</td>
<td>Personnel with appropriate medical/clinical/scientific credentials, expertise, and responsibilities</td>
<td>Personnel with appropriate medical/clinical/scientific credentials, expertise, and responsibilities</td>
<td>Personnel with appropriate medical/clinical/scientific credentials, expertise, and responsibilities</td>
</tr>
<tr>
<td>Who can receive dossier?</td>
<td>HCDMs, payers, and entities that make or influence formulary, coverage, policy, and reimbursement decisions</td>
<td>HCDMs, payers, and entities that make or influence formulary, coverage, policy, and reimbursement decisions</td>
<td>HCDMs, payers, and entities that make or influence formulary, coverage, policy, and reimbursement decisions</td>
</tr>
<tr>
<td>What clinical content about the product should be in the dossier?</td>
<td>Factual presentation of clinical evidence for unapproved product that is available at the time of communication</td>
<td>Published and unpublished clinical evidence regarding on-label and off-label uses</td>
<td>Factual presentation of clinical evidence for unapproved use that is available at the time of communication</td>
</tr>
<tr>
<td>What economic content about the product should be in the dossier?</td>
<td>Anticipated product price; anticipated budget impact</td>
<td>Health economic and outcomes research; economic models</td>
<td>Anticipated budget impact</td>
</tr>
<tr>
<td>Other Common and Acceptable Terminology</td>
<td>Pre-approval Dossier Pipeline Dossier</td>
<td>Post-approval Dossier Product Dossier AMCP Dossier</td>
<td>New Indication Dossier</td>
</tr>
</tbody>
</table>
Post-Approval Product Dossiers

Post-approval product dossiers consistent with the AMCP Format have historically been provided under the unsolicited request process by manufacturers because the Format calls for information that goes beyond the product’s FDA-approved label.

In December 2011, the FDA issued a draft guidance called "Guidance for Industry: Responding to Unsolicited Requests for Off-Label Information About Prescription Drugs and Medical Devices" which outlines the FDA’s current thinking the manner in which manufacturers of pharmaceutical products and medical devices can respond to unsolicited requests for information about products. Manufacturers should follow this FDA guidance for the provision of post-approval dossiers in response to an unsolicited request.

To qualify as an unsolicited request, the request for information must be truly unsolicited. Specifically, the inquiry must be initiated by the requester (formulated in his/her own mind) without prompting, suggestion or solicitation by the manufacturer or its employees. Manufacturers should place a statement on the dossier that it is being provided in response to an unsolicited request.

Given the complex regulatory and legal environment, manufacturers should consider and establish their own acceptable rules or policies and procedures on handling unsolicited requests for dossiers. For example, consider policies and procedures to address: 1) What specifically constitutes a request for a dossier versus request for other medical information; 2) How to fulfill requests for dossiers that have multiple indications, or products for which a manufacturer has more than one dossier; and 3) How to handle requests for future updates to dossiers (also see section on Updating Dossiers).

Substantial on-going communication between the HCDM and manufacturer throughout the product evaluation process is critical to manage expectations and maximize the quality of available evidence. When a dossier is requested from a HCDM, it is important for that organization to communicate to the manufacturer basic information such as review timelines, the evaluation process, and any special needs that might exist. This allows the manufacturer an opportunity to provide timely, relevant, and specific information that meets the needs of the HCDM. If the manufacturer cannot provide specific information, it is better to understand the limitations up front. Early, ongoing dialogue between the HCDM and manufacturer is a critical success factor in optimizing the exchange of relevant, credible and timely clinical and economic evidence for decision making. HCDMs should consider requesting a presentation from or discussion with appropriate manufacturer personnel (e.g., medical personnel, health economists) on specific questions that they may have about the dossier.

Dossiers have often been criticized by HCDMs about being ‘biased’. Therefore, HCDMs should share concerns or questions about the evidence presented in a dossier, including assumptions related to economic models, to facilitate a productive dialogue with manufacturers. Feedback from dossier users can help improve the quality of dossiers developed and provided by manufacturers. Feedback includes dossier completeness, objectiveness, usability, readability, and other user experience of the document, NOT feedback about formulary review status or approval.

Pre-Approval Information Dossiers

It is common for HCDMs to request a dossier well before FDA approval, generally 6 to 12 months in advance. HCDMs need such information to plan and budget for coverage and reimbursement of products and drug classes well in advance of FDA approval. Historically, it has been challenging for HCDMs to obtain and manufacturers to communicate such information.

In April 2016 AMCP, in collaboration with other stakeholders first outlined guidance for manufacturers’ provision of information prior to FDA approval under the section Dossier Information Before FDA Approval in Version 4.0 of the AMCP Format. Due to regulatory and compliance constraints, manufacturers had been limited in what they could proactively communicate before FDA approval. As such, the guidance in Version 4.0 is primarily based on manufacturers responding to unsolicited requests for pre-approval information from HCDMs. Now, with the Format Version 4.1 aligned with the FDA Final Guidance (Section III.C) published in June 2018, pre-approval information dossiers may be
developed and communicated proactively by manufacturers to eligible HCDMs before anticipated FDA approval. The FDA guidance contains the following examples of information that may be shared:

- Product information (e.g., drug class, device description and features).
- Information about the indication(s) sought, such as information from the clinical study protocol(s) about endpoint(s) being studied and the patient population under investigation (e.g., number of subjects enrolled, subject enrollment criteria, subject demographics).
- Anticipated timeline for possible FDA approval/clearance/licensure of the product or of the new use.
- Product pricing information.
- Patient utilization projections (e.g., epidemiological data projection on incidence and prevalence).
- Product-related programs or services (e.g., patient support programs).
- Factual presentations of results from studies, including clinical studies of drugs or devices or bench tests that describe device performance (i.e., no characterizations or conclusions should be made regarding the safety or effectiveness of the unapproved product or the unapproved use).

The 2018 FDA Final Guidance further recommends that manufacturers provide the following information to HCDMs when communicating information about an unapproved product or about an unapproved use of an approved product:

- A clear, conspicuous statement that the product has not been approved by FDA, and that the safety or effectiveness of the product or use has not been established.
- Information related to the stage of product development, whether a marketing application has been submitted to the FDA.
- For communications that include factual presentations of results from studies, manufacturers should describe material aspects of study design and methodology and also disclose material limitations related to the study design, methodology, and results. Both positive and negative or null findings should be presented.
- For communications about unapproved uses of approved products, manufacturers should include a prominent statement disclosing the indication(s) for which FDA has approved the product and a copy of the most current FDA-required labeling.

FDA notes that for the provision of pre-approval information in accordance with the FDA Final Guidance, it does not intend to enforce postmarketing requirements for these materials. At the time of the release of Format 4.1, the allowance for dissemination of pre-approval information is limited to FDA’s final guidance and is not included in statute. AMCP and other stakeholders have been supportive of passing legislation to codify these provisions.

**Bi-Directional Communication of Information**

Eligible recipients of dossiers include HCDMs, payers, and any entity that makes or influences formulary, coverage, and/or reimbursement decisions on a population basis based on expertise or credentials. This guidance does not apply to other audiences, such as healthcare providers who are making individual patient prescribing decisions or consumers (including patients and caregivers).

Medically/scientifically/clinically trained and credentialed personnel with such technical responsibilities from manufacturers should be the individuals to communicate, provide, present, share, and discuss dossiers and content to HCDMs. Such personnel should have clinical or scientific degrees (PharmD, MD, PhD, etc.) and possess medical, scientific, or health economics and outcomes research (HEOR) roles and responsibilities within the company (not sales or marketing roles).

The information and evidence elements recommended in the Format are guidelines only. It is fully understood that certain elements may not be provided by manufacturers for a variety of reasons (e.g., timing, availability, regulatory, legal, compliance, confidentiality, manufacturer discretion, etc.) However, it is strongly recommended that information and evidence be updated and communicated throughout the development of the unapproved product or unapproved indication of an approved product until the time of FDA approval. Hence, one can view the pre-approval dossier as a living, evolving document that will
ultimately be updated and revised to become the post-approval dossier. Furthermore, HCDMs should provide feedback and insight on emerging evidence and information as well as content of the dossiers. This bi-directional communication process will help improve information-sharing and provide more complete product knowledge.

**AREA FOR COMMENT 3: UPDATING DOSSIERS**

Does this section properly convey information for updating dossiers?

**UPDATING POST-APPROVAL DOSSIERS**

A common question from manufacturers is, “When should a dossier be updated?” Dossiers should be reviewed and updated when there are significant changes, e.g., changes to the prescribing information, line extensions, new safety information, or any information that materially impacts the overall evidence. While most HCDMs request dossiers for products when they are newly approved by the FDA, dossiers should be used beyond initial launches for subsequent product or class reviews. Ideally, dossier updates should be evidence-based, i.e., updates are triggered by availability of new evidence, for example:

- The manufacturer files a supplemental application to the FDA for a new indication; the regulatory decisions should be included in the dossier whether the new indication is approved or denied
- The FDA issues advisory statements about the use of a product, e.g. established a new boxed warning, etc.
- Significant new clinical or economic evidence becomes available, such as:
  - Further support the use of the product for the approved indication
  - Identify patients or sub-populations who should or should not receive the product
  - Demonstrate real world effectiveness and long-term effectiveness
  - Elucidate long-term safety.

When updating a dossier, the manufacturer should conduct a complete revision to incorporate new evidence, delete obsolete and less relevant information, and revise content and format to keep the dossier concise and relevant. The manufacturer may update the dossier by re-writing a new version of the dossier or amend the existing dossier with a supplemental document that acknowledges new evidence with proper citations, identifies obsolete information in the existing dossier, and describes any additional relevant information to the HCDM. The manufacturer should provide HCDMs with a way to identify newly added information (e.g., highlight revised/new sections or content, describe changes in an appendix, include a summary of changes in a cover letter, etc.).

When a manufacturer reviews a dossier for potential revision, and determines that a revision is not necessary, this should be indicated on the title page of the dossier. In the absence of new evidence, dossiers should be evaluated for technical accuracy on an annual basis, e.g., price increase, new model assumptions, etc. All dossiers should have the original date of issue as well as the dates of any revisions or reviews for potential revisions.

When a HCDM requests a dossier that is under revision, the manufacturer should supply the current (last completed) version of the dossier, inform the requestor of the status of the dossier and the expected timeframe for completion of the revision, and offer to send the revised version when completed. Alternatively, the manufacturer may only provide the updated version when completed.

Another common question from manufacturers, “Can an updated dossier be provided to HCDMs who had previously requested and received a dossier?” HCDMs may make an additional unsolicited request for a post-approval dossier. This information is based on discussions with FDA on previous versions of the Format.

A HCDM may, at the time of original dossier request, include a statement that he/she would like to receive updated dossiers, if any, subsequent to the first dossier received. The request for updated dossiers
must be for the same product as the original request, and the request must specify a specific length of
time, e.g., for 6 months, or at the discretion of the manufacturer’s policies. While the Format does not
specify a maximum length of time, the request for updated dossiers should not be indefinite and
manufacturers should determine their own policies and procedures. Allowance for this process will avoid
HCDMs from having to submit numerous requests for updated information, especially since they may not
be aware when updated dossiers may be available. Additionally, the explicitness of the unsolicited request
for an updated dossier within a specific time frame will help manufacturers maintain compliance to the
unsolicited request process. Whether to fulfill an unsolicited request for the dossier is at the discretion of
the manufacturer.

The manufacturer may determine that a dossier will no longer be kept current, e.g., the product is near the
end of its branded lifespan or lost exclusivity. If the manufacturer continues to provide the dossier to
requesters, then the status and currency of the dossier should be indicated on the dossier. If the
manufacturer discontinues the availability of the dossier, then a rationale for its discontinuation should be
provided to requesters of that dossier.

Development and organization of the dossier for a product with multiple FDA approved indications
should be handled at the discretion of the manufacturer. For example, a manufacturer may develop
separate sections for each indication within the same dossier or may develop separate dossiers for each
indication or group of indications.

It is at the manufacturer’s discretion whether updates are required for ANY sections of the dossier to
provide information that is concise, relevant, and objective.

**UPDATING PRE-APPROVAL DOSSIERS**

In its 2018 Final Guidance, FDA suggests “... that firms provide follow-up information to payors if
previously communicated information becomes materially outdated as a result of significant changes or as
a result of new information regarding the product (e.g., failure to meet the primary effectiveness endpoint
in the pivotal trial) or its review status (e.g., an application is determined to not be ready for approval
upon completion of the review cycle, a study is placed on a clinical hold).”

Manufacturers may use discretion on when to develop a pre-approval dossier as well as how often to
update the pre-approval dossier to ensure its usefulness to HCDMs. Certain timepoints or milestones may
be considered for triggering the development or update, such as initiation of Phase 3 trial(s), completion
of Phase 3 trial(s), application/submission for FDA approval, etc. There is no one, right approach. Each
manufacturer may use its own discretion as deemed appropriate yet aligns with the FDA Final Guidance
as described above.

Specifically, for unapproved indication dossiers, a post-approval dossier most likely exists for the
approved product. Because the unapproved indication dossier may be communicated proactively to
HCDMs while the post-approval dossier can only be provided upon an unsolicited request, there may
exist two dossiers for one approved dossier: 1) post-approvals dossier with comprehensive clinical and
economic information on on-label and off-label indications, and 2) unapproved indication dossier with
clinical and economic information primarily focused on the unapproved indication that is being studied
(and for which FDA approval is being sought).

**PAGE LIMITS**

The Format provides guidance regarding page limit recommendations for individual sections of a dossier.
These recommendations are for general guidance only, as there are many factors that may influence the
appropriate section length for a product. Manufacturers should present relevant evidence and product
information as concise and clear as possible to streamline the evidence acquisition and review process.
Specifically, manufacturers should NOT include overly verbose or superfluous content to meet page limit
recommendations.
SUBMISSION OF DOSSIER AND MODELS

Manufacturers should submit dossiers in an electronic format rather than in print. Electronic formats may include email, online platforms (e.g., AMCP eDossier System, manufacturer websites, etc.), or other electronic technologies. This will help reduce resource expenditures and improve health care system staff’s ability to transfer evidence directly into P&T committee submission monographs. This includes any economic model(s) provided in the dossier, which should be presented electronically as an Excel workbook or an alternative electronic format that is agreed upon by the requesting organization or its consultants and the manufacturer to facilitate ongoing dialogue as well as allow flexibility for user defined analyses.
Area for Comment 4: Evidence Requirements for Pre-Approval Information Dossier and Unapproved Indication Dossier

Please review this new section and determine whether it sufficiently explains evidence requirements for pre-approval information dossiers and unapproved indication dossiers.

Evidence Requirements for Pre-approval Information Dossier and Unapproved Indication Dossier

Section 1.0 – Highlights and Overview
Section 2.0 – Product Information and Disease Description
Section 3.0 – Clinical Evidence
Section 4.0 – Economic Information
Section 5.0 – Additional Supporting Evidence
Section 6.0 – Dossier Appendices
1.0 **HIGHLIGHTS AND OVERVIEW**

The recommended length of Section 1.0 is 1 page (maximum 3).

Consider a table format with a brief overview of studies and information.

This section provides an at-a-glance overview of the key information contained in a pre-approval dossier. Be brief. If information is not available or cannot be disclosed, indicate “NA”.

### 1.1 TABLE OF HIGHLIGHTS FOR UNAPPROVED PRODUCT

<table>
<thead>
<tr>
<th>Table Last Revision Date</th>
<th>List the dates of revisions to this table in reverse chronological order</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manufacturer Name</td>
<td>List name(s) of companies involved in developing and marketing unapproved product</td>
</tr>
<tr>
<td>Unapproved Product Name</td>
<td>List the name(s) of unapproved product (brand, generic, chemical, molecular, company-assigned name, research compound number)</td>
</tr>
<tr>
<td>Disease or Anticipated Indication</td>
<td>List the disease(s), indication(s), and target population(s) for which the unapproved product is being studied and/or FDA approval is being sought</td>
</tr>
<tr>
<td>Special FDA Designations</td>
<td>List special designations per FDA, e.g., fast-track, orphan, break-through, etc. and the date of designation; provide links to source information, e.g., FDA, press-release, etc.</td>
</tr>
<tr>
<td>NDA/BLA Submission Date</td>
<td>List the date of NDA/BLA submission to the FDA</td>
</tr>
<tr>
<td>FDA Advisory Committee Meeting</td>
<td>List the date of planned or anticipated FDA Advisory Committee meeting</td>
</tr>
<tr>
<td>PDUFA or FDA Approval Date</td>
<td>List the date or time frame (2023, Q1’22, etc) of anticipated FDA approval</td>
</tr>
<tr>
<td>Product Launch Data</td>
<td>List the date of anticipated product launch in the market</td>
</tr>
<tr>
<td>Approval Dates in Other Countries (ex-US)</td>
<td>List other countries and (anticipated) approval dates</td>
</tr>
<tr>
<td>Phase 3 Trials Completed</td>
<td>List the name or citation of trials and dates completed; provide links to clinicaltrials.gov or Pub Med</td>
</tr>
<tr>
<td>Phase 3 Trials in Progress</td>
<td>List the name or citation of trials with start and anticipated completion dates; provide links to clinicaltrials.gov or Pub Med</td>
</tr>
<tr>
<td>Phase 2 Trials Completed</td>
<td>List the name or citation of trials and dates completed; provide links to clinicaltrials.gov or Pub Med</td>
</tr>
<tr>
<td>Phase 2 Trials in Progress</td>
<td>List the name or citation of trials with start and anticipated completion dates; provide links to clinicaltrials.gov or Pub Med</td>
</tr>
<tr>
<td>Anticipated Route(s) of Product Administration</td>
<td>Describe the route(s) of administration for unapproved product that were used in clinical trials and anticipated to be approved by the FDA</td>
</tr>
<tr>
<td>Anticipated Location/Setting(s) for Product Administration</td>
<td>Describe the location or healthcare setting where product was administered in clinical trials and anticipated to be given when approved by the FDA</td>
</tr>
<tr>
<td>Prevalence of Condition Associated with Anticipated Indication in the US</td>
<td>Express results per 100,000</td>
</tr>
<tr>
<td>Annual Incidence of Condition Associated with Anticipated Indication in the US</td>
<td>Express results per 100,000</td>
</tr>
<tr>
<td>Anticipated Annual Cost per Patient</td>
<td>Indicate the anticipated annual cost per patient (AWP or WAC) of the product</td>
</tr>
<tr>
<td>-----------------------------------</td>
<td>--------------------------------------------------------------------------</td>
</tr>
<tr>
<td>[ ] ≥ $300,000</td>
<td></td>
</tr>
<tr>
<td>[ ] $100,000 to $299,999</td>
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<tr>
<td>[ ] $50,000 to $99,999</td>
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<tr>
<td>[ ] $10,000 to $49,999</td>
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</tr>
<tr>
<td>[ ] ≤$9,999</td>
<td></td>
</tr>
<tr>
<td>Alternatively, and in addition, indicate any other information about the anticipated costs of unapproved product</td>
<td></td>
</tr>
</tbody>
</table>

### 1.2 TABLE HIGHLIGHTS FOR UNAPPROVED USE OF AN APPROVED PRODUCT

<table>
<thead>
<tr>
<th>Table Last Revision</th>
<th>List the dates of revisions to this table in reverse chronological order</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manufacturer Name</td>
<td>List name(s) of companies involved in developing and marketing unapproved product</td>
</tr>
<tr>
<td>Approved Product Name</td>
<td>List the name(s) of unapproved product (brand, generic, chemical name)</td>
</tr>
<tr>
<td>Proposed Unapproved Use</td>
<td>List the disease(s), indication(s), and target population(s) for which the unapproved product is being studied and/or FDA approval is being sought</td>
</tr>
<tr>
<td>Approved Use and Indication</td>
<td>List the approved use(s) and indication(s) for the approved product</td>
</tr>
<tr>
<td>Special FDA Designations</td>
<td>List special designations per FDA, e.g., fast-track, orphan, break-through, etc. and the date of designation; provide links to source information, e.g., FDA, press-release, etc.</td>
</tr>
<tr>
<td>sNDA/sBLA Submission Date</td>
<td>List the date of sNDA/sBLA submission to the FDA</td>
</tr>
<tr>
<td>FDA Advisory Committee Meeting</td>
<td>List the date of planned or anticipated FDA Advisory Committee meeting</td>
</tr>
<tr>
<td>PDUFA or FDA Approval Date</td>
<td>List the date or time frame (2023, Q1’22, etc) of anticipated FDA approval</td>
</tr>
<tr>
<td>Approval Dates and Indications in Other Countries (ex-US)</td>
<td>List other countries and (anticipated) approval dates and indications</td>
</tr>
<tr>
<td>Phase 3 Trials Related to Unapproved Use Completed</td>
<td>List the name or citation of trials and dates completed; provide links to clinicaltrials.gov or Pub Med</td>
</tr>
<tr>
<td>Phase 3 Trials Related to Unapproved Use in Progress</td>
<td>List the name or citation of trials with start and anticipated completion dates; provide links to clinicaltrials.gov or Pub Med</td>
</tr>
<tr>
<td>Phase 2 Trials Related to Unapproved Use Completed</td>
<td>List the name or citation of trials and dates completed; provide links to clinicaltrials.gov or Pub Med</td>
</tr>
<tr>
<td>Phase 2 Trials Related to Unapproved Use in Progress</td>
<td>List the name or citation of trials with start and anticipated completion dates; provide links to clinicaltrials.gov or Pub Med</td>
</tr>
<tr>
<td>Anticipated Route(s) of Product Administration</td>
<td>Describe the route(s) of administration for unapproved product that were used in clinical trials and anticipated to be approved by the FDA</td>
</tr>
<tr>
<td>Anticipated Location/Setting(s) for Product Administration</td>
<td>Describe the location or healthcare setting where product was administered in clinical trials and anticipated to be given when approved by the FDA</td>
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[ ] $\leq 9,999  
Alternatively, and in addition, indicate any other information about the anticipated costs of unapproved product |
2.0 **PRODUCT INFORMATION AND DISEASE DESCRIPTION**

2.1 **PRODUCT DESCRIPTION**

The recommended length of Section 2.1 is 5 pages (maximum 10).

Manufacturers are encouraged to provide as much detailed information about their unapproved product or unapproved use of an approved product as possible. Information should be updated regularly and noted in Section 1 Highlights and Overview.

Manufacturers may not make claims about an unapproved product or unapproved indication of an approved product. However, companies should provide objective scientific information about the unapproved product or unapproved indication in the pre-approval dossier. Information should include that found in the anticipated FDA-approved label or prescribing information/package insert (PI). Information that goes beyond the scope of the PI is also welcomed, but companies must ensure compliance with FDA laws, regulations, and guidance when providing this information.

The following are the components that should be included:

1. A clear statement that the unapproved product or unapproved use of an approved product is not FDA approved, and that the safety or effectiveness of the unapproved product or unapproved use has not been established.
2. Generic, brand, chemical, or other given name of the unapproved product
3. Therapeutic class or category of the unapproved product; AHFS or other drug classification
4. For communications about an unapproved product, manufacturers should provide information about the indication(s) being sought, such as information from the clinical study protocol(s) about endpoint(s) being studied and the patient population under investigation (e.g., number of subjects enrolled, subject enrollment criteria, subject demographics).
5. For communications about an unapproved use of an approved product, manufacturers should provide a prominent statement disclosing the indication(s) for which FDA has approved the product and a copy of the most current FDA-approved prescribing information.
6. Information related to the stage of product development for the unapproved product or unapproved use of an approved product (e.g., the status of any studies in which the unapproved product or unapproved use of an approved product is being investigated and how it relates to the overall product development plan for the manufacturer, whether a marketing application for the product or use has been submitted to FDA or when such a submission is planned).
7. Anticipated timeline for possible FDA approval/clearance/licensure of the unapproved product or the unapproved use of an approved product.
   - Date of New Drug Application (NDA) or supplemental New Drug Application (sNDA)
   - Date of FDA Advisory Committee Review, if any
   - Date of anticipated FDA approval or Prescription Drug User Fee Act (PDUFA) date
8. Proposed mechanism of action, drug class, device description, and other features of an unapproved product.
9. Patient utilization projections (e.g., epidemiological data projection on incidence and prevalence).
10. All dosage forms, including strengths and package sizes
11. Pharmacology
12. Pharmacokinetics/Pharmacodynamics
13. Contraindications/Warnings/Precautions/Adverse Effects
14. Special Populations (e.g., pregnancy, pediatric use, renal impairment, etc.)
15. Interactions with suggestions on how to avoid them
   - Drug/Drug
   - Drug/Food
   - Drug/Disease
16. Dosing and Administration
17. Access, e.g. restrictions on distribution, supply limitations, anticipated shortages, and/or prescribing restrictions
18. Co-Prescribed / Concomitant Therapies, including dosages, recommended use of other agents or treatments with the product, and the rationale and clinical benefit associated with the co-prescribed/concomitant therapies. It may be helpful to refer to the PI when determining which therapies would be co-prescribed/used concomitantly.
19. Describe how product may impact quality measures, e.g., HEDIS scores. 30-day readmissions, CMS Star rating, etc. Include studies that support this information in Section 4.0
20. Product-related programs or services, e.g., patient support programs.
21. If possible, indicate relevant Healthcare Common Procedure Coding System (HCPCS) billing codes applicable to unapproved product or unapproved use of an approved product, as well as any Current Procedural Terminology (CPT) codes applicable for reimbursement. Identify likely International Classification of Diseases (ICD)-10 and ICD-9 codes that are relevant for unapproved product or unapproved use of an approved product. Inclusion of ICD-9 is to allow retrospective review of claims that contain ICD-9 since conversion to ICD-10 occurred in October 2015.
22. Product pricing information

2.1.1 Product Comparison
Concise comparison of PI information of likely and relevant comparator products in the same therapeutic area as the unapproved product such as: dosing, indications, pharmacokinetic/pharmacologic profile, adverse effects, warnings, contraindications, interactions and other relevant characteristics (expand as appropriate for the therapeutic class). The material may include a discussion of comparator product(s) or services that the proposed product is expected to substitute for or replace. This information should be presented in tabular form. If direct head-to-head trials have been conducted on the product and its comparators, this should be noted here, and the reader referred to the review of those trials in Section 4.0 of the dossier.

For an unapproved product, the manufacturer has the option to include the unapproved product in the comparator table. For an unapproved use of an approved product, the manufacturer should include the approved product in the comparator table.

For unapproved biosimilar products, comparator information about the reference product should be included as well as evidence that demonstrate biosimilarity or interchangeability.

A statement as to why the comparators were selected should be included (e.g. meta-analyses, guidelines, literature search, etc.). If comparator products are selected based on guidelines, it may be necessary to include information from the guidelines in the comparator table.

2.2 Place of the Product in Therapy
The recommended length of Section 2.2 is 5 pages (maximum 10) for each anticipated indication.
Information presented in this section should be brief. Ideally, information should be provided in a table or bulleted list or other easy-to-read format. For products with multiple anticipated indications, the following information should be provided for each indication. Do not duplicate information presented in other sections of the pre-approval dossier.

### 2.2.1 Disease Description

It is understood that the exact indication of an unapproved product is not fully known until final FDA approval. However, manufacturers are requested to provide as much information as possible about the anticipated FDA-approved indication, medical condition, and disease state for the unapproved product. The intent is to give the reader a good overall sense of the disease. The disease description should be brief and should include the disease and characteristics of the patients who are treated for the condition. Manufacturers should provide a description of specific patient subpopulations in which the product is expected to be most effective, if known. Include clinical markers, diagnostic or genetic criteria, or other markers, if known, that can be used to identify these subpopulations. Present a brief summary of information from the literature for each topic.

Disease specific descriptive information may include, but not be limited to:

1. Epidemiology and relevant risk factors, with a focus on identifiable subpopulations that would be appropriate for the use of the product
2. Pathophysiology
3. Clinical presentation
4. Societal, humanistic and/or economic burden

Specialty pharmaceuticals often treat rare diseases with relatively little information available in the public domain. This section may be expanded to provide greater detail for rare conditions treated with specialty pharmacy.

### 2.3 Unmet Need

Describe the specific unmet medical need that unapproved product is anticipated to fulfill.

### 2.4 Comparator Products and Treatments

Describe other products and non-pharmacologic treatments that are available and used in this disease state.

### 2.5 Approaches to Treatment

The key questions to address are: How is the disease/condition currently treated? How does the new product fit into standard or existing therapy?

Provide a very brief summary of information from the literature for each topic; do not duplicate information included in other sections:

1. Summarize current approaches to treatment including principal therapeutic options (pharmacologic and non-pharmacologic), common practice patterns, or standards of care; briefly include recommendations supported by well-accepted or nationally recognized clinical practice guidelines and consensus statements, however summarize details of these sources in Section 5.0.
2. Describe the place and anticipated uses of the proposed product for treating disease, especially for certain subpopulations that can be targeted for the use of the product.
3. Indicate the anticipated care setting(s) for the product such as self-administration by the patient, by a health care professional in the home, in an infusion therapy clinic, in a physician office, or in a hospital.
4. Describe potential heterogeneity of treatment effect, if any, related to the use of the product. Response to therapy may vary from patient to patient. Any information that
null
3.0 CLINICAL EVIDENCE

Section 3.0 should consist of all clinical studies that support the unapproved product or unapproved use of an approved product, reported in a clear and concise format. Manufacturers should provide factual presentations of results from studies, including clinical studies of the unapproved product or bench tests that describe unapproved product performance (i.e., no characterizations or conclusions should be made regarding the safety or effectiveness of the unapproved product or the unapproved use).

Manufacturers should describe material aspects of study design and methodology and disclose material limitations related to the study design, methodology, and results. Manufacturers should also ensure that results are not selectively presented (e.g., both positive and negative or null findings should be presented). Examples of the types of clinical evidence include but are not limited to: clinical trial information from Phase 1, 2, and 3 studies (e.g., peer-reviewed publications; medical congress abstracts, posters, presentations; medical information/communication departments’ response letters); information from clinicaltrials.gov; pre-clinical studies; data on file per company’s discretion.

3.1 STUDY SUMMARIES

The recommended length of each study summary is 2 pages (maximum 5).

Study summaries should include the following items where available and applicable:

1. Publication citation(s), study name, Clinicaltrials.gov ID number, funding source
2. Objective, location, and study start and completion dates
3. Trial design, randomization, and blinding procedures
4. Setting, inclusion, and exclusion criteria
5. Baseline patient characteristics and demographics
6. Drop-out rates and procedures for handling drop-outs (ITT, per protocol, etc.)
7. Treatments, interventions, dosage regimens, washout period, concomitant therapies, etc.
8. Clinical outcome(s) evaluated, measured, and collected, delineating primary vs secondary endpoints as well as pre-specified vs post hoc
9. Measures of effect (e.g., risk difference, risk ratio, odds ratio, number needed to treat), statistical significance of outcomes, and power calculations
10. Validation of outcomes instruments (if applicable)
11. Generalizability of the population treated
12. Study limitations, as stated by the authors

3.2 EVIDENCE TABLES

The recommended length of an evidence table row is <1 page (maximum 2) for each study.

Evidence tables should include the following items where available and applicable:

1. Citation, (if unpublished, give abstract information or indicate “data on file”)
2. Treatments
3. Sample size and length of follow-up
4. Inclusion/exclusion criteria
5. Design
6. Primary Endpoints
7. Secondary Endpoints
8. Results: Provide an explicit statement of effect size, not just relative risk reduction and/or statistical significance. Within the Results column, include a table of key results.
9. Statistical significance

4.0 ECONOMIC INFORMATION

While it is difficult for a manufacturer to disclose the price or cost of an unapproved product and compliance issues beyond FDA oversight must be considered, companies are encouraged to provide as much information as possible so that HCDMs may plan and budget for future coverage and/or
reimbursement decisions prior to FDA approval. Information should help HCDMs consider the potential budget impact and cost-effectiveness of an unapproved product. While full and complete budget impact models and cost-effective models may not be feasible to construct prior to FDA approval and ultimate price determination, companies should share and discuss relevant information. When deemed necessary, manufacturers may request execution of non-disclosure agreements so that sensitive or confidential information is protected.

Information related to the economics surrounding an unapproved product may be provided in a variety of ways, which may include but not limited to:

- Estimated cost or range of cost (per year, per patient, per course, etc.)
- Preliminary cost-effectiveness and budget impact models; discussion of evidence and information that support assumptions and rational in models or proposed models
- Rationale for pricing strategy
- Value-based agreements—(note, this information must be provided consistent with laws, regulations, and guidance outside of FDA regulatory oversight.)
- Potential cost offsets, avoidances, and savings
- Estimate costs relative to current therapeutic options
- Estimate of overall economic impact to health care system

5.0 **ADDITIONAL SUPPORTING EVIDENCE**

The recommended length of Section 5.0 is 2 pages (maximum 5) for each study or source.

Section 5.0 should consist of all other types of evidence and studies that do not fit in Section 3.0 that may support the use of the unapproved product reported in a clear and concise format. Examples of evidence in this section includes clinical practice guidelines (CPGs), health technology assessments (HTAs) and systematic reviews (SRs), compendia, other economic or outcomes evidence, relevant quality measures, and any other important and relevant evidence or information that may not fit into any other sections as described in this document.

6.0 **DOSSIER APPENDICES**

1.1 **REFERENCES CONTAINED IN DOSSIERS**

Include citations for all known published clinical and economic studies in the bibliography section. Reprints of relevant published studies should be available upon request, and where possible, provide a link to original sources if they are free.

1.2 **ECONOMIC MODEL(S)**

Include draft economic model(s), if possible.

1.3 **PRODUCT PRESCRIBING INFORMATION**

Include draft or anticipated label, package insert (PI), or prescribing information, if possible.

1.4 **PATIENT INFORMATION**

Include any draft patient information such as patient package inserts (PPI), if possible
1.5 **Material Safety Data Sheet**

Include draft Material Safety Data Sheet (MSDS) for product, if possible.
REFERENCES

16. Berger ML, Dreyer N, Anderson F, Towse A, Sedrakyan A, Normand SL. Prospective observational studies to assess comparative effectiveness: the ISPOR good research practices task


46. Food & Drug Administration (FDA). Quality considerations in demonstrating biosimilarity of a therapeutic protein product to a reference product - guidance for industry. April 2015; Available at:


56. Adapted from Guidance for the submission of evidence supporting coverage and reimbursement decisions for medical tests (‘The Guidance’), Version 5/12/10, by Josh Carlson, David L Veenstra, Scott D Ramsey, Lou P Garrison, Sean D Sullivan, and Rick Carlson of the University of Washington, with permission.


