CMC Risk-based Product Reviews

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Abstract

Objectives: Ensuring that CMC information is current and appropriate is an important consideration to minimize product risk, especially in regard to legacy products or the divestment and/or acquisition of products. A thorough review supports activities within Regulatory Affairs, QA/QC, and Production, and can provide key data for commercial decision-making.

Methods: The review of CMC submissions and supporting documentation serves several purposes, and is of particular relevance in regard to legacy or in-licensed products. Potential product risks include recalls, out-of-stock situations, or regulatory sanctions. The documentation of the review provides an administrative and legal record to support decisions; can identify problems and remedies; can serve as a reference guide for other reviewers; and, it provides a concise technical information source for Regulatory Affairs, Quality Assurance/Quality Control, Production, and other disciplines as needed.

Results: An essential aspect of the review process is to determine if the information is current and appropriate. The starting point for reviews is often the IND or NDA (plus amendments and supplements), annual reports, change control documents, the Drug Master File, and vendor audits. Information in the following areas is reviewed: manufacturing and testing facilities, raw materials, purity, methods validations and specifications, process controls, container and closure systems, stability and batch data, outer packaging labels, and environmental considerations.

Conclusions: A properly prepared CMC information summary can prove indispensable when products are divested or acquired. The review will either confirm that information is current and appropriate, or if gaps exist. If informational gaps are identified, solutions to these problem areas are identified and corrective actions taken to minimize risks to product commercialization and continued marketing.

Introduction

Ensuring that CMC information is current and appropriate is an important consideration to minimize product risk, especially for legacy products or the divestment and/or acquisition of products. Potential product risks include out-of-stock situations, recalls, or regulatory actions. A thorough review of the CMC information in an application supports activities within Regulatory Affairs, QA/QC, and Production, and can provide key data for commercial decision-making.

The review itself can identify problems and remedies. The documentation of the review provides an administrative, regulatory, and legal record to support decisions; serves as a reference guide for other reviewers; and provides a concise technical information source for Regulatory Affairs, Quality Assurance/Quality Control, Production, and other disciplines as needed.

The following data are provided for illustrative purposes and serve only to dimensionalize the nature of the approval history for several well-known drugs. This information is available on the following FDA web site:

http://www.accessdata.fda.gov/scripts/cder/drugcat

The web site is under revision and is expected to be available this summer

The site lists all applications for drugs of interest and also characterizes the approval history of individual applications. An example (ranitidine) is provided to the right.

Drug products do not remain static; typically, many changes, additions, and revisions to an application are needed over the marketed life of a product. The amount of chemistry, manufacturing, and controls (CMC) and other information in an application is highly variable and depends upon the individual application and unique history of each drug product. As shown in the following table, most drugs have a history of change, particularly if the product has had multiple sponsors.

The types of information that contribute to compiling a full CMC information summary, including identification of data sources, the process for conducting a review, and the types of observations that arise from a review are examined in this presentation. In addition, the overall benefits that may result from a rigorous CMC review are described.

Objectives

The objectives of the CMC review are as follows:

- To develop a process to systematically identify available CMC information
- To review the CMC information in order to determine:
  - If information is current and appropriate
  - If there are problems or gaps
  - If the Sponsor is in compliance with applicable regulations
- To summarize available information, referencing source documents, for ease of retrieval

Methods

Step 1: The review is conducted according to established SOPs.

Step 2: Data are abstracted and entered into a draft report.

Step 3: Abstracted data are checked by Quality Assurance.

Step 4: Data are finalized in a concise report containing tabular summaries.

Information Reviewed

- Manufacturing/testing facilities
- Raw materials
- Purity
- Stability and batch data
- Outer packaging labels
- Suppliers
- Process controls
- Analytical methods, methods validation, and specifications
- Container/closure systems
- Environmental considerations

Sources of Information

- Original Application
- Supplements to the application
- Annual Reports
- Production Records
- User Fee Lists
- CMC Re-submission
- Amendments to submissions
- Annual Product Reviews
- Change Control Records
- The Drug Master File

Results

The final document fully characterizes the CMC history of the product. Information is organized for easy retrieval, in that the location (i.e., volume/page) of information in the application, submission dates, and any cross-referencing is tabulated.

The review either confirms that information is current and appropriate or shows that gaps exist. It also identifies any current potential compliance issues, such as:

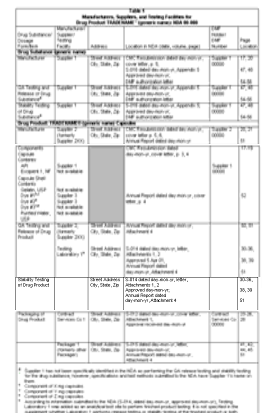
- Unresolved legal/regulatory actions directed at the sponsor or the subcontractors referenced in the proposed submission
- Pending compliance issues (e.g., 483s, warning letters, establishment inspection reports, etc.)
- Change control process activities that need to be communicated to health authorities (e.g., changes to site; manufacturing process for active; manufacturing process for product; analytical methods for active; analytical methods for product; test or process equipment); container/closure suppliers
- Potential patent problems and related intellectual property issues
- Outstanding reports/protocols from the client or planned for the client and referred to in the documents planned for submission

The final CMC information compilation can be categorizing effectively into four classes:

- Manufacturers, Suppliers, and Testing Facilities
- Container/Closure Systems
- Analytical Methods
- Storage Conditions / Expiry Dating

If CMC informational is inappropriate or gaps are identified during the review, solutions to these problem areas are formulated and corrective actions can be taken to minimize risks to product commercialization and ensure continued marketing.

An example of a manufacturers, suppliers, and testing facilities summary table is provided below



Conclusions

A properly prepared CMC information summary can prove indispensable when issues requiring a rapid response or decision arise. CMC summaries are particularly useful when products are divested or acquired, or if a technology transfer is required. The review will either confirm that information is current and appropriate, or if gaps exist. If informational gaps are identified, solutions to these problem areas are proposed and corrective actions can be taken to minimize risks to product commercialization and continued marketing. In our experience, the availability of CMC summaries has allowed quick action to be taken to avoid out-of stock situations, to facilitate the preparation

For More Information Please Contact:

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