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Strategic Statistical Programming for ADR Table Generation in Regulatory Submissions and Corporate Applications

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ABSTRACT

Adverse Drug Reactions (ADRs) are critical components in regulatory documentation, including Module 2.7.4 (Summary of Clinical Safety), Summary of Product Characteristics (SmPC), Company Core Data Sheet (CCDS) and any other documents concerning labeling. These elements are essential for both regulatory submissions and internal corporate use.

This paper outlines a comprehensive statistical programming strategy for the generation of ADR tables, emphasizing regulatory compliance and procedural rigor. It details how programming support contributes to meeting health authority requirements and delivering timely, high-quality outputs. Additionally, the paper describes a structured workflow designed to efficiently respond to requests from cross-functional teams, ensuring consistency and accuracy in ADR data presentation.

INTRODUCTION

Adverse Drug Reaction (ADR) defined as “an undesirable effect, reasonably associated with the use of a drug, that may occur as part of the pharmacological action of the drug or may be unpredictable in its occurrence. This definition does not include all adverse events observed during use of a drug, only those for which there is some basis to believe there is a causal relationship between the drug and the occurrence of the adverse event.”1 from 21 CFR 201.57(c)(7).

While ICH Topic E2A adopted by EMA has similar definition but more detailed to distinguish the definition for pre-approval and marketed medicinal products[2]: Pre-approval with a new medicinal product “all noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions.”. Marketed medicinal products “A response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of disease or for modification of physiological function.”. ICH E2A also pointed that “The old term "side effect" has been used in various ways in the past, usually to describe negative (unfavourable) effects, but also positive (favourable) effects. It is recommended that this term no longer be used and particularly should not be regarded as synonymous with adverse event or adverse reaction.”

ADR will help prescription drug labeling significantly, and what health authorities really approved is the drug label.

Per FDA guidance[1] “If there are no major study-to-study differences in study design, study population, and adverse reaction rates, an overall pooling of safety data from multiple studies may increase the precision of adverse reaction rates and provide a more clinically useful representation of a drug’s adverse reaction profile.”. We usually use SCS (Summary of Clinical Safety) data to generate ADR tables for each labeling update purpose.

HOW ADR TABLES SUPPORT M2.7.4, SMPC AND CCDS

The presentation of ADR tables should comply with FDA requirement, and ADR tables will act as a key driver in M2.7.4, SmPC, CCDS, or any other documents concerning product labeling, see Figure 1.

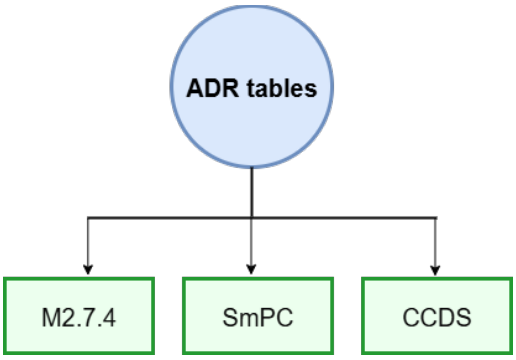


Figure 1. ADR tables as a key driver

GENERAL PRINCIPLES FOR PRESENTING ADR DATA IN A TABLE OR LIST

Per FDA industry guidance "Adverse Reactions Section of Labeling for Human Prescription Drug and Biological Products — Content and Format"[1], 10 general principles should be followed.

1. Pooling Data:

   If no major differences in study design, population and ADR rates, an overall pooling of safety data from multiple studies may increase the precision of ADR rates and provide a more clinically useful representation of a drug's adverse reaction profile. So we usually draft ADR tables from Summary of clinical safety (SCS) data.

2. Classifying Adverse Reactions:

   Adverse reactions should be classified using meaningful and specific terms that best communicate the nature and significance of the reaction. There should ordinarily be a common classification scheme across all studies in the safety database. Events that are reported under different terms in the database, but that represent the same phenomenon (e.g., sedation, somnolence, drowsiness) should ordinarily be grouped together as a single adverse reaction to avoid diluting or obscuring the true effect. Similarly, adverse events reported in more than one body system that appear to represent a common pathophysiologic event should be grouped together to better characterize the reaction. For example, an allergic-type adverse event that has respiratory (wheezing) and dermatologic (rash, urticaria) manifestations should be classified as a single adverse reaction (e.g., hypersensitivity).

   Study clinical safety & pharmacovigilance (CSPV) department should provide the ADR listing in grouping/single term and classify the grouping/single terms into one body system by phenomenon.

3. Categorizing Adverse Reactions:

   Within a listing, adverse reactions must be categorized by body system, by severity of reaction, in order of decreasing frequency, or by a combination of these, as appropriate. Within a category, adverse reactions must be listed in decreasing order of frequency. If frequency cannot be reliably determined, adverse reactions must be listed in decreasing order of severity.

4. Frequency Cutoff:

   The frequency cutoff for the listing of common adverse reactions identified from clinical trials (usually the adverse reactions table) must be appropriate to the safety database. Factors that could influence selection of a frequency cut-off include the size of the safety database, the designs of the trials in the database, and the nature of the indication. The frequency cutoff should be noted in the listing or table header, in the text accompanying the listing or table, or in a footnote.

5. Quantitative Data:

   For quantitative data (e.g., abnormal laboratory values, vital signs, ECGs), it is usually preferable to present rates of abnormal values and to specify the cutoff value for inclusion (e.g., five times the upper limit of normal) than to refer to a grading system.

6. Denominator:

   “N = number of patients” should be provided for each column as we did usually.

7. Subgroup Rates:

   The rates for reactions that are specific to a subgroup (e.g., sex-specific reactions such as menstrual irregularity) should be determined using the appropriate denominator, and that denominator should be identified in a footnote. If rates of specific adverse reactions were gathered for only a subgroup of patients or studies (e.g., an adverse effect on a laboratory test), that fact should be disclosed in a footnote.

8. Percentages:

   Adverse reaction rates expressed in percentages should ordinarily be rounded to the nearest integer. An exception would be for particularly serious adverse reactions (e.g., stroke, intracranial hemorrhage, agranulocytosis) occurring at low rates in a large study where fractions of a percent may be meaningful.

9. Adverse Reaction Rates for Drug Less Than for Placebo:

   Adverse reactions for which the placebo rate equals or exceeds the rate for the drug (after rounding) should not be included in the ADVERSE REACTIONS section unless there is some compelling factor (e.g., timing) that suggests that the event is caused by the drug. In that case, the adverse reaction should be discussed in the commentary following the table.

10. Significance Testing:

    Results of significance testing should be omitted unless they provide useful information and are based on a prespecified hypothesis in an adequately designed and powered study.

Because ADR tables are usually used in summary reports, for better supporting author for drafting summary reports, stats programmers will provide ADR tables in in-text format to facilitate copy & paste directly. See an example of ADR table in Display 1.

Table xx.x: Adverse Drug Reactions in Drug X Reported in >= 10% of Subjects or Events of Grade 3 or Grade 4 Reported >= 2% of Subjects in Drug X Arm, by MedDRA System Organ Class and Preferred Term/Grouped Term (Safety Analysis Set)

MedDRA System Organ Class	Drug X (N = 200)					Comparison Drug (N = 190)				
Preferred Term/ Grouped Term		Number (%) of Subjects					Number (%) of Subjects			
		CTCAE Grade			SAE		CTCAE Grade			SAE
	Frequency [1]	All Grades	Grade 3 or 4	Grade 5		Frequency [1]	All Grades	Grade 3 or 4	Grade 5	
Subjects with any ADR	--	182 (91.0)	100 (50.0)	6 (3.0)	51 (25.5)	--	165 (86.9)	138 (72.6)	1 (0.5)	42 (22.1)
SOC 1										
Group term 1 [a]	Very Common	125 (62.5)	63 (31.5)	0	4 (2.0)	Very Common	111 (58.4)	63 (33.2)	0	6 (3.2)
Group term 2 [b]	Very Common	89 (44.5)	56 (28.0)	0	10 (5.0)	Very Common	98 (51.6)	48 (20.6)	1 (0.5)	8 (4.2)
Single term 1	Common	7 (3.5	0	0	12 (6.0)	Common	11 (6.8)	13 (6.8)	0	6 (3.2)

Display 1. Example for presenting ADR table

M2.7.4 SUMMARY OF CLINICAL SAFETY

M2.7.4 refers to Summary of Clinical Safety (SCS). This section should be a summary of data relevant to safety in the intended patient population, integrating the results of individual clinical study reports as well as other relevant reports[3].

Based on the available guidance documents for the Common Technical Document (CTD), Module 2.7.4, which is the Summary of Clinical Safety, does not explicitly require ADR tables. However, it does require a comprehensive summary of safety data, which often includes[4]:

- Analysis of adverse events.
- Common adverse events.
- Deaths.
- Other serious adverse events.
- Other significant adverse events.
- Analysis of adverse events by organ system or syndrome.

While ADR tables are not mandated by name, including them can be highly beneficial for clarity and completeness, especially when summarizing safety data across multiple studies. The use of tables and figures is encouraged when they enhance readability, and lengthy tables may be placed in appendices or referencing them from Module 5.3.5.3 (Integrated Summary of Safety (ISS)) if they originate from pooled analyses.

SMPC

A document describing the properties and the officially approved conditions of use of a medicine. Summaries of product characteristics form the basis of information for healthcare professionals on how to use the medicine safely and effectively. Abbreviated as SmPC.

The European Medicines Agency (EMA) makes guidance and templates available to provide marketing authorisation applicants with practical advice on how to draw up the product information for human medicines, which includes the summary of product characteristics, labelling and package leaflet.

SmPC required at M1.3.1 per “EU Module 1 Specification”[5].

Per EMA guideline “A GUIDELINE ON SUMMARY OF PRODUCT CHARACTERISTICS (SmPC)”[6], In order to provide clear and readily accessible information, ‘Undesirable effects’ (ADR section) should be structured according to the following recommendations:

1. Summary of the safety profile.
2. Tabulated summary of adverse reactions.
3. Description of selected adverse reactions.
4. <Paediatric population>.
5. <Other special population(s)>.

All ADRs should be grouped according to the following order based on the MedDRA system organ classes (SOC). As a general rule, MedDRA terms should be classified according to the most relevant SOC related to the target organ. A pragmatic approach to the location of terms should be taken in order to make the identification of adverse reactions simpler and clinically appropriate for the reader. For example, it may be helpful on some occasions – solely in the context of the SmPC - to use secondary SOC locations of some MedDRA Preferred Terms (PT), or sometimes to use locations that do not strictly accord with the MedDRA architecture. For example, if the PT ‘Liver function test abnormal’, ‘Hepatitis’ and ‘Hepatic encephalopathy’ are to be included in an SmPC, it would be acceptable to include them all under the SOC ‘Hepatobiliary disorders’ instead of distributing the reactions among the SOCs ‘Hepatobiliary disorders’, ‘Nervous system disorders’ and ‘Investigations’ as dictated by their primary location in MedDRA.[6]

CCDS

CCDS is a document prepared by the marketing authorisation holder (MAH) containing, in addition to safety information, material relating to indications, dosing, pharmacology and other information concerning the product (see Annex IV, ICH-E2C(R2) Guideline)[7]. Speaking of CCDS, it is a master labeling document. This is also used as a reference document for the national label.

The structure of CCDS is an internal company decision, but it can be based on a local format like:

- SmPC (Summary of Product Characteristics) Format
- USPI (United States Prescribing Information) Format – Old
- USPI Format (PLR – Patient Labelling Rule) – New

The following are the mandatory and the optional contents to be included in Company Core Data Sheet.

- Therapeutic class
- Indications
- Dosage and Administration
- Contraindications
- Warnings/Precautions
- Drug Interactions
- Pregnancy/Nursing
- Special Populations
- Adverse Reactions/Side Effects
- Overdosage
- Chemistry (optional)
- Structure (optional)
- Mechanism of Action (optional)
- Clinical Pharmacology (optional)
- Clinical Studies (optional)
- Animal Toxicity (optional)

CASE STUDY SHARING

STUDY BACKGROUND

A pivotal phase III oncology study was planned to do the EU Global Submission.

For ISS, our pooling strategy is to pool 10 studies with the same indication, and two pooling arms along with the arms in pivotal study.

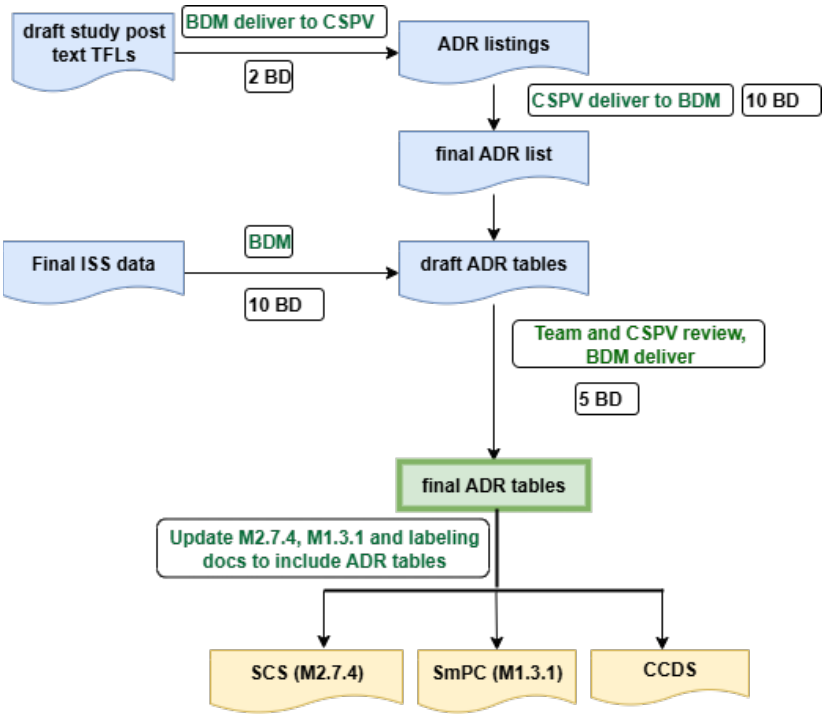
ADR TABLES GENERATION PROCESS

Determination and delivery of ADRs is not on the critical path for the submission, but is a key driver of M2.7.4 and the labeling.

As stats programmer, although we are not the author of summary or labeling documents, we are the key supporting function for ADR tables generation.

Figure 2 shows the general process for ADR tables generation and where ADR tables will go finally.

- Biostatistics and Data Management (BDM) (mainly refers to stat and stats programmer) will deliver ADR listing to Clinical Safety and Pharmacovigilance (CSPV) in 2 business days (BD) from draft pivotal study post text TFLs.
- CSPV deliver final ADR list to BDM in 10 BD from ADR listing.
- BDM deliver draft ADR tables in 10 BD from final ADR list.
- BDM deliver final ADR tables in 15 BD from final ADR list.



BDM: Biostatistics and Data Management

CSPV: Clinical Safety and Pharmacovigilance

Figure 2. ADR tables generation process

CHALLENGES FROM CASE STUDY

Due to the complexity of pooling safety data, interrelated and interdependent processes and the varying definitions and requirements across different submission documents, we truly faced significant challenges. Below I will pick up the outstanding challenges we had from stats programming view.

- Difficult timeline planning.

  As described in section of ADR generation process, we can see ADR tables will impact the earlier steps and process in the whole submission package. If the timeline not planned well or one step delayed, the whole process will not wheel. Thus, it is very important to identify the decisive step which will impact ADR tables programming. And our experience is to start programming with draft ADR listing, but to avoid multiple update for each ADR table, an external macro for ADR listing is recommended. When final ADR listing arrived, we can just update the external macro and rerun all tables.

- SOC and grouping term/single PTs is re-defined for ADR tables rather than regular SOC we put in ISS dataset.

  We need to identify each SOC and grouping terms/single PTs by the ADR listing provided by CSPV. And re-derive them at table level.

- Adjudicated events and adjudicated as non-events but with the same PT term need to be presented separately.

  Same PT terms outputted in both adjudicated events and adjudicated as non-events is not expected. We need to distinguish them carefully and double check by lead programmer is critical.

- Footnotes added by descending frequency order for each grouping term with superscript a, b, c…, we need to handle footnotes by dynamic programming method.

- Different sources for grouping term and toxicity grades.

  Other than the source from AE collected form, we may have the source from lab or other tests, which will increase the programming difficulties. If we choose to develop at table level, then we need to figure out the correct definition for each ADR term when they also come from other source. E.g. "Ejection fraction decreased (grouped term) includes Laboratory parameters of LVEF decrease and PTs of Acute left ventricular failure, Acute right ventricular failure, Cardiac failure, Cardiac failure acute, Cardiac failure chronic, Cardiac failure congestive, Chronic left ventricular failure, Chronic right ventricular failure, Ejection fraction decreased, Left ventricular dysfunction, Left ventricular failure, Right ventricular failure and Ventricular failure."

  For toxicity grades, we may also have different sources. E.g. adjudicated events and non-adjudicated ADR term. Adjudicated events need to consider the grades from adjudication committee.

CONCLUSION

Usually stats programming are the supporting function for submission, but if we can know more about regulatory requirements and know what the authors really expected, then we can serve the purpose better and more precisely. Back and forth communications between functions can be reduced significantly. Hope this paper can clarify the ADR tables purpose and what we can do to support study team better.

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