A Data-Driven CMC Review Process To Minimize Risk

By Dolores R. Massari, MS, Glenn A. Diegnan, PhD, Margaret E. Hurley, MD, Mark E. Rosengarten, MS, and Susan M. Mondabaugh, PhD

Minimizing product risk, especially for legacy products or when divesting or acquiring products, is an important activity for regulatory affairs. It is especially critical to ensure that chemistry, manufacturing and controls (CMC) information is current and appropriate in order to avoid potential product risks, such as recalls, out-of-stock situations or regulatory sanctions. Examples of CMC-related reasons for pharmaceutical recalls in 2002 and 2003 are shown in **Table 1**.

TABLE 1: EXAMPLES OF CMC-RELATED REASONS FOR DRUG RECALLS IN 2002 AND 2003

RECALL NO.	REASON FOR RECALL
D-265-3	New Drug Application 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.

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

Complex Approval History

The approval history of a drug is often multifaceted. The complexity of an application is compounded when several dosage forms and dosage strengths are marketed for the same drug. According to the Food and Drug Administration, there are nine different new drug applications encompassing branded ranitidine in multiple dosage forms, strengths, and salts.[1] A total of 57 supplements have been approved for new drug application 18-703 for Zantac 150 mg since the drug was first approved for marketing in 1983. At least 16 of the approved supplements have been related to CMC changes.

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. The approval history for several well-known drug products is shown in **Table 2**.

The number of approved supplements associated with manufacturing and packaging in these applications varies, but as many as one in every three supplements can be related to CMC changes.

Keeping track of all the information

TABLE 2: SUPPLEMENTS APPROVED FOR SEVERAL MARKETED PRODUCTS

					NUMBER OF APPROVALS					
DRUG	Sponsor	Approval	Dosage Form	Applic.	Labeling Revision	Control Supplemt.	Manuf.	Packaging	Other / Misc.	Total
Zantac	GSK	1983	Tablet	018703	20	12	8	6	11	57
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	11	7	9	1	4	32
Fosamax	Merck	1995	Tablet	020560	11	3	2	5	11	32
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

Source: www.accessdata.fda.gov/scripts/cder/drugsatfda/index, accessed 31 August 2004.

submitted in an application can be an arduous task, especially for older legacy products where detailed documentation may be lacking or may not be as rigorous as one would expect by current standards. Organizing this information into a well-documented and cross-referenced CMC summary can help to manage the information and make it readily available when questions arise.

Properly Prepared CMC Assessment and Documentation

A properly conducted CMC assessment and the associated documents will accomplish the following:

- Support activities in regulatory affairs, quality assurance/quality control and production
- Provide data for commercial decision-making
- Identify problems and areas requiring corrective action
- Provide an administrative, regulatory and legal record
- Support decisions
- Serve as a reference guide for other reviewers
- Provide a concise technical information source for regulatory affairs, quality assurance/quality control, production and other disciplines

The objectives of the CMC assessment and documentation are to systematically identify available CMC information; to assess the CMC information to determine if the data are current and appropriate, if there are problems or gaps, and if information complies with applicable regulations and guidance; and to summarize information, referencing source documents, for ease of retrieval.

CMC assessments are conducted according to standard operating procedures and involve abstracting the data to include in a draft report, a quality assurance check of that data, and a finalized report. The information and source documents that are reviewed to prepare a CMC summary include the original application, the amendments to submission, annual reports and production records, user list fees, supplements to an application, annual product reviews and drug master files.

A review of the information with respect to compliance with the regulations and guidance documents listed in **Table 3** is required. Finally, summary tables for each of the following categories are prepared: manufacturers, suppliers, and testing facilities; specifications; container/closure systems; analytical methods; and storage conditions and expiration dating.

The final CMC summary should fully characterize the CMC history of the product, be organized for easy information retrieval and identify the location (i.e., volume, page) of the information in the application, submission dates, and any cross-referencing.

Such a summary either confirms that information is current or shows that gaps exist. It can also identify any compliance issues, such as unresolved legal/regulatory issues pending compliance issues (e.g., 483s, warning letters, unsatisfactory establishment inspection reports), change control process activities that need to be communicated to the health authorities (e.g., changes to site, manufacturing process for the active pharmaceutical ingredient and manufacturing process for the product) and outstanding unfulfilled commitments to the health authorities.

TABLE 3: REGULATORY REQUIREMENTS FOR CMC

		GUIDANCE DOCUMENTS	
Application	**21 CFR Sections**	**FDA**	**ICH**
Investigational New Drug	312.23(a)(7) 312.31 312.33		
New Drug Application	314.50 314.60 314.81	SUPAC IR SUPAC SS SUPAC MR	
Both		Container Closure Systems for Packaging Drugs and Biologics	Q2B Validation of Analytical Procedures: Methodology Q1C Stability Testing for New Dosage Forms Q3A Impurities in New Drug Substances Q3B (R) Impurities in New Drug Products Q3C Impurities: Residual Solvents

Conclusion

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 CMC assessment will either confirm that information is current and appropriate or show that gaps exist. If gaps are identified, solutions can be proposed and corrective actions can be taken to minimize risks to product commercialization and continued marketing.

The availability of CMC summaries can allow quick action to avoid out-of-stock situations, preparation of responses to regulatory authorities and identification and rectification of gaps in the application.

NOTES

1. Food and Drug Administration. Drugs@FDA. Available at: www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm. Accessed 31 August 2004.

Dolores R. Massari, MS, is FDA liaison, Regulatory Affairs; Glenn A. Diegnan, PhD, is pharmaceutical chemist, Scientific Affairs; Margaret E. Hurley, MD, is President & CEO; Mark E. Rosengarten, MS, is Director, Regulatory Affairs; and Susan M. Mondabaugh, PhD, is Vice President, Regulatory Affairs, at Hurley Consulting Associates Ltd., Chatham, NJ.