

Why FDA Medical Queries (FMQs) for Adverse Events of Special Interest? Implementation and Case Study

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ABSTRACT

There are many challenges associated with safety analyses and reporting of adverse events in clinical trials, including, but not limited to, study design issue, coding of the AEs, selection of the AEs of special interest (AESIs), inadequate grouping of likely or potential related AEs, events present in different ways or are reported with different terms, or AEs that are too specific can result in underestimation of an event.

To standardize the NDA/BLA safety data review process, the U.S. FDA/CDER has published two documents on 05 September 2022 and collaborated with the Duke-Margolis Center for Health Policy to host a public workshop on 14 September 2022 to introduce the FDA Medical Queries (FMQs) and Standard Safety Tables and Figures Integrated Guide.

The author has actively reviewed and promoted the implementation of FMQs at the author company to resolve AESIs issue of un-identifiable legacy studies defined Customized MedDRA® Queries (CMQs), that led to the official implementation of this newly released AE grouping.

This paper will share the experience of promoting and implementing FMQs, evaluating FDA published FMQ docket for potential issues and providing feedback to enhance future releases. Developing of efficient standardized end-to-end FMQ data pulling, AESIs data analysis and reporting processes. Incorporating Standardized MedDRA Queries (SMQs), FMQs, along with potential company defined CMQs to standardize medical monitoring process to ensure the consistent implementation within company itself.

The paper will also share an FMQ case study for NDA ISS analysis and CSR reporting.

INTRODUCTION

The safety analyses provide a broad evaluation of the safety profile to support the regulatory submissions and proposed label application. A comprehensive summary of all data pertaining to safety of an investigational drug will be provided in the following ways:

- Safety data from all sponsored studies will be provided in the form of Clinical Study Reports (CSRs) or an abbreviated CSR if the study is ongoing.
- Data from legacy and/or ongoing studies with similar characteristics will be pooled to improve precision of estimates and sensitivity in comparison between treatment groups. The Integrated Summary of Safety (ISS) provides clinical evidence of the safety and is used to support the global regulatory filing for the marketing of the investigational drug.

Analysis of Adverse Events, Deaths, and Adverse Events of Special Interest (AESIs) are some of the major safety analysis endpoints for most clinical trials CSR and ISS. Study CSR and ISS will present treatment-emergent AEs coded by System Organ Class (SOC) and Preferred Term (PT) using MedDRA dictionary, the verbatim terms will be included in the AE Listings.

Reporting AESI is an emerging and more critical aspect related to characterizing the safety profile of an investigational drug in clinical trials. It is important to define clearly in the protocol or Statistical Analysis Plan (SAP) and to specify close monitoring and prompt reporting.

Sponsors have adopted the Council for International Organizations of Medical Sciences (CIOMS) VII definition of an Adverse Event of Special Interest (AESI), which is *“An adverse event of special interest (serious or non-serious) is one of scientific and medical concern specific to the sponsor’s product or programme, for which ongoing monitoring and rapid communication by the investigator to the sponsor may be appropriate. Such an event may require further investigation in order to characterize and*

understand it. Depending on the nature of the event, rapid communication by the trial sponsor to other parties may also be needed (e.g., regulators)."

ADVERSE EVENT OF SPECIAL INTEREST (AESI) - CHALLENGES AND GAP ANALYSIS

At the time of writing of this document, the author company investigational drug has been or is being evaluated in 53 legacy and 3 ongoing studies. NDA ISS consists of 5 legacy phase 2a/2b/3 open-label/double-blinded studies and 2 ongoing Phase 2/3 pivot trials, the AE MedDRA versions span across versions 13.0 to 24.0. The individual studies and ISS Statistical Analysis Plans (SAPs) specify how the safety data from each of the individual studies will be presented, the pooling/integrating strategies, and the statistical analyses to be performed with pooled/integrated data for the ISS. Results from the analyses with pooled/integrated data will become the basis for the ISS.

One of the challenges we have encountered with ISS is the definition of AEs of special interest (AESIs), they were defined differently across varied legacy studies which are part of an in-licensed product from another biopharmaceutical company, with limited or no access to the original studies documentation and coding information except the studies CSR reports. Based on the gap analysis, we have identified that the company has defined AESIs using the combinations of MedDRA PTs grouping, SMQs and/or sponsor defined customized MedDRA queries (CMQs) without supported documentation and specification. Our ISS statistics and statistical programming team have spent significant amount resources and time to investigate the potential AESIs definition and criteria, the questions remain unclear, were these AESIs defined based on MedDRA grouping (PTs, HLTs, HLTGs, SOC), SMQs, CMQs or all those combined?

In the mist of working on the AESIs definition without perfect data match with legacy studies CSR reports, FDA has published two documents - FDA Medical Queries (FMQs) and Standard Safety Tables and Figures (ST&F) Integrated Guide on September 5, 2022 to standardize the safety data review process within the agency and hosted the workshop for public comments.

In need of determining AE groupings to match CSR reports yet have better estimates of the AESIs, the author has reviewed FDA docket, performed impacts analysis and recommendations to the author company NDA ISS team and to FDA as per October 31, 2022 public review comments deadline. The efforts have led to high level stakeholders team discussions and later decided to implement FMQs as standard AESIs selection process for the author company.

POTENTIAL ADVERSE EVENT GROUPINGS FOR AESI

There are many approaches sponsors use to identify AESIs, including but not limited to:

- PTs
- Pre-defined SMQs
- CMQs that are specific to a therapeutic area (TA) or a compound or a study, but they are not pre-defined with the MedDRA
- Medical Monitoring or Clinical confirmed adjudication process for selected AEs
- Protocol/CRF defined AESIs that are captured at the database

This section provides a summary of adverse event groupings that can be used to identify AESIs.

MEDDRA LEVELS

The Medical Dictionary for Regulatory Activities (MedDRA) (<http://www.meddra.org>) is a clinically validated international medical terminology dictionary used by regulatory authorities and the biopharmaceutical industry during the regulatory process. MedDRA terminology is hierarchical, multi-axial, multilingual, regularly updated, and strictly maintained.

MedDRA versioning: MedDRA is updated twice a year.

- 1 March xx.0 release (all levels)
- 1 September xx.1 release (LLT and PT levels only)

The hierarchical structure of MedDRA consists of 5 levels, arranged from very general to very specific. As of MedDRA version 24.0 released in March 2021 which supports the ongoing studies and NDA ISS submissions, there are total of:

- 27 unique System Organ Classes (SOCs)
- 337 unique High Level Group Terms (HLGTs)
- 1737 unique High Level Terms (HLTs)
- 24820 unique Preferred Term (PTs)
- 83291 unique Lowest Level Terms (LLTs)

SMQ

Standardized MedDRA Queries (SMQs) (<https://www.meddra.org/standardised-meddra-queries>) are tools developed to facilitate retrieval of MedDRA-coded data as a first step in investigating drug safety issues in pharmacovigilance and clinical development. SMQs are validated, pre-determined sets of MedDRA terms grouped together after extensive review, testing, analysis, and expert discussion. SMQs include a large list of PTs which may span across different SOC which are used for assessing a safety topic of interest. SMQs are a unique feature of MedDRA and provide a strong tool to support safety analysis and reporting.

The SMQs are maintained with each release of MedDRA by the MSSO. As of SMQ version 24.0 released in March 2021 for our NDA ISS and ongoing studies AE analysis, there are a total of:

- 108 unique SMQ1CODE/SMQ1NAME
 - 2 more SMQs were added to later versions - v24.1 added Sexual dysfunction (SMQ), v25.0 added Noninfectious myocarditis/pericarditis (SMQ).
- 82 unique SMQ2CODE/SMQ2NAME
- 20 unique SMQ3CODE/SMQ3NAME
- 16 unique SMQ4CODE/SMQ4NAME
- 2 unique SMQ5CODE/SMQ5NAME

Some SMQs are a simple set of PTs while other SMQs are hierarchical containing subordinate SMQs. The search strategy for SMQs can be narrow or broad. The preferred Terms (PTs) that are narrow in scope have high specificity for identifying event of interest, whereas the broad terms have high sensitivity. By definition, all narrow terms are also considered within the broad scope. Therefore, to summarize all broad terms, terms with either narrow or broad would be considered.

The MedDRA higher levels grouping (HLT, HLGT, and SOC), as well as SMQs, are used for searching and for organizing and subtotaling outputs.

CMQ

Customized MedDRA Queries (CMQs) are sponsor defined tools developed to address their investigational drugs safety analysis needs. CMQs are typically defined per TA, compound, or study-by-study basis with TA, compound, or study-specific rules applicable to the sponsor only.

Often time, sponsors utilize their defined standard search strategies to develop a specification and an operational definition of the AESI. An AESI may be identified and determined by following methods to represent the safety risk:

- PTs in a SMQ

- List of SMQs with study-specific modifications
- An ad hoc list of PTs agreed by clinical/sponsor
- Can be programmatically defined with criteria and algorithm provided by clinical
- The results of the laboratory tests

Identifying AESI using CMQs often involve adjudication process that statistics/programming team need to work closely with medical/clinical team, it is important to document why and what changed (i.e., removal or addition of the existing/pre-defined AE groupings) and it is best to set up standard programming and clinical reviewing/confirming process and timeline if a CMQ method is utilized.

FDA MEDICAL QUERIES (FMQS)

To improve safety signal detection, the FDA/CDER has developed 104 standardized groupings of PTs known as “FDA Medical Queries” (FMQs), each FMQ represents a distinct medical concept (e.g., Anemia, Nausea, Vomiting, etc.) and stand on their own that may be shared by dozens or even hundreds of PTs.

The FMQ is a standardized approach to group preferred terms. Recognizing the limitation of the current analysis of adverse event data by preferred term, using FMQs can consolidate a medical condition with scattered preferred terms and be more likely to identify any signal of safety issues.

FDA MEDICAL QUERIES (FMQS)

The rationales for FDA's efforts in developing various FMQs are described in Figure 1.

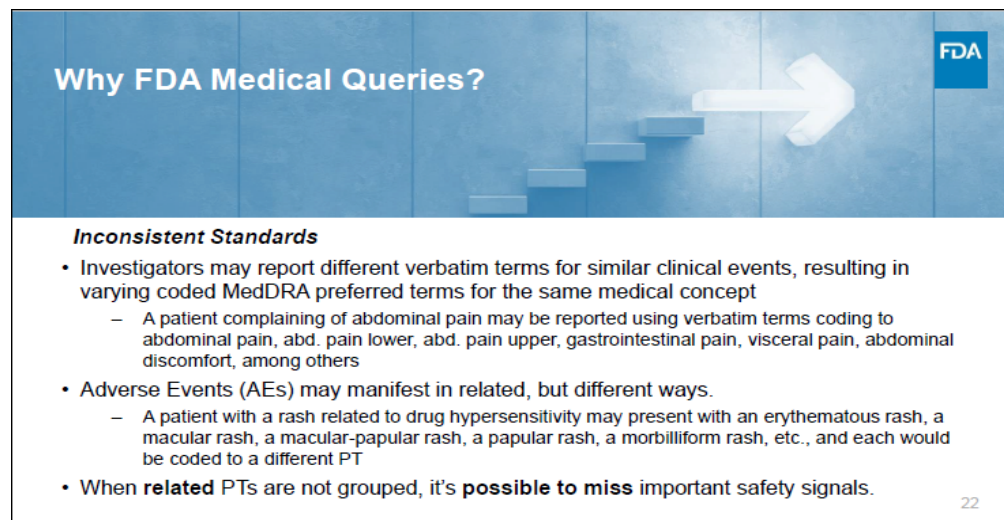


Figure 1. Why FDA Medical Queries?

FMQ Concepts

- Narrow FMQ terms: Specific for the medical concept, indicate that the FMQ occurred, more than ~90% probability.
- Broad FMQ terms: Less specific, provide reasonable assurance (more than ~30% probability) that the medical concept occurred.
- Algorithmic FMQs:
 - Uses data from AE, laboratory, concomitant medications, medical history data sets and temporal relationships to leverage the available information.
 - Cumulative Approach: includes current PTs, former PTs, misspelled terms. PTs from MedDRA v7.0 (March 2004) through v25.0 (March 2022) were added if met the FMQ

Ground Rules, therefore, FMQ can be applied to any legacy and/or ongoing trials using MedDRA v7.0 and later versions.

- NDA/BLA clinical trial database of over 10,000 studies.

FMQ Ground Rules

- Narrow Queries: Indicates FMQ concept occurred.
- Broad Queries: Reasonably suggestive of FMQ concept occurrence.
- PTs Excluded from FMQs: terms that are too vague.

FMQ Terms

FDA FMQ version 2.1 published on September 5, 2022, consists of 104 unique FMQs (Figure 2).

1 Abdominal Pain	27 Diabetic Ketoacidosis	53 Hypotension	79 Rash
2 Abnormal Uterine Bleeding	28 Diarrhea	54 Insomnia	80 Renal & Urinary Tract Infection
3 Acute Coronary Syndrome	29 Dizziness	55 Irritability	81 Respiratory Depression
4 Acute Kidney Injury	30 Dry Mouth	56 Leukopenia	82 Respiratory Failure
5 Alopecia	31 Dysgeusia	57 Lipid Disorder	83 Rhabdomyolysis
6 Amenorrhea	32 Dyspepsia	58 Local Administration Reaction	84 Seizure
7 Anaphylactic Reaction	33 Dyspnea	59 Malignancy	85 Self-Harm
8 Anemia	34 Erectile Dysfunction	60 Mania	86 Sexual Dysfunction
9 Angioedema	35 Erythema	61 Myalgia	87 Somnolence
10 Anxiety	36 Excessive Menstrual Bleeding	62 Myocardial Infarction	88 Stroke and TIA
11 Arrhythmia	37 Fall	63 Myocardial Ischemia	89 Study Agent Abuse Potential
12 Arthralgia	38 Fatigue	64 Nasopharyngitis	90 Syncope
13 Arthritis	39 Fracture	65 Nausea	91 Systemic Hypertension
14 Back Pain	40 Fungal Infection	66 Opportunistic Infection	92 Tachycardia
15 Bacterial Infection	41 Glaucoma	67 Osteoporosis	93 Tendinopathy
16 Bacterial Vaginosis	42 Gout	68 Palpitations	94 Thrombocytopenia
17 Bronchospasm	43 Gynecomastia	69 Pancreatitis	95 Thrombosis
18 Cachexia	44 Headache	70 Parasomnia	96 Thrombosis Arterial
19 Cardiac Conduction Disturbance	45 Heart Failure	71 Paresthesia	97 Thrombosis Venous
20 Cholecystitis	46 Hemorrhage	72 Peripheral Edema	98 Tremor
21 Confusional State	47 Hepatic Failure	73 Pneumonia	99 Urinary Retention
22 Constipation	48 Hepatic Injury	74 Pneumonitis	100 Urticaria
23 Cough	49 Hyperglycemia	75 Pruritus	101 Vertigo
24 Decreased Appetite	50 Hyperprolactinemia	76 Psychosis	102 Viral Infection
25 Decreased Menstrual Bleeding	51 Hypersensitivity	77 Purulent Material	103 Volume Depletion
26 Depression	52 Hypoglycemia	78 Pyrexia	104 Vomiting

Figure 2. FDA Published 104 FMQs (September 5, 2022)

FDA STANDARD SAFETY TABLES AND FIGURES (ST&F) INTEGRATED GUIDE

The rationales for FDA's efforts in developing Standard Safety Tables and Figures (ST&F) Integrated Guide document are described in Figure 3.



Why Standard Safety Tables & Figures?



<i>Inconsistent Standards</i>	<i>A Collective Way Forward</i>	<i>An OND Standard</i>
<ul style="list-style-type: none"> • Tables and figures not produced in a standard manner across Divisions/ Teams/Applicants. • Significant variability in similar safety signal evaluation related tables and figures 	<ul style="list-style-type: none"> • Develop standard safety analyses in a consistent format to facilitate safety evaluation • Create uniform data presentation & visualization that reflect formatting standards used in major medical journals 	<ul style="list-style-type: none"> • Launched standardized safety analyses • Created a set of standard safety analyses considered important for premarket clinical safety evaluation • Established formatting standards that create consistency in analyses produced

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Figure 3. Why FDA ST&F?

Adverse Event Analyses are one of the ST&F Integrated Guide section, including Overview of AEs, Serious AEs, AEs Leading to Discontinuation, AEs of Special Interest (AESIs) and FDA Medical Queries (FMQs) arranged by System Organ Class (SOC). All AE tables and figures present treatment-emergent adverse events (TEAEs) as a default.

Figure 4 provides the FDA proposed FMQs related tables, including Table 10. SAEs by SOC and FMQ (Narrow) table, and Table 34. SAE by SOC, FMQ (Narrow) and PT.

System Organ Class ³	Drug Name Dosage X N = XXX n (%)	Drug Name Dosage Y N = XXX n (%)	Active Control N = XXX n (%)	Placebo N = XXX n (%)	Risk Difference (%) (95% CI) ⁴
SOC1					
FMQ1	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
FMQ2	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
SOC2					
FMQ3	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
FMQ4	n (%)	n (%)	n (%)	n (%)	X (Y, Z)

System Organ Class ³	Drug Name Dosage X N = XXX n (%)	Drug Name Dosage Y N = XXX n (%)	Active Control N = XXX n (%)	Placebo N = XXX n (%)	Risk Difference (%) (95% CI) ⁴
FMQ (Narrow) ³					
SOC1					
FMQ1	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
PT1	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
PT2	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
FMQ2	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
PT1	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
PT2	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
SOC2					
FMQ1	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
PT1	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
PT2	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
FMQ2	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
PT1	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
PT2	n (%)	n (%)	n (%)	n (%)	X (Y, Z)

Figure 4. FDA Proposed FMQ Tables

FDA FMQS AND ST&F INTEGRATED GUIDE PUBLIC REVIEW AND COMMENTS

As FDA were collecting public comments for the published FMQs and ST&F documents by October 31, 2022, the author has conducted impact analyses and reviews for potential implementation issues and submitted comments to the FDA to make improvements for the future release.

The general FMQs related comments for the two documents are:

- Consider providing a document describing detailed rationale behind the FMQs definitions and their proposed use.
- There are inconsistencies in the Microsoft Excel® formatting, for example, when the Heart Failure FMQ is sorted by scope category (Narrow/Broad), there are 4 rows at the end which do not sort.
- The FMQ References worksheet tab SOC terms inconsistency issue, SOC with mixed cases need to be standardized per MedDRA AESOC naming convention.
- There are several un-matched/inconsistent items between the Consolidated_List worksheet tab and other worksheet tabs, below lists the issues identified:
 - [Consolidated_List] Heart Failure FMQ has 4 less records than the individual FMQ worksheet tab.

FMQ	PT	Final Classification
Heart Failure	Dynamic cardiomyoplasty	Narrow
Heart Failure	Heart transplant failure	Broad
Heart Failure	Heart-lung transplant failure	Broad
Heart Failure	Septic cardiomyopathy	Narrow

- [Consolidated_List] has two records with inconsistent FMQ term names than other worksheet tabs.

TOC, FMQ References and Individual FMQ Worksheet Tabs	Consolidated_List Worksheet Tab
Renal & Urinary Tract Infection	Renal and Urinary Infection
Self-Harm	Self Harm

- For ST&F with FMQ nested under SOC, for ease of programming implementation, either include the SOC in the Consolidated_List worksheet tab, or alternatively forgo nesting within SOC in tables as it does not seem necessary.
- Currently, there is no guidance on how SOC are ordered in tables with PTs/FMQs nested within SOC. If there is a preference, consider including such guidance (e.g., by decreasing frequency versus alphabetical).

FMQ IMPLEMENTATION AND PROGRAMMING E2E PROCESS

As we have encountered issues and challenges when determining the AESIs for the ISS submissions, FDA released FMQs and ST&F documents provided potential resolutions considering sponsors may be required to implement these standards once FDA finalize the documents. With this in mind, the author has reviewed and utilized FMQs to perform impact analyses and recommendations to our NDA ISS leadership team in October 2022, we then got the green light to utilize FMQs to identify AESIs for ISS and ongoing studies AE related analyses.

We have set up global standard FMQ metadata/lookup, CDISC ADaM data, Tables and Figures reporting end-to-end programming process for FMQ implementation.

SOURCE DATA FROM FDA FMQS DOCUMENT

The FDA Medical Queries (FMQs) document is a MS Excel Macro-Enabled file (FDA-2022-N-1961-0001_attachment_1.xlsm), it consists of 108 worksheet tabs, including Table of Contents, FMQ References, Instructions, Consolidated_List, and 104 individual FMQs.

Here is the breakdown of FMQ Excel file:

- 104 unique FMQs (Figure 2).
- 204 not 208 unique FMQ/Scope pair, assuming there are 104 FMQs would have 104 Narrow scope and 104 Broad scope, however, the total number of the FMQ/Scope are 204, 4 FMQs only have Narrow scope.
 - 100 FMQs have both Broad and Narrow scope.
 - 4 FMQs have only Narrow scope: Irritability, Palpitations, Purulent Material, Tachycardia.
- 20 unique SOC of FMQs, 6 SOC have mixed-cases terms that need to be standardized using MedDRA AESOC when generate the SOC/FMQ/PT set of lookup and report:
 - Gastrointestinal Disorders vs. Gastrointestinal disorders
 - General Disorders and Administration Site Conditions vs. General disorders and administration site conditions
 - Nervous System Disorders vs. Nervous system disorders
 - Psychiatric Disorders vs. Psychiatric disorders
 - Renal and Urinary Disorders vs. Renal and urinary disorders
 - Skin and Subcutaneous Tissue Disorders vs. Skin and subcutaneous tissue disorders
- 8842 total unique PTs of FMQs, 2186 PTs are included in more than 1 FMQs, 25 PTs are included in 5 to 8 FMQs.
- 11710 unique FMQ/PT pair.
- 11715 unique FMQ/PT/Scope pair.
- SOC, FMQ and PT relationship: 1 FMQ is included in 1 SOC, 1 SOC includes multiple FMQs, 1 FMQ includes multiple PTs, a PT can be included in an FMQ with Narrow scope and another FMQ with Broad scope.

We have foreseen implementation challenges of FDA ST&F Integrated Guide proposed AE analyses by SOC and by FMQ and by PT tables, as PTs records may be multiplied if all FMQs need to be included.

PROGRAMMING END-TO-END PROCESS

By evaluating the FMQ end products based on FDA FMQs, ST&F Integrated Guide document, and the unmet needs of AESIs selection criteria, two potential FMQ use cases and programming implementation processes including:

- AESIs Selection Criteria: leadership team have determined to utilize FMQs as ISS and ongoing studies AESIs selection criteria to facilitate agency reviewing of the safety data.
- AE Grouping for TEAE Summary Tables by SOC/FMQ (Narrow or Broad) and by SOC/FMQ (Narrow or Broad)/PT tables: provided feedback to FDA for clarification and conducted gap analysis before implementing the tables, we have set up standard programming process to create mockup table for implementation once such tables are required.

Currently there are 104 FMQs, this is an ongoing process and efforts, will create the latest and versioned FMQ lookup data set per FDA publication schedule.

AESIs Selection Criteria Lookup and Process

To streamline the end-to-end programming process, a global FMQ lookup data set was created by converting all 108 FMQ MS Excel worksheet tabs to one single FMQ SAS® data set for all current 104 FMQs terms and their associated PTs and Scope (Narrow or Broad). The global lookup Excel file will be shared with projects team that clinical can use the Excel file to identify the AESIs criteria and programming team can use the global FMQ lookup data set for individual studies or ISS ADAE data merging. Standard macro and programming process was in place to generate AESIs related ADaM ADAE CQzzNAM variables (Figure 5) till CDISC ADaM team publish related variables or process.

VIEWTABLE: Fmq.Fmq (FMQ Dataset)				VIEWTABLE: Adam.Adae (Adverse Events Analysis Dataset)						
FMQ	PT	SCOPE		AETERM	AEDECOD	AEBOISYS	DICTVER	ASTDT	CQ01NAM	CQ02NAM
250	Anemia	Addisonian pernicious anaemia	Narrow	25	Anemia	Anaemia	Blood and lymphatic system disorders	MedDRA 24.0	2022-03-19	ANEMIA
251	Anemia	Anaemia	Narrow	173	Anemia related to kidney disease	Nephrogenic anaemia	Blood and lymphatic system disorders	MedDRA 24.0	2022-03-25	ANEMIA
252	Anemia	Anaemia Heinz body	Narrow	271	anemia	Anaemia	Blood and lymphatic system disorders	MedDRA 24.0	2022-07-05	ANEMIA
253	Anemia	Anaemia NOS	Narrow	334	Iron deficiency anemia	Iron deficiency anaemia	Blood and lymphatic system disorders	MedDRA 24.0	2022-07-27	ANEMIA
254	Anemia	Anaemia NOS aggravated	Narrow	377	Anemia	Anaemia	Blood and lymphatic system disorders	MedDRA 24.0	2022-02-03	ANEMIA
255	Anemia	Anaemia folate deficiency	Narrow	385	Anemia	Anaemia	Blood and lymphatic system disorders	MedDRA 24.0	2022-07-04	ANEMIA
256	Anemia	Anaemia haemolytic autoimmune	Narrow	487	Anemia	Anaemia	Blood and lymphatic system disorders	MedDRA 24.0	2022-02-21	ANEMIA
257	Anemia	Anaemia macrocytic	Narrow	587	anemia	Anaemia	Blood and lymphatic system disorders	MedDRA 24.0	2022-09-29	ANEMIA

Figure 5. AESI FMQ Lookup Data Set and ADAE Data Set

AE Grouping SOC/FMQ/PT Tables Lookup and Process

For the ST&F AE analyses by SOC/FMQ/PT tables, another global lookup data set was created to combine SOC to FMQ lookup with proposed ADaM ADAE FMQs grouping variable (e.g., FMQ_NAME or AEFMQ) for tables creation.

FMQ document consists of an FMQ References worksheet tab for all 104 FMQs and their associated System Organ Class (SOC) terms, a SOC term may include multiple FMQs. There is an inconsistent SOC terms mixed-cases issue that needs to be standardized/corrected per MedDRA AESOC naming convention.

There are 27 unique SOC of MedDRA version 24.0 compared to 20 unique SOC (FDA FMQ v2.1), SOC that are only available at MedDRA are:

- Congenital, familial and genetic disorders
- Injury, poisoning and procedural complications.
- Investigations
- Pregnancy, puerperium and perinatal conditions
- Social circumstances

- Surgical and medical procedures
- Product issues

Although this is not recommended based on the ST&F document review comment to FDA since PTs/FMQs nested within SOC tables do not seem necessary for the AE analysis purpose. However, if sponsors choose to generate this set of tables, then can use this master SOC/FMQ/PT/Scope lookup data set to merge with actual individual studies or ISS ADAE data for TEAEs by SOC/FMQ (Narrow/Broad)/PT summary tables per ST&F document specified.

Figure 6 shows the FMQs associated SOC worksheet tab and FMQ SOC mixed cases MedDRA SOC_NAME justified master SOC/SMQ/PT/Scope lookup data set.

1	FMQ NAME	FIRST	LAST	SYSTEM ORGAN CLASS
2	Abdominal Pain	v1.0	v2.1	Gastrointestinal disorders
3	Abnormal Uterine Bleeding	v1.0	v2.1	Reproductive system and breast disorders
4	Acute Coronary Syndrome	v1.0		
5	Acute Kidney Injury	v1.0		

VIEWTABLE: WorkFmqsc

	FMQ_NAME	FIRST_PUBLISHED	LAST_UPDATED	SYSTEM_ORGAN_CLASS	soc
1	Abdominal Pain	v1.0	v2.1	Gastrointestinal disorders	GASTROINTESTINAL DISORDERS
2	Abnormal Uterine Bleeding	v1.0	v2.1	Reproductive system and breast disorders	REPRODUCTIVE SYSTEM AND BREAST DISORDERS
3	Acute Coronary Syndrome	v1.0	v2.0	Cardiac disorders	CARDIAC DISORDERS
4	Acute Kidney Injury	v1.0	v2.0	Renal and urinary disorders	RENAL AND URINARY DISORDERS
5	Asiopia	v1.0	v2.1	Skin and subcutaneous tissue disorders	SKIN AND SUBCUTANEOUS TISSUE DISORDERS

< > ... FMQ References

VIEWTABLE: AdhocFmqscpt FDA FMQ V2.1

MedDRA V24.0

	fmg_name	pt_name	SCOPE	SYSTEM_ORGAN_CLASS	soc	pt_code	soc_code	soc_name
1	Anemia	Anse syndrome	Broad	Blood and lymphatic system disorders	BLOOD AND LYMPHATIC SYSTEM DISORDERS	10063429	10005329	Blood and lymphatic system disorders
2	Thrombocytopenia	Acquired amegakaryocytic thrombocytopenia	Narrow	Blood and lymphatic system disorders	BLOOD AND LYMPHATIC SYSTEM DISORDERS	10076747	10005329	Blood and lymphatic system disorders
3	Anemia	Addisonian pernicious anaemia	Narrow	Blood and lymphatic system disorders	BLOOD AND LYMPHATIC SYSTEM DISORDERS			
4	Leukopenia	Agranulocytosis	Broad	Blood and lymphatic system disorders	BLOOD AND LYMPHATIC SYSTEM DISORDERS	10001507	10005329	Blood and lymphatic system disorders
5	Thrombocytopenia	Amegakaryocytic thrombocytopenia	Narrow	Blood and lymphatic system disorders	BLOOD AND LYMPHATIC SYSTEM DISORDERS	10076744	10005329	Blood and lymphatic system disorders
6	Anemia	Anaemia	Narrow	Blood and lymphatic system disorders	BLOOD AND LYMPHATIC SYSTEM DISORDERS	10002034	10005329	Blood and lymphatic system disorders
7	Anemia	Anaemia Heinz body	Narrow	Blood and lymphatic system disorders	BLOOD AND LYMPHATIC SYSTEM DISORDERS	10002058	10005329	Blood and lymphatic system disorders
8	Anemia	Anaemia NOS	Narrow	Blood and lymphatic system disorders	BLOOD AND LYMPHATIC SYSTEM DISORDERS			

Figure 6. Master SOC/FMQ/PT/Scope Lookup Data Set and MedDRA Justified SOC_NAME

AE Data Multiplying Issue and Solution

AE data multiplying is the foreseen issue and challenge for FDA ST&F proposed TEAEs by SOC/FMQ (Narrow/Broad)/PT table implementation, for an integrated safety analysis with hundreds of thousands of AE records, if a PT falls into multiple FMQs (maximum 8), then we need to create additional (maximum number -1) records to the ADAE data set, it may increase the data size and run time significantly.

What is the best data and programming process for these additional PTs by FMQs multiplied records? should we add them to the existing ADAE data set using the same ADAE program? or should we use a post ADAE process to create another ADAE program and data set (e.g., ADAEFMQ) to host these multiplied records if the TEAEs by SOC by FMQ (Narrow/Broad) by PT summary tables are required.

Figure 7 shows the potential data and programming process options, the author will suggest Option #2 to simplify the data and programming process and improve the data traceability.

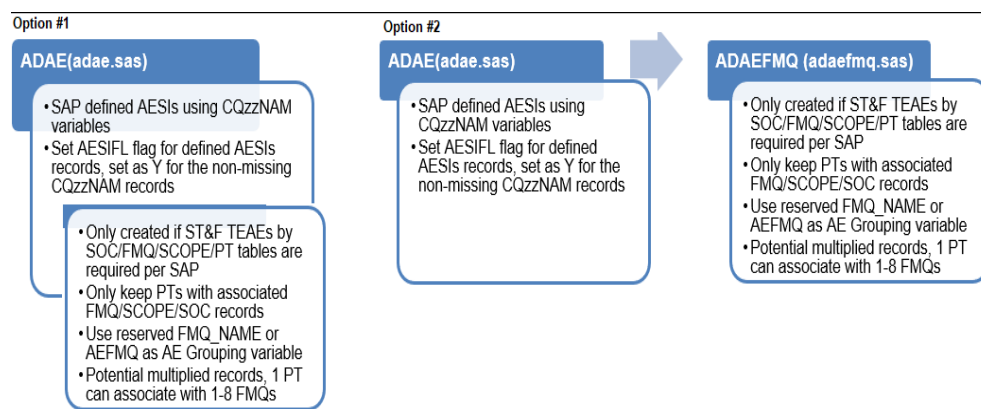


Figure 7. Data and Programming Options for TEAEs by SOC/FMQ(Narrow/Broad)/PT Table

FMQ IMPLEMENTATION CASE STUDY

AESI SELECTION CRITERIA USING SMQ, FMQ OR CMQ?

Which selection criteria to choose from for the AESIs analyses? SMQ? FMQ? or CMQ? To answer this question, the author has conducted an AESIs data comparison between SMQ and FMQ groupings using ISS pooled AE data.

Table 1 shows the number of the PTs and differences between FMQs v2.1 and SMQs v24.0 Narrow and Broad scope search criteria. The major differences are FMQs have removed those PTs that are too vague or broad in scope, and redefined those SMQ narrow term to broad that will be excluded from the FMQ (Narrow) summary reports.

AESI	AE Grouping	Search Criteria	Scope	# of PTs	Difference
Cardiac Failure	FMQ	Heart Failure	Narrow	40	<ul style="list-style-type: none"> • 8 more PTs than SMQ • 6 FMQs Narrow scope are defined as SMQs Broad Scope
			Broad	107	<ul style="list-style-type: none"> • 62 more PTs than SMQ • 3 FMQs Broad scope are defined as SMQs Narrow Scope
	SMQ	Cardiac failure (SMQ)	Narrow	31	<ul style="list-style-type: none"> • 2 more PTs than FMQ • 3 SMQs Narrow scope are defined as FMQs Broad Scope
			Broad	68	<ul style="list-style-type: none"> • 20 more PTs than FMQ • 6 SMQs Broad scope are defined as FMQs Narrow Scope
Hypersensitivity	FMQ	Hypersensitivity	Narrow	108	<ul style="list-style-type: none"> • 7 more PTs than SMQ • 6 FMQs Narrow scope are defined as SMQs Broad Scope
			Broad	197	<ul style="list-style-type: none"> • 22 more PTs than SMQ • 132 FMQs Broad scope are defined as SMQs Narrow Scope
	SMQ	Hypersensitivity (SMQ)	Narrow	292	<ul style="list-style-type: none"> • 65 more PTs than FMQ • 132 SMQs Narrow scope are defined as FMQs Broad Scope
			Broad	157	<ul style="list-style-type: none"> • 108 more PTs than FMQ • 6 SMQs Broad scope are defined as FMQs Narrow Scope

Table 1. AESI Selection Criteria Comparison SMQ vs. FMQ

Figure 8 shows an example of AESI Cardiac Failure percent of patients analysis using 5% cut-off based on SMQ or FMQ selection criteria, they are almost identical for this AESI based on the actual pooled ISS AE data. However, for other ISS defined AESIs, only FMQs provide direct match search criteria.

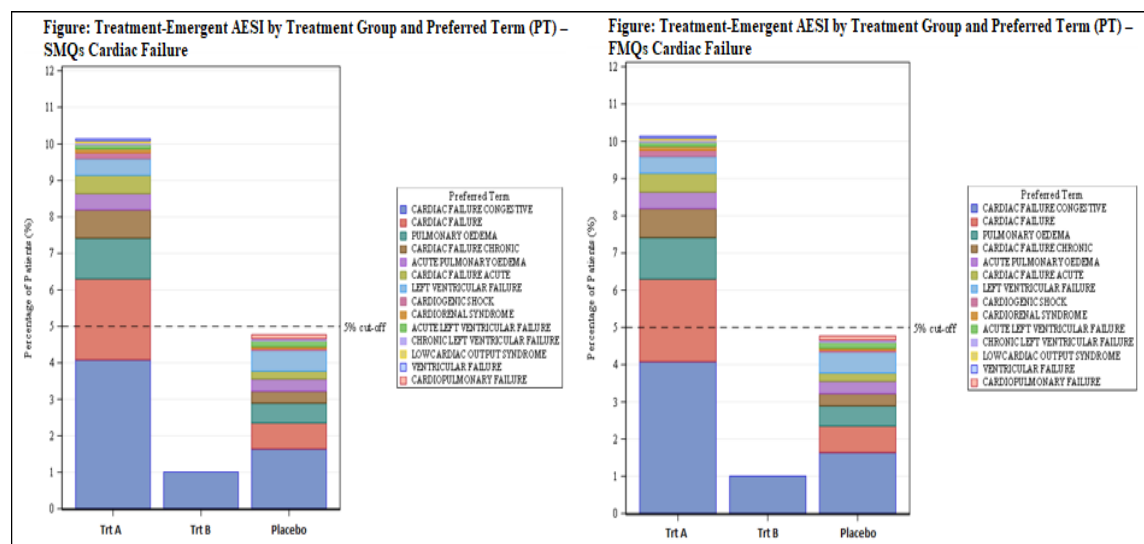


Figure 8. AESI Cardiac Failure % of Patients Using SMQ and FMQ Selection Criteria

NDA ISS ANALYSIS CASE STUDY FOR FMQ IMPLEMENTATION

There are two types of FMQ related summary tables, one is to utilize FMQ AE Grouping as selection criteria to determine the individual studies and ISS SAP defined AESIs, the number and percentage of TE AESIs will be summarized by AESI FMQs category and by PT within each FMQ category (Table 2).

Category Preferred Term	Active Treatment						Total (N=nnnn)	Overall Total (N=nnnn)
	Placebo (N=nnnn)	Trt A (N=nnnn)	Trt B (N=nnnn)	Trt C (N=nnnn)	Trt D (N=nnnn)	Trt E (N=nnnn)		
Subjects with Any TEAE of Special Interest, n (%)	731 (38.1)	5 (22.7)	5 (31.3)	864 (44.8)	53 (53.5)	12 (54.5)	939 (45.0)	1670 (41.7)
Anemia	197 (10.3)	1 (4.5)	0	343 (17.8)	10 (10.1)	1 (4.5)	355 (17.0)	552 (13.8)
Cardiac Failure	69 (3.6)	0	0	108 (5.6)	1 (1.0)	0	109 (5.2)	178 (4.4)
Anemia	197 (10.3)	1 (4.5)	0	343 (17.8)	10 (10.1)	1 (4.5)	355 (17.0)	552 (13.8)
Anaemia	140 (7.3)	1 (4.5)	0	249 (12.9)	7 (7.1)	0	257 (12.3)	397 (9.9)
Nephrogenic Anaemia	29 (1.5)	0	0	46 (2.4)	1 (1.0)	0	47 (2.3)	76 (1.9)
Iron Deficiency Anaemia	21 (1.1)	0	0	35 (1.8)	0	0	35 (1.7)	56 (1.4)
Haemoglobin Decreased	7 (0.4)	0	0	19 (1.0)	1 (1.0)	1 (4.5)	21 (1.0)	28 (0.7)

Table 2. TE AESIs FMQ/PT Table

The other type of AE analysis as per FDA Standard Safety Tables and Figures (ST&F) Integrated Guide document is TEAEs by FMQ arranged by SOC summary table, and the potential TEAEs by SOC and by FMQ (Narrow or Broad) and by PT summary table.

Table 3 shows an example of ISS TEAEs by SOC and FMQs summary table.

Figure 14.3.3.1: Treatment-Emergent Adverse Events by System Organ Class (SOC) and FMQs Safety Population – Pooled Analyses						
System Organ Class FMQ	Active Treatment					Total (N=nnnn)
	Trt A (N=nnnn)	Trt B (N=nnnn)	Trt C (N=nnnn)	Trt D (N=nnnn)	Trt E (N=nnnn)	
Subjects With Any TEAE, n (%)	15 (68.2)	12 (75.0)	3209 (61.6)	70 (70.7)	19 (86.4)	3325 (62.0)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	1 (4.5)	0	552 (10.6)	8 (8.1)	0	561 (10.5)
Anemia	1 (4.5)	0	537 (10.3)	8 (8.1)	0	546 (10.2)
Thrombocytopenia	0	0	30 (0.6)	1 (1.0)	0	31 (0.6)
Leukopenia	0	0	5 (<0.1)	0	0	5 (<0.1)
CARDIAC DISORDERS	0	0	451 (8.7)	2 (2.0)	1 (4.5)	454 (8.5)
Myocardial Ischemia	0	0	182 (3.5)	1 (1.0)	0	183 (3.4)
Heart Failure	0	0	157 (3.0)	1 (1.0)	0	158 (2.9)
Arrhythmia	0	0	119 (2.3)	0	0	119 (2.2)
Cardiac Conduction Disturbance	0	0	40 (0.8)	0	1 (4.5)	41 (0.8)

Table 3. TEAEs by SOC and FMQs Table

CONCLUSION

As there is no universal regulatory or industry defined AESIs selection criteria. Which AE grouping to choose from? Using MedDRA defined grouping (i.e., SOC, HLT, HLT) and SMQ, FDA newly developed FMQ, or sponsor defined CMQ? The ultimate questions of AESIs criteria remain unanswered. It is up to sponsors to find their most appropriate criteria for their company, TA, compound, and study AEs safety analysis needs.

The recommendation is to utilize an existing list from a published source - this can be FMQ, MedDRA SMQ, SOC, HLGT or HLT. One thing for sure is that we will hear the term FMQ more often in the future and may see FDA request to provide FMQs related grouping term and summary tables once they finalize the FMQs and ST&F documents.

Therefore, if an AESI can be clearly identified using the narrow or broad FMQ, then it is best to use the narrow or broad FMQ directly. If not, then can proceed with SMQ or other MedDRA groupings selection criteria per clinical and safety statistics AESI definition.

If there are no clear definitions using FMQ, SMQ or SOC/HLGT/HLT groupings, then sponsor can define customized MedDRA queries (CMQs) per analysis needs either by modifying an existing list or developing custom grouping of PTs/LLTs. If CMQs are in use, sponsor needs to well document the rationales to avoid the sponsor bias for the safety analysis.

REFERENCES

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