

Information Requests During an FDA Review

Hong Qi, Lei Xu, Mary N. Varughese, Merck & Co., Inc., Kenilworth, NJ, USA

ABSTRACT

Filing a marketing application is a pivotal and exciting milestone for the long-term effort of product development. Even though there are industry standards to follow, the requirements and processes of submissions vary among products, indications, and sponsoring companies. Despite the extraordinary efforts in preparing a comprehensive submission package, regulatory agencies often issue information requests (IRs) from the pre-supplemental biologics license application (pre-sBLA) meeting, during the application review, and labeling process. IRs may involve different aspects of the product including the target indication, patient population, safety profile, reviewers' scientific interest on getting further information on the potential benefits of the medicine, additional case-report forms, and/or even the collected previous therapies not included in the ADaM datasets.

This paper describes the data preparation and submission pertaining to IRs received from the pre-sBLA, during the sBLA review and the labeling, with the focus on the approaches being taken to handle the IRs, and some thoughts on future strategies.

INTRODUCTION

Before biological products are marketed in the United States, sponsors, typically pharmaceutical companies, file the marketing application to the Food and Drug Administration (FDA). FDA reviews the application for scientific evidence pertaining to the safety and efficacy of products and determines whether they can be marketed in the United States.

Filing a marketing application is a pivotal and exciting milestone for the long-term effort of product development. Even though there are industry standards to follow, the requirements and processes of submissions vary among products, indications, and sponsoring companies. Despite the extraordinary efforts in preparing a comprehensive submission package, regulatory agencies often issue IRs from the pre-sBLA meeting, during the application review, and labeling process. IRs may involve different aspects of the product including the target indication, patient population, safety profile, reviewers' scientific interest on getting further information on the potential benefits of the medicine, additional case-report forms, and/or even the collected previous therapies not included in the ADaM datasets.

This paper describes the general data preparation and submission pertaining to some IRs received from the pre-sBLA meeting, during the sBLA expedited review and the labeling process, with the focus on the approaches being taken to handle the IRs, and some thoughts on future strategies. Selected IRs from the FDA that needed extra effort in dataset and programming preparation are discussed. Experiences shared in this paper are based on the approved submission(s) for single-arm oncology trials, in which certain biomarkers were collected in the study population. For confidentiality, all the patient identification, study medicine, biomarkers, numbers, and dates are masked in the paper.

REQUESTS FROM THE PRE-sBLA MEETING

This section discusses two information requests received from the pre-sBLA meeting, that we addressed with a new ADaM dataset and a program respectively.

REQUEST 1: Additional reports for baseline characteristics and efficacy results for the study population with a biomarker, by certain categories of a biomarker, and specific geographic regions.

BACKGROUND: The variables to categorize the population as requested by the agency were not

included in the available ADaM datasets and needed to be derived from either SDTM or ADSL for the reports.

These variables would have been included in ADSL if they were planned early. Adding them to fully validated ADaM datasets after the pre-sBLA meeting would have had a direct impact on CSR reports and submission timelines.

SOLUTION: Instead of updating ADSL or any ADaM datasets, we created an ADaM compliant, subject-level, ADaM Other dataset, ADxx, to derive the variables needed for the agency requested reports. ADxx contained the following analysis-ready variables that allowed generation of the requested reports with the macros already developed (illustrated in Table 1):

- Core variables from ADSL
- Derived variables:
 - Derived bio-marker identifier variables from SDTM (BLxx / BLxxN)
 - Derived bio-marker categorical variables from ADSL (BLyyG / BLyyGN)
 - Derived geographic region variables based on ADSL.COUNTRY (GEOGRP / GEOGRPN)

	SUBJID	popFL	TRT01P	TRT01PN	BLxx	BLxxN	BLyyG	BLyyGN	COUNTRY	GEOGRP	GEOGRPN
1	10001	Y	MK9999	1	BLxx High	1	BLyy High	1	AUS	GEOGRP1	GEOGRP
2	10002	Y	MK9999	1	BLxx Normal	2	BLyy Low	3	BRA	GEOGRP2	GEOGRP

Table 1. Display of an abbreviated ADxx

Additional reports were generated using ADxx, and the available ADaM datasets. ADxx was documented in Section 5 Analysis Dataset Descriptions of the Analysis Data Reviewer’s Guide (ADRG) for the completeness of the submission document and as the aid for agency review. The key takeaway from this experience is to create a new ADaM dataset when needed rather than updating the existing ADaM datasets at the time close to the study document finalization.

REQUEST 2: A non-standard category of electronic case report form (eCRF), i.e., including all treated patients.

BACKGROUND: Patient eCRFs are required in the drug submission document. Normally, the statistical programmer generates the CRF table of contents (TOC) listing patients with adverse events (AE). The CRF TOC links each patient with his/her CRFs to be included in the submission. For the US submission, there are four standard AE categories required (death, discontinuation due to AE, discontinuation due to any other reason, and Serious AE, and two additional oncology specific categories (Drug-related SAE and AE of special interest).

SOLUTION: We used a new category “Other” to include all patients not included in the existing six categories. Since this could be an infrequent request, we created a separate version of macro to add the new category to the CRF TOC, instead of overwriting the existing macro that generates six categories of the CRF TOC. Caution must be given to display each patient in only one category and the categories are displayed in the order of death, drug-related serious AE, discontinuation due to AE, discontinuation due to any other reason, all other serious AE, AE of special interest, and other. All treated patients are included in the output file.

REQUESTS DURING THE sBLA EXPEDITED REVIEW

This section discusses three information requests received during the sBLA expedited review.

REQUEST 1: A new ADaM dataset from which we can derive ALL prior therapies for all subjects. This should include surgery, radiation, chemotherapy, biologic therapy, investigational therapy, etc. and which line each therapy was counted in. Therapies in the metastatic setting should be in a separate column.

BACKGROUND: Prior lines of therapy (LOT) are anti-cancer therapies received before the patients entered the oncology trial with a set treatment regimen. It includes chemotherapy, chemoradiation, and surgery collected via different oncology drugs and biologics eCRFs and mapped to different SDTM domains and SUPPQUAL.

SOLUTION: Acknowledging that the new ADaM dataset will be used to facilitate agency review, it is designed to be comprehensive, integrating data from various SDTM domains and their SUPPQUALs and key variables from ADSL within one ADaM dataset, ADPRIOR. Groups of variables included are (an abbreviated example is illustrated in):

- Core variables from ADSL
- Module of therapy (MODULE)
- Chemotherapy: chemotherapy name (CHEDECOD), line number (CHELNTHP)
- Radiation therapy: type of radiation therapy performed (RADTYPTH)
- Surgery: surgery performed (SURGERY), location, whether surgery is the primary treatment
- Dates: start and end dates of chemotherapy, chemoradiation therapy, and surgery
- Chemotherapy in metastatic setting (METASTAT)

	SUBJID	MODULE	STARTDT	ENDDT	CHEDECOD	CHELNTHP	METASTAT	RADTYPTH	...		SURGERY	...
1	10001	SURGERY	mmddy	mmddy							SURGERY 1	
2	10001	RADIATION	mmddy	mmddy				RADIATION 1				
3	10001	CHEMO	mmddy	mmddy	DRUG 1	ADJUVANT	No					
4	10001	CHEMO	mmddy	mmddy	DRUG 2	FIRST LINE	Yes					
5	10001	CHEMO	mmddy	mmddy	DRUG 3	SECOND LINE	Yes					

chemo related
Radiation related
Surgery related Variables

Table 2. An abbreviated example of ADPRIOR

This ADaM dataset contains one record per subject per treatment with ADaM Other as the data structure. It indicates who received surgery, radiation in conjunction with the chemotherapies, and each chemotherapy. It also provides the metastatic setting, number of prior LOT, number of LOT during the radiation, and whether the progressive disease occurred within 12 months after the chemotherapy.

To be ADaM compliant, in the response, we delivered the SAS transport files for ADSL and the new ADaM dataset ADPRIOR, and the define files for the two datasets. This is a real example of joint effort from multiple functional areas to understand what were needed in ADPRIOR requested by the agency, and to design the display of the information in it. Clear data specification was written based on the review and understanding of eCRF and SDTM data, which enabled the accurate and quick coding of ADPRIOR.

REQUEST 2: To summarize the reasons for corticosteroids use as concomitant medication

BACKGROUND: For immunotherapy, corticosteroids could be used to treat immune-related AEs, including AEs of special interest (AEOSI) and those not of special interest. AEOSI referred to a list of prespecified AE terms developed by the Sponsor.

ADAE.CORTFL is the corticosteroid usage flag, which is derived for subjects with AEs treated with corticosteroids systemically. It is derived from CM, AE, and RELREC domains. ADAE.AEOSIFL is the flag for AE of special interest. A patient could have CORTFL flagged as “Y” while AEOSIFL not as “Y”.

SOLUTION: We reviewed our datasets and programs and identified all the subjects to whom corticosteroids were administered during the study. Among them, we investigated the subjects who

received corticosteroids administered for any AE, including AEOSIs, i.e. the AEs that were identified (flagged) with the CORTFL. Of these subjects, we identified those administered corticosteroids for AEOSIs (indicated with AEOSIFL). Then, we categorized the remaining subjects who received corticosteroids for AEs that were not classified as AEOSIs. Of note, our protocol allows corticosteroid treatment for other AEs, including immune-related AEs, drug-related AEs, and infusion-reactions. Moreover, the use of physiologic doses of corticosteroids may be approved after consultation with the sponsor. In addition, subjects who received corticosteroids for reasons other than an AE were also described.

In the response, we summarized the reasons for corticosteroid use (see the examples below) and explained that coding in the dataset is consistent with the protocol, protocol-associated and guidance documents (Figure 1). Thus, the submitted datasets will not require revision or update.

Examples of Categories of Corticosteroid Administration

- Corticosteroids administered for any AE (CORTFL)
- Corticosteroids administered for AEOSI (CORTFL, AEOSI)
- Corticosteroids administered for AEs not categorized as AEOSI
- Corticosteroids administered for immune-related AEs not classified as AEOSIs (allowed per protocol)
- Corticosteroids administered for study medication-related AEs (allowed per protocol)
- Corticosteroids begun after study medication discontinuation
- Corticosteroids administered for other reasons

Further information for the derivation of the CORTFL variable can be found in the define.pdf, Analysis Derivation section and is copied below for reference.

1. Select CM records where CMGRPID='CM' and with SUPPCM.QVAL= 'CORTICOSTEROIDS FOR SYSTEMIC USE' where SUPPCM.QNAM='CMCLAS2' and CM.CMROUTE contains 'INTRA' or 'ORAL' or ' '.
2. Select AE related records from RELREC, where RDOMAIN='AE' and IDVAR='AESEQ' and merge with AE domain to get corresponding RELID for each AESEQ.
3. Select CM related records from RELREC, where RDOMAIN='CM' and IDVAR='CMSEQ' and merge with CM domain to get corresponding RELID for each CMSEQ.
4. Select the records which exists in both domains AE and CM records

Figure 1. Coding Detail and Guidance for CORTFL

REQUEST 3: Efficacy ADaM data with the same data cut-off date as Safety Update Report (SUR).

BACKGROUND: Both efficacy and safety data were continuously being collected after the sBLA submission. However, the efficacy ADaM datasets were not generated for the SUR package due to the focus of the deliverable. This request came during the simultaneous review of sBLA package and SUR, as the agency wanted to confirm whether there is a change in the efficacy profile that would have an impact to the approval or the label. The updated efficacy reports were not requested. The reason could be that the agency already had the reporting programs we submitted for sBLA and could re-generate the reports with the updated data if needed.

SOLUTION: To address this request, our design was to generate the updated efficacy data with the consistent programming logic for the sBLA. Therefore, the efficacy SDTM data with the same data cut-off date as the SUR were used as the source data; the same ADaM data programs from the sBLA submission were used to generate the efficacy ADaM datasets.

In the response, we included SAS transport files for ADSL and the efficacy ADaM datasets, and the corresponding define files.

The lesson learned from this experience is to keep and clean all the efficacy data collected in the database, although it is not required by certain deliverables, e.g., SUR, data monitoring committee meeting. This allows the quick response to IRs for the efficacy data and/or results.

REQUESTS DURING LABELING

Requests during the labelling process may target the all-commers or a subgroup of the study population depending on the indication to be approved. Requests could be for the reports of baseline characteristics, disposition, exposure duration, follow-up duration, and AE summary. This section describes a request for the summary of pooled AE term.

REQUEST 1: Pooled AE summary report.

BACKGROUND: For the labeling, the agency compiled a table to aggregate similar AEs in calculating and tabulating AEs observed. A PDF file containing the list of pooled terms were received (Refer to Table 3 as an example).

Pooled Term	Preferred Term (PT)
Pooled Term 1	PT 1
	PT 2
	PT 3
	PT 4
	PT 5
Pooled Term 2	PT 6
	PT 7

Table 3. Pooled Term for AE Analysis from the Agency

However, our ADAE dataset does not have a variable for the pooled AE term, and our existing program summarizes AE by the body system or organ class, or by the preferred term, instead of the pooled AE term.

SOLUTION: As only the summary report is requested, we generated an ADAEPL dataset in the OUTDATA folder naming the pooled AE terms as the preferred terms and produced the report. Four steps were taken to accomplish this.

Step 1. Convert the pooled AE listing from the agency into a SAS dataset, AETERM (Refer to Table 4), with two variables, AEPOOL (pooled term) and AEDECOD (PT).

Step 2. Generate a SAS dataset, ADAEPL, using ADAE and AETERM as the source data. ADAEPL is used as the input dataset for the existing report program, in which variable AEDECOD is the pooled AE term. ADAEPL is generated following the process shown in Figure 2.

	AEPOOL	AEDECOD
1	Pooled Term 1	PT1
2	Pooled Term 1	PT2
3	Pooled Term 1	PT3
4	Pooled Term 1	PT4
5	Pooled Term 1	PT5
6	Pooled Term 2	PT6
7	Pooled Term 2	PT7

Table 4. AETERM SAS dataset

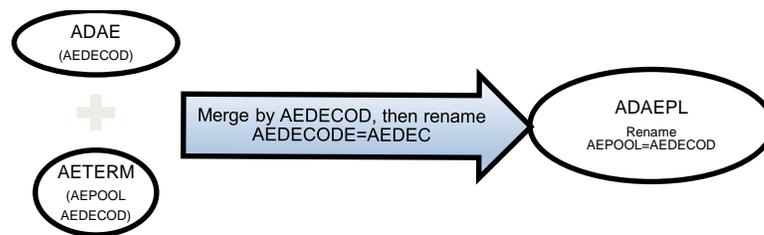


Figure 2. ADAEPL generated with variable AEDECOD

Step 3. Generate a footnote for each pooled AE term in an Excel file, footnote.xlsx (Refer to Table 5), using AETERM from Step 1.

1	Pooled Term	Footnote
2	Pooled Term 1	Includes PT1, PT2, PT3, PT4, PT5.
3	Pooled Term 2	Includes PT6, PT7.

Table 5. footnote.xlsx

Step 4. Generate the report with ADAEPL as the input dataset and footnote.xlsx as the input for the footnote (Refer to Table 6 as a sample report). We reviewed the report and communicated to the physician for the AE terms seemed shall be combined but were not listed in the Pooled Term for AE Analysis file, e.g. anaemia vs. Iron deficiency anaemia, oedema peripheral vs. peripheral swelling. Datasets and the report were then updated based on the confirmation from the physician.

IRs during labelling are generally issued close to the marketing approval, and with very tight timeline for the additional reports. Quick and accurate responses are always required.

	MK-9999 100 mg Q3W	
	n	(%)
Subjects in population	XXX	
with one or more adverse events	XXX	(XX.X)
with no adverse events	XX	(XX.X)
Pooled Term 1	XX	(XX.X)
Pooled Term 2	XX	(XX.X)
...		
...		
Pooled term 1 includes PT1, PT2, PT3, PT4, and PT5.		
Pooled term 2 includes PT6, and PT7.		
...		

Table 6. Subjects with Adverse Events by Alphabetic Order

CONCLUSION

To support the drug approval process effectively, it is important to address IRs accurately in a timely manner, during which knowledge about the study and submission requirements, collaboration with different functional areas, and communication about the questions and timelines are all critical.

It is even more critical to turn the experience working on IRs into an opportunity to configure the future strategies that can be adapted by multiple filings as the basic principles. For example, IRs can be considered in two categories, ADaM dataset and report. For the ADaM dataset, IRs are mainly for requesting new ADaM data, or questions about the data. Therefore, it is essential to include all the variables needed for the summary and analysis in the ADaM datasets if possible. Meanwhile, we also need to be prepared to generate the new ADaM data from different data sources, with the appropriate data structure upon the request. For the report, especially the report for subgroups of the study population, it is ideal to use the existing programs without any revision. A practical way to accomplish this is to allow the flexibility to specify the parameters for report population, sub-titles, and filenames outside the report program.

To conclude, compliance with the CDISC data standards and FDA submission standards are vital for a successful new drug submission, understanding the regulatory requirements will help streamline the process, and a good planning of submission package in the early stage of ADaM datasets and reports design will help maintain a high quality of the submission documents and address IRs with seamless effort.

RECOMMENDED READING

1. Kimberly Umans, Katherine Riester, Manjit McNeill, Maidenhead, Wei Liu, USALukasz Kniola, Maidenhead. Paper CD06 of PhUSE 2016. "Analysis Datasets for Baseline Characteristics and Exposure Time for Multi-stage Clinical Trials". Available at <https://www.lexjansen.com/phuse/2016/cd/CD06.pdf>
2. April 1, 2018. "CFR - Code of Federal Regulations Title 21", Available at <https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=312.6>
3. Hong Qi, Majdoub Haloui, Larry Wu, Gregory T. Golm. Paper DS11 of PhUSE 2018. "Automate Analysis Results Metadata in the Define-XML v2.0", Available at <https://www.lexjansen.com/phuse-us/2018/ds/DS11.pdf>

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CONTACT INFORMATION <HEADING 1>

Your comments and questions are valued and encouraged. Contact the author at:

Hong Qi
Principal Scientist, Statistical Programming
Merck & Co., Inc.
hong_qi@merck.com

Lei Xu
Director, Biostatistics
Merck & Co., Inc.
lei_xu2@merck.com

Mary N. Varughese
Executive Director, Statistical Programming
Merck & Co., Inc.
mary_varughese@merck.com

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