FDA Medical Query Update

Scott Proestel, M.D.

Senior Medical Officer
Biomedical Informatics and Regulatory Review Science
ODES, OND, CDER, FDA

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The views expressed during this presentation are my own and do not represent the official policies or positions of the FDA. In addition, I have no relevant conflicts of interest to disclose.

Agenda

- **Introduction to FMQs**
  - What Are FMQs?
  - Ground Rules
  - FMQ Structure
- **FMQ Updates**
  - FAQs
  - Labeling Considerations
  - Resources

What Are FMQs?

- Groupings of AE terms developed by FDA staff.
- Used on clinical trial data to improve safety signal detection.
- Each FMQ consists of Narrow and Broad terms.
- Some FMQs also contain an Algorithmic component.

Why Are AE Groupings Needed?

Inconsistent Interpretation or Clinical Presentation

- Investigators may report different verbatim terms for similar AEs, resulting in different coded MedDRA PTs for the same medical concept.
  - Abdominal pain may be reported as abdominal pain, abdominal pain lower, gastrointestinal pain, visceral pain, or abdominal discomfort.
- AEs may manifest in different ways.
  - A rash caused by drug hypersensitivity may present with an erythematous rash, a macular rash, macular-papular rash, papular rash, or morbilliform rash.

- When **related** PTs are not grouped, it's **possible to miss** important safety signals.

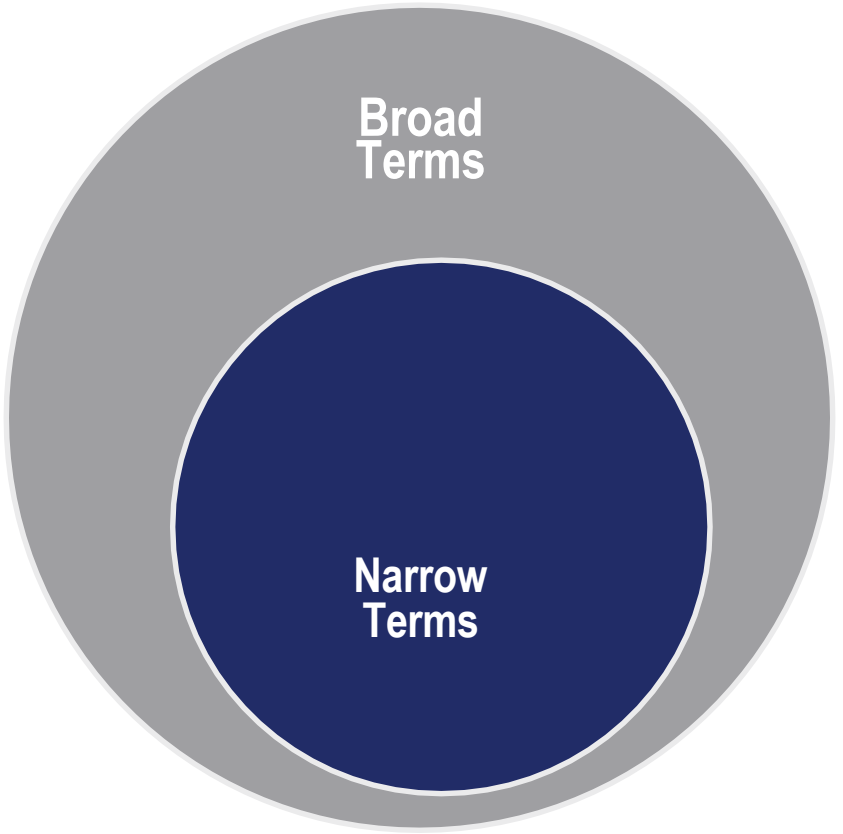
FMQ: Narrow vs. Broad Queries

Narrow FMQ terms

- Specific for the medical concept.
- > ~90% probability that the medical concept occurred.

Broad FMQ terms

- “Cast a wider net” than narrow query terms for signal detection.
- Less specific.
- Provide reasonable assurance (more than ~30% probability) that the medical concept occurred.



FMQ Ground Rules: Narrow Queries

PTs that are near-synonyms of the FMQ concept	• "*Abdominal discomfort*" in FMQ Abdominal Pain
PTs that are subgroups of the FMQ concept	• *"Anaemia neonatal"* in FMQ Anemia
PTs that specify an etiology for the FMQ concept	• *"Uremic Pruritus"* in FMQ Pruritus
PTs that ensure the occurrence of the FMQ concept	• *"Aortic Rupture"* in FMQ Hemorrhage

FMQ Ground Rules: Broad Queries

PTs that may result in the FMQ concept	• *"Osteopenia"* in FMQ Osteoporosis
PTs that provide laboratory, radiologic, or other diagnostic test results reasonably suggestive of an FMQ, including PTs with ambiguous results such as "abnormal"	• *"Blood glucose abnormal"* in FMQ Hyperglycemia
PTs reasonably suggestive of the FMQ concept, but not required by the FMQ concept	• *"Bronchospasm"* in FMQ Hypersensitivity
PTs that indicate a "carrier" status for FMQ concepts that specify an infectious disease	• *"Bacterial disease carrier"* in FMQ Bacterial Infection

Algorithmic FMQs

- **Narrow** – contains PTs highly specific to the FMQ concept; indicates that the FMQ occurred.

- **Broad** – casts a wider net to capture additional cases of the FMQ concept.

- **Algorithmic** – uses multiple datasets to leverage more of the available information:

    - Adverse event datasets
    - Laboratory datasets
    - Concomitant meds datasets
    - Medical history datasets
    - Temporal relationships

Algorithmic FMQ Example: Drug-Induced Muscle Injury

Patients qualify for the algorithm if they meet any of the following criteria:

1. Any Rhabdomyolysis FMQ Narrow term
2. Urine myoglobin >ULN
3. CPK >5 x ULN **AND NO:**
   - CPK >ULN at baseline OR
   - CPK-MB/CPK >0.05 with start date within 3 days
4. [PT Myalgia + PT Muscular Weakness + (PT Myoglobin Urine Present OR PT Chromaturia)] with start date within 7 days of each other

ULN= Upper limit of normal, CPK = creatine phosphokinase

FMQ FAQs (#1-3)

1. **Are sponsors who submit product marketing applications required to use FMQs in their submissions or other documents such as annual reports? Can a sponsor modify the groupings based on a drug's safety profile?**

   Answer: The use of FMQs by sponsors in whole or in part is entirely voluntary. FDA uses FMQs as part of its safety assessment of clinical trial data, and the public dissemination of FMQs is simply intended to make FDA internal processes more transparent. Any modifications to FMQs should be clearly identified.

2. **Will there be additional documentation for the definitions of FMQs including criteria for inclusion or exclusion of terms in the Narrow or Broad scopes of the query?**

   Answer: One of the goals of the FMQ project was to use a consistent set of Ground Rules for the creation of FMQs so that additional documentation on inclusion and exclusion criteria would not be needed. When this was not possible for particular FMQs, a comment was created to provide explanation.

3. **How will FMQs be maintained?**

   Answer: A major new version of FMQs will be created following each major annual update of MedDRA in March. We may also publish minor FMQ version updates during the year if needed. The major updates will be designated by a sequential increase in the version whole number (i.e., an increase from version 2.0 to 3.0) while minor updates will be designated by an increase in the version number of one-tenth (i.e., version 2.1 to 2.2).

FMQ FAQs (#4-6)

4. **The FMQs do not indicate any MedDRA version(s) they are set-up for. How can a user verify if an FMQ can be used for a given MedDRA version?**

   Answer: When each new FMQ version is released, the range of MedDRA versions that it is intended to be applied to will be provided. For instance, FMQ version 3.0 is intended to be used with all versions of MedDRA through 26.0.

5. **Where will FMQ updates be publicly published?**

   Answer: FMQ versions and other FMQ-related resources will be publicly available at: https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/biomedical-informatics-and-regulatory-review-science-birrs

6. **There are terms within the FMQs that are former PTs or have never been PTs. Is that intentional?**

   Answer: Yes, we have included terms that have been submitted to FDA in clinical trial data sets that have used other terminologies as well as misspellings in an attempt to make the groupings as comprehensive as possible.

FMQ FAQs (#7-10)

7. **Are there plans to harmonize adverse event groupings across international regulatory authorities?**

   Answer: FDA understands the importance of harmonizing clinical trial analytic strategies whenever possible and will be pursuing harmonization with other regulatory bodies as we gain greater experience with the use of FMQs.

8. **Does FDA plan to create more FMQs?**

   Answer: Yes, current plans are to create up to 30 additional FMQs in addition to the current 104.

9. **Will the FDA allow users to submit change requests to modify existing FMQs. If so, will the FDA provide guidance on how to do this?**

   Answer: Yes, sponsors and other members of the public can submit change requests at the same webpage where the FMQs and FMQ-related resources are located. The email address is: ONDBiomedicalinformatics@fda.hhs.gov.

10. **How will sponsors and other members of the public be notified when a new version of the FMQs becomes available?**

    Answer: You will be notified if you subscribe to the FDA CDER SBIA website to receive update notifications: https://www.fda.gov/drugs/development-approval-process-drugs/cder-small-business-industry-assistance-sbia.

FMQ Labeling Considerations

- Combine synonymous or near-synonymous AE terms.
- Avoid terms such as FMQ, FDA Medical Query, MedDRA, and Preferred Term - healthcare providers are generally unfamiliar with them.
- When AE groupings such as FMQs are used in labeling, indicate with a footnote in the common AR table, including cases where no individual terms in the group are listed.
- Use regulatory criteria (as per 21 CFR 201.57(c)(7)) to determine if an AE qualifies as an AR. FMQs do not alter this standard.
- Use Narrow FMQs in labeling as appropriate. Broad FMQs should not be used in labeling as they don't provide sufficient assurance that the FMQ concept occurred.

Three FMQ Labeling Scenarios

Scenario #1 – Safety concern observed in Narrow FMQ when individual AEs within FMQ are combined, but no individual AE terms meet regulatory requirement for labeling.

Scenario #2 – Safety concern observed in Narrow FMQ that is driven by one or more individual AEs that meet regulatory requirement for labeling.

Scenario #3 – Combination of above two scenarios.

While this discussion will be limited to differences in incidence rates for simplicity, please remember that assessing causality requires consideration of multiple factors, such as biologic plausibility, timing information, and differences in the severity of events.

Scenario #1 – Safety Issue Identified Only with All Terms Combined

ANALYSIS	Drug	Control
FMQ Anxiety	**12%**	**8%**
Stress	3%	2%
Fear	3%	2%
Nervousness	3%	2%
Panic attack	3%	2%

PRODUCT LABELING	Drug	Control
Anxiety*	12%	8%
Bradycardia	9%	5%
Cachexia	9%	5%
Headache	9%	5%
Nausea	9%	5%

*Anxiety is composed of multiple similar terms.

Scenario #2 – Safety Issue Driven by One or More Individual Terms

ANALYSIS	Drug	Control
FMQ Anxiety	**16%**	**8%**
Stress	2%	2%
Fear	2%	2%
Nervousness	2%	2%
Panic attack	10%	2%

PRODUCT LABELING	Drug	Control
Panic attack	10%	2%
Bradycardia	9%	5%
Cachexia	9%	5%
Headache	9%	5%
Nausea	9%	5%

Scenario #3 – Combination of Scenarios #1 and #2

ANALYSIS	Drug	Control
FMQ Anxiety	**19%**	**8%**
Stress	3%	2%
Fear	3%	2%
Nervousness	3%	2%
Panic attack	10%	2%

PRODUCT LABELING	Drug	Control
Anxiety*	19%	8%
Bradycardia	9%	5%
Cachexia	9%	5%
Headache	9%	5%
Nausea	9%	5%

*Anxiety consists of multiple similar terms including *panic attack*.

PRODUCT LABELING	Drug	Control
Anxiety*	19%	8%
Panic attack	10%	2%
Bradycardia	9%	5%
Cachexia	9%	5%
Headache	9%	5%
Nausea	9%	5%

*Anxiety consists of multiple similar terms including *panic attack*.

Resources

- **FMQ Documents** (https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/biomedical-informatics-and-regulatory-review-science-birrs)

    - FMQ Version 3.0
    - FMQ FAQs
    - FMQ Ground Rules
    - FMQ List of Changes in Version 3.0

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