A Data-Driven CMC Review Process to Minimize Risk

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Introduction

To minimize product risk, especially for legacy products or when divesting or acquiring products, it is important to ensure that CMC information is current and appropriate.

Potential Product Risks

- Recalls (Table 1)
- Out-of-stock situations
- Regulatory sanctions

Table 1. CMC-Related Reasons for Drug Recalls in 2002 and 2003

Recall No.	Reason for Recall
D-265-3	NDA filing discrepancy; supplement not filed for new supplier of inactive ingredient.
D-120-3	Stability; product was distributed in a new container closure system without stability data to support expiration dating.
D-265-2	Labeling; product label declares inactive ingredients that are not contained in the product (Dextrose Hydrous, USP, Sodium Citrate Hydrous, USP and Hydrochloric Acid).
D-398-2	Tablets changed to capsules.
D-417-2	Labeling; product label does not declare inactive ingredient sodium saccharin.
D-048-3	Misbranding; product contains undeclared cherry flavoring.

Sources: www.fda.gov/po/enforceindex/2003enforce.html and www.fda.gov/po/enforceindex/2002enforce.html.

A Properly Prepared CMC Review and Documentation

- Supports activities: Regulatory Affairs, QA/QC, Production
- Provides data for commercial decision-making
- Can identify problems and remedies
- Provides an administrative, regulatory, and legal record
- Supports decisions
- Serves as a reference guide for other reviewers
- Provides a concise technical information source for Regulatory Affairs, QA/QC, Production, Other Disciplines

Complex Approval History

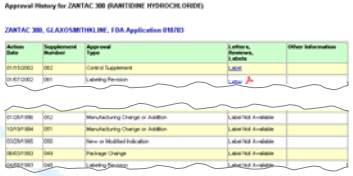
The approval history of a drug is often complex. The complexity of an application is often compounded when several dosage forms and dosage strengths are marketed for the same drug (Table 2).

An example of the complexity of an application is shown in Table 3. At least 14 CMC-related supplements have been approved for Application 018703 since 1983.

Information in Tables 2 through 4 is provided for illustrative purposes only and is available from the FDA's web site: www.accessdata.fda.gov/scripts/cder/drugsatfda.

Table 2. Drugs Marketed Under Zantac

Table 3. Approval History for Zantac (ranitidine hydrochloride)



Dynamic Nature of Drug Applications

The amount of CMC information in applications varies and depends on the individual application and the unique history of the product. Typically, many changes, additions, and revisions are made over the life of a product (Table 4).

Table 4. Supplements Approved for Several Marketed Products

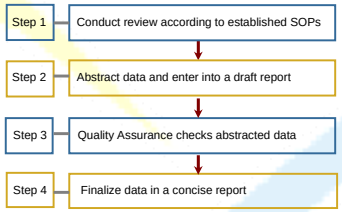
Drug	Sponsor	Approval	Dosage Form	Application	Number of Approvals: Labeling Revision	Control Supplement	Manufacturing	Packaging	Other / Miscellaneous	Total
Zantac	GSK	1983	Tablet	018703	20	12	8	6	10	58
Ranitidine HCl (generic)	Teva	1997	Tablet	074488	4	1	1	1	9	16
Motrin	McNeil	1974	Tablet	017463	19	16	10	3	11	59
Ibuprofen (generic)	Geneva	1986	Tablet	070735	4	0	0	1	9	14
Estraderm	Novartis	1986	Transdermal Patch	019081	9	7	9	1	4	30
Fosamax	Merck	1995	Tablet	020560	8	3	2	5	10	28
Dilantin	Parke-Davis	1956	Injection	010151	9	0	2	5	3	19
Dilantin	Parke-Davis	1953	Suspension	008762	10	6	1	3	0	20
Phenytoin (generic)	Alpharma	1992	Suspension	089892	0	2	1	0	7	10

Data as of September 10, 2003 from FDA's web site: www.accessdata.fda.gov/scripts/cder/drugsatfda/index.

Objectives

- To systematically identify available CMC information
- To review the CMC information in order to determine if
  - Information is current and appropriate
  - There are problems or gaps
  - Information complies with applicable regulations
- To summarize information, referencing source documents, for ease of retrieval

Methods



Sources of Information

- Original application
- Amendments to submission
- Annual reports
- Production records
- User Fee Lists
- CMC re-submissions
- Supplements to application
- Annual product reviews
- Change control records
- Drug Master Files

Information Reviewed

- Manufacturing facilities
- Testing facilities
- Raw Materials
- Stability and batch data
- Container/closure systems
- Outer packaging labels
- Expiry dates
- Suppliers
- Process controls
- Analytical methods
- Specifications
- Methods validation
- Storage conditions
- Environmental considerations

Categories of CMC Information

Summary tables for each of the following categories are prepared:

- Manufacturers, suppliers, and testing facilities
- Specifications
- Container/closure systems
- Analytical methods
- Storage conditions / expiry dating

Results

Final CMC Summary

- Fully characterizes the CMC history of the product
- Is organized for easy information retrieval
- Identifies the location (i.e., volume, page) of the information in the application, submission dates, and any cross-referencing

The review either confirms that information is current or shows that gaps exist.

Current, Potential Compliance Issues

The review identifies any compliance issues, such as

- Unresolved legal/regulatory issues
- Pending compliance issues (e.g., 483s, warning letters, established inspection reports, etc.)
- Change control process activities that need to be communicated to the health authorities, for example changes to
  - Site
  - Manufacturing process for the active pharmaceutical ingredient
  - Manufacturing process for the product
  - Analytical methods for the active pharmaceutical ingredient
  - Analytical methods for the product
  - Test or process equipment
  - Container/closure supplier
- Outstanding unfulfilled commitments to the health authorities

Solutions to CMC Deficiencies

Solutions to CMC deficiencies are formulated and corrective actions can be taken to minimize risks to product commercialization and ensure continued marketing.

Examples of summary tables for manufacturers, suppliers, and testing facilities for the drug substance and drug product are shown in Tables 5 and 6.

Table 5. Manufacturers, Suppliers, and Testing Facilities for Drug Substance

Item	Manufacturer/ Supplier/ Testing Facility	Address (Street address City, State)	Location in NDA (date, volume, page)	DMF Number/ DMF Holder	Page location in summary
Manufacturer	Manufacturer A	322 Industrial Way City, State 00000	CMC Resubmission dated 21 Aug 1999, cover letter, p. 5; S-016 dated 31 Sep 2001, Appendix 5 Approved 7 Nov 2001	Manufacturer A 0050	17, 21 38, 39 51-53
QA Testing and Release of Drug Substance	Manufacturer A	322 Industrial Way City, State 00000	S-016 dated 31 Sep 2001, Appendix 5 Approved 7 Nov 2001	Manufacturer A 0050	38, 39 51-53
Stability Testing of Drug Substance[a]	Manufacturer A	322 Industrial Way City, State 00000	S-016 dated 31 Sep 2001, Appendix 5 Approved 7 Nov 2001	Manufacturer A 0050	38, 39 51-53

[a] Manufacturer A was not specifically identified in the NDA as performing the QA release testing and stability testing for the drug substance; however, specifications and test methods submitted to the NDA have Manufacturer A's name on them.

Table 6. Manufacturers, Suppliers, and Testing Facilities for Drug Product (generic name) 2, 5, and 10 mg Capsules

Item	Manufacturer/ Supplier/ Testing Facility	Address (Street address City, State)	Location in NDA (date, volume, page)	DMF Number/ DMF Holder	Page location in summary
Components Capsule Contents: API Lactose, USP Capsule Shell Components: Gelatin, USP Dye #1[a,c] Dye #2[b] Dye #3[c] Purified water, USP	 Manufacturer A Not available Not available Supplier 1 Supplier 1 Not available Not available		CMC Resubmission dated 21 Aug 1999, cover letter, p. 4, 5; Annual Report dated 23 Jun 2002, cover letter, p. 4		17, 20, 21 55, 59
QA Testing and Release of Drug Substance	Manufacturer B Testing Laboratory A[d]	76 Orient Way City, State 00000 44 Avenue B City, State 00000	Annual Report dated 23 Jun 2002, Attachment 4 S-014 dated 15 Aug 2001 , letter, Attachment 1, 2 Approved 15 Oct 2001		60-62 30-36 41, 42
Stability Testing of Drug Substance	Testing Laboratory A	44 Avenue B City, State 00000	S-014 dated 15 Aug 2001 , letter, Attachment 1, 2 Approved 15 Oct 2001		30-36 41, 42
Packaging of Drug Product	Packager B (formerly Packager A)	13 Broadway City, State 00000	S-012 dated 17 Jul 2001, cover letter, Attachment 1 Approved 21 Oct 2001		23-26, 28 44, 45

[a] Component of 2 mg capsules.
[b] Component of 5 mg capsules.
[c] Component of 10 mg capsules.
[d] According to information submitted to the NDA (S-014 dated 15 Aug 2001, approved 15 Oct 2001), Testing Laboratory A was added as an analytical site to perform finished product testing. It is not specified in the supplement whether Testing Laboratory A performs release testing or stability testing of the finished product or both.

Conclusions

Properly prepared CMC information summaries accomplish the following:

- Are indispensable when issues requiring a rapid response or decision arise
- Are particularly useful when products are divested or acquired, or if a technology transfer is required
- Confirm that information is current and appropriate or identify gaps
- If gaps are identified, solutions are proposed and corrective actions are taken to minimize risks to product commercialization and continued marketing

In our experience, the availability of CMC summaries has allowed for

- Quick action to avoid out-of-stock situations
- Preparation of responses to regulatory authorities
- Identification and rectification of gaps in the application