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Rarely do manufacturers of biologics need to prepare a Biological Product Deviation Report (formerly called an Error and Accident Report); in fact, few manufacturers ever have to complete one. But all manufacturers need to have an SOP describing how to complete this report, in case it becomes necessary.

Preparing Biological Product Deviation Reports Suggestions for Manufacturers

A Biological Product Deviation Report (BPDR), previously called an Error and Accident Report, is not a routine submission prepared by manufacturers of therapeutic biologics (1). In fiscal year 2001, only 19 of these reports were submitted by manufacturers (2). In contrast, nearly 24,000 reports were submitted by blood banks and the blood products industry. Because most regulatory and quality professionals in the biotech industry never participate in preparing this type of submission, if their company faces this challenge, the learning curve can be steep.

Although the suggestions made here are routinely incorporated into preparation of other types of regulatory submissions, preparing a BPDR under a time deadline limits both the preparation time and the review time, during which inconsistencies are normally identified and resolved. The BPDR referred to is the FDA form 3486 without additional attachments. The term *submission* includes both the BPDR and the supporting information in attachments and appendices.

Time Is of the Essence

To move quickly and efficiently in filing a BPDR requires that manufacturers have a standard operating procedure (SOP) for determining the need to submit the report and have identified the groups that are responsible for its preparation and approval (3). In some companies, the quality department “owns” this activity, whereas in other companies the ultimate responsibility resides in the regulatory department. Operationally, however, preparation of a BPDR is frequently a shared responsibility. If the regulatory component makes the final decision regarding the need for submission, however, then personnel in the quality unit must recognize which deviations fall into the BPDR category and quickly bring any such deviations to the attention of the regulatory

staff. Coordinating that evaluation can be difficult, particularly when contract manufacturers or manufacturing operations are separated geographically from the regulatory staff.

Contacting CBER. Prudent sponsors contact CBER when a deviation is identified that may require submission of a BPDR. Recent guidelines provide a general discussion of situations for which a report is expected (4). Specific deviations, however, rarely fit neatly into the guidance examples, and agency staff can provide additional insight on whether a report is needed. Communication with the agency is particularly important if the sponsor either anticipates a product recall or has initiated a product recall or withdrawal.

Sponsors also need to consider that the timeline for preparing and submitting a BPDR can be driven by factors other than the timing specified in the regulations. When product inventory is available to continue to supply the marketplace, the 45-day filing period can define the timing of the submission. Alternatively, a limited product inventory combined with inventory impounded as a result of the deviation can create a more urgent situation. If CBER concurrence is required to release the impounded product, the sponsor will want to file the BPDR as soon as possible to avoid being unable to supply the marketplace (1).

Content of the Submission

FDA form 3486 is available on the agency’s website (5). Final reports can be submitted to the agency either electronically or as hard (paper) copy. Additional detailed information supplementing the completed form 3486 is often necessary and prudent. For example, additional information may be required to respond to specific agency requests, to provide data tables, or to provide toxicological evaluations.

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Organization of a BPDR

A Biological Product Deviation Report typically includes the following items.

- I. Background**
(approximately 0.5 page)
- II. Description of the Event**
(approximately 0.5–.75 page)
- III. Initial Investigation**
(approximately 1 page)
- IV. Expanded Investigation**
(approximately 1 page)
- V. FDA Requested Information**
(if any)
- VI. Conclusions and Corrective Actions**
(approximately 0.5–.75 page)

The BPDR form and related FDA guidance documents can be found at www.fda.gov/cber/biodev/biodev.htm

As described here, the completed FDA form 3486 can be 5–8 pages in length, including the administrative information page and the lot listings. Rather than using the three discussion categories on page one of the form, an alternative is for the sponsor to attach additional pages — per FDA instructions — and organize the report as shown in the “Organization of a BPDR” sidebar.

The completed form 3486, therefore, serves as a summary of events, conclusions, and actions. Technical details and data are provided in attachments and appendices. However, the completed form 3486 should not require the attachment for the deviation, investigation, and corrective action to be understood.

Organizing the submission. The organization and relationship of the BPDR documents are key to ensuring that the incident and follow-up actions are easily understood by FDA reviewers, are internally consistent, and make no unintended commitments. An example of the table of contents for a BPDR submission is shown in the “Example BPDR Table of Contents” sidebar. The table of contents shown is for a complex situation in which the deviation occurred at a contract manufacturer, and CBER requested additional information. Other deviation reports can be less complex.

Establish a hierarchy. It is important to establish a hierarchy of investigation reports and supporting documentation (Figure 1). Establishing that hierarchy is particularly valuable when a deviation originates at the site of a contract manufacturer or supplier, and the product sponsor has related deviation investigations or conducts additional supporting evaluations. The sponsor might then write a single deviation investigation summary that ties together multiple investigations and reports. When attachments and appendices are included in the submission, nomenclature within the Table of Contents and within form 3486 can appear complex. For example, a statement might reference data presented in (a hypothetical) Table 3 in Attachment B of Appendix 1. Retitling documents to reduce the complexity is usually unrealistic when more than one company, or more than one component within a single company, contributes controlled documents that become part of the submission.

Effective organization of the submission ensures that reviewers can easily find relevant information. Similar attachments

may be grouped together to achieve this goal. For example, attachments that address safety or toxicology are arranged together so that the toxicology and medical reviewers do not have to search throughout the report. Another example would be to group together attachments that address analytical issues such as purity evaluations and stability. When a variety of analytical data are presented in multiple appendices or attachments, it may be useful to prepare a summary tabulation that identifies data and its location in the submission.

Within the complex submission, several supporting documents and form 3486 refer to important dates. Those dates might include the date when the need for a BPDR became apparent and the dates of all communications with CBER. Authors of supporting documentation should agree on those dates before incorporating them into separate documents.

Authors of attachments and appendices should be careful to present a consistent perspective on the deviation, the investigation, and the appropriate corrective actions. A submission that presents

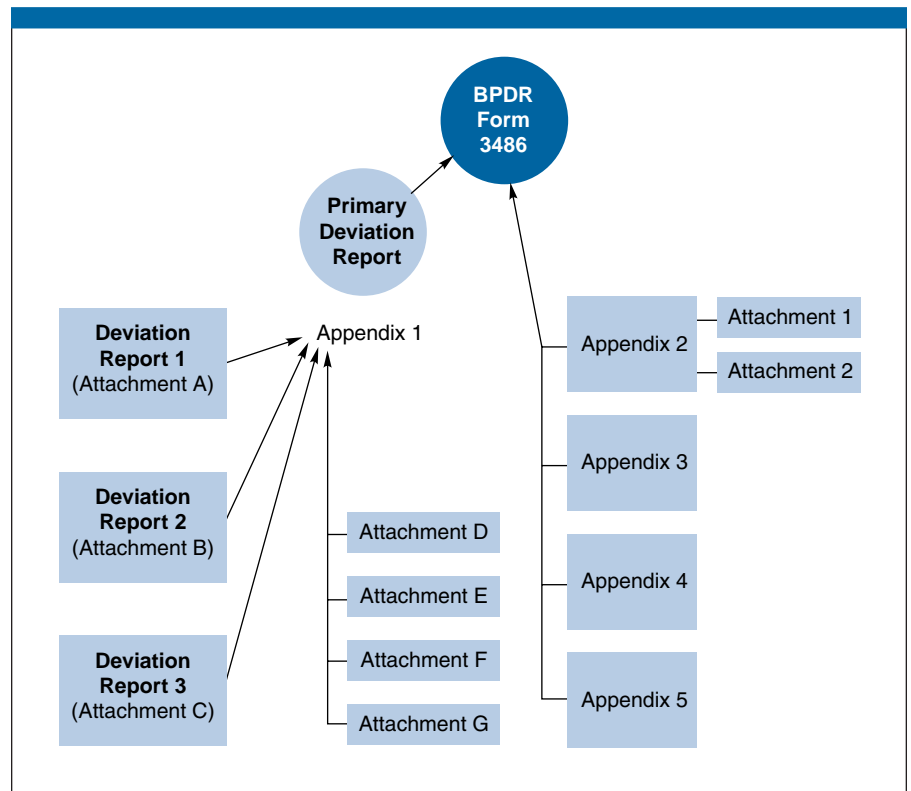


Figure 1. A completed BPDR is a summary of events, conclusions, and actions. However, attachments and appendices should not be required for the deviation, investigation, and correction action to be understood.

Example BPDR Table of Contents		
Section	Title	Page
Administrative Information		
	Cover Letter	
	Table of Contents	1
	Form FDA 3486	2
Supporting Documentation		
Appendix 1	Company Summary Deviation 1233456	8
Attachment A	Deviation Report 345678	28
Attachment B	Deviation Report 456789	35
Attachment C	Deviation Report 538296	47
Attachment D	Toxicology Evaluation of Potential Impact on Patient Safety and Public Health, Literature Included	55
Attachment E	Calibration of XXXXXXXX	64
Attachment F	Method, Validation, and Test Results for YYYYY	66
Attachment G	Method, Validation, and Test Results for ZZZZZ	78
Appendix 2	Routine Maintenance of Equipment	89
Attachment A	PM records for Tpatchco Incubator Serial #5421AR678	98
Attachment B	Work Order for Tpatchco Incubator Serial #5421AR678, January 2000–September 2002	107
Appendix 3	Stability Data	115
Appendix 4	Effect of Elevated Temperature on Stability of Drug Product	135
Appendix 5	IQ/OQ of Tpatchco Incubator Serial #5421AR678	152
Appendix 6	Identification of Location of Analytical Test Results	167

variations on a theme only confuse the reviewers and can result in multiple rounds of questions from the agency. Variations may also result in unintended sponsor commitments to FDA. An alternative approach that minimizes those complications is to write or edit supporting documents so that they include neither a traditional “background” (in which the deviation is described), nor a “conclusion” (in which commitments are made). The background, conclusions, and corrective actions are provided only within form 3486 for this alternative.

After Submission

After the BPDR is submitted to CBER, the

group that wrote the report may want to consider some final activities. Follow-up activities should be identified and listed to ensure they aren’t lost or forgotten in the rush of activity surrounding preparation of the submission. The group should also identify procedures, protocols, batch records, BLA supplements, or other documents that must be written or revised to implement corrective actions. Activities required by company procedures for preparing and completing deviation reports must be completed. The group should also evaluate existing SOPs on BPDRs and determine whether any more changes need to be made.

Making the outcome positive. The challenge of preparing and submitting a complete, well-organized BPDR within the required time period can be minimized with advance preparation. Manufacturers should have an SOP that clearly describes the roles and responsibilities for both identifying the need for a BPDR and for preparing and reviewing the submission. When contract manufacturers are involved, the nature of the relationship and the requirements specified in a quality agreement can minimize the challenges of working with two or more organizations (6). These activities, combined with attention to the submission’s organization, can contribute to a positive outcome from a difficult situation.

References

- (1) “Reporting of Errors,” *Code of Federal Regulations, Food and Drugs*, Title 21 Part 600.14, Vol. 7 (U.S. Government Printing Office, Washington, DC), revised 1 April 2001, pp. 12–13.
- (2) Center for Biologics Evaluation and Research, *Biological Product Deviation Reports: FY01 Annual Summary* (FDA, Rockville, MD). Available at www.fda.gov/cber/biodev/bpdrfy01.htm#iii.
- (3) “Biological Products: Definitions,” *Code of Federal Regulations, Food and Drugs*, Title 21 Part 600.3(t), Vol. 7 (U.S. Government Printing Office, Washington, DC), revised 1 April 2001, p. 6.
- (4) Center for Biologics Evaluation and Research, *Guidance for Industry: Biological Product Deviation Reporting for Licensed Manufacturers of Biological Products Other than Blood and Blood Components* (FDA, Rockville, MD), July 2001. Available at www.fda.gov/cber/gdlns/devnblid.htm.
- (5) Center for Biologics Evaluation and Research, *Biological Product Deviation Report*, form FDA 3486 (FDA, Rockville, MD), 8 November 2001. Available at www.fda.gov/cber/biodev/bpdrform.pdf.
- (6) Bobrowicz G., “The Quality Agreement: Compliance Considerations in Selecting a Contract Manufacturer,” *BioPharm* 14(2), 14–18 (February 2001). **BP**