POLICY AND PROCEDURES

OFFICE OF NEW DRUGS

Good Review Practices: OND Custom Medical Queries

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PURPOSE

- This Manual of Policies and Procedures (MAPP) and its attachments describe good review practices (GRPs) for the Office of New Drugs (OND) within the Center for Drug Evaluation and Research (CDER) when developing and updating OND Custom Medical Queries (OCMQs)[1] and use of OCMQs during review of new drug applications (NDAs), biologics license applications (BLAs), and supplemental NDAs and BLAs.

- The purpose of the OCMQs is to provide a standard grouping of adverse event (AE) terms designed to help identify potential safety issues during review of clinical trial AE data. OCMQs are not intended to replace review of individual reported AE terms or other available and appropriate groupings of AE terms during clinical trial data safety analysis.

- The focus of this MAPP is on the presentation of clinical data during scientific reviews of clinical data submitted to FDA. This MAPP does not address the interpretation of safety data.

[1] Renamed from FDA Medical Queries (FMQs) in January 2025.

BACKGROUND

- OCMQs are standardized groupings of AE terms intended to assist with the identification of potential safety issues during the review of AE safety data.

- OCMQs are similar to customized queries associated with the Medical Dictionary for Regulatory Activities (MedDRA). OCMQs are used by OND staff for premarket safety evaluation.

- The use of OCMQs promotes a standardized approach to safety signal detection across OND Clinical review divisions.

- The use of OCMQs is not meant to replace custom groupings for signal detection that may be informed by specific study populations or pharmacology of a drug product.[2]

- Some OCMQs contain an algorithmic component that uses additional information to identify safety signals, such as combinations of AE terms instead of a single term, laboratory data, concomitant medications, medical history, or timing information. Each algorithm includes a series of criteria, and patients who meet the specified criteria are considered to have met the requirement of the algorithm. For additional information about an algorithmic OCMQ, refer to the Targeted Analysis Guides available on the internal *Standard Safety Tables and Figures* site.

POLICY

- The entire set of OCMQs is applied to all new molecular entity (NME) NDAs, original 351(a) BLAs, and relevant supplements to those applications received by OND. OND staff also may use OCMQs to analyze data in other applications.
- Other grouping strategies such as custom queries, Standardised MedDRA Queries (SMQs), or the MedDRA hierarchy may be used as appropriate.
- The use of OCMQs by applicants for the purpose of safety evaluation is voluntary.
- OCMQs are available through some review software. OND Clinical reviewers can generate OCMQ tables and figures, adjust specific OCMQs, and export outputs for inclusion in their review document for applications, whether they are using the integrated review template or not.
- OND review staff can access current and previous versions of OCMQs on the internal *OND Custom Medical Queries* site.

[2] For the purposes of this MAPP, all references to drugs or drug products include both human drugs and biological drug products regulated by CDER, unless otherwise specified.

RESPONSIBILITIES

- OND/Office of Drug Evaluation Science (ODES)/Biomedical Informatics and Regulatory Review Science (BIRRS) team is responsible for:
  - Providing program oversight for OCMQ development, publication, and policies.
  - Supporting the OCMQ Steering Committee, including member recruitment.
- OCMQ Steering Committee Group is responsible for:
  - Creating a new major version of OCMQs following each major annual update of MedDRA, including a change log; minor OCMQ version updates may also be created during the year if needed.
  - Validating newly created OCMQs on their performance.
  - Establishing and maintaining OCMQ Ground Rules for Creating OND Custom Medical Queries (see Attachment 1).
  - Instituting new policies and procedures related to OCMQs as needed.
- OND Immediate Office (IO)/Clinical Data Science Staff (CDS) are responsible for:
  - Using OCMQs when generating Standard Safety Tables and Figures (ST&F).
  - Providing feedback on the performance of OCMQs.
- OND Clinical Reviewers are responsible for:
  - Reviewing OCMQ results created by the CDS team during safety evaluations for marketing applications.
  - Providing feedback on the performance of OCMQs.

PROCEDURES

OCMQ Generation and Maintenance

- A new OCMQ major version is created following each major annual update of MedDRA, including a change log. Minor OCMQ version updates may be

published as needed, throughout the year. Major OCMQ version updates are designated by a sequential increase in the version whole number (i.e., from version 2.0 to 3.0), while minor updates are designated by an increase in the first decimal place (i.e., from version 2.1 to 2.2).

- New MedDRA Preferred Terms (PTs) are assessed by two OND Clinical reviewers following the Ground Rules for Creating OND Custom Medical Queries (see Attachment 1) for incorporation into the new version of OCMQs.

- Discrepancies between OND Clinical reviewers regarding PT adjudication are resolved through a review by the OCMQ Steering Committee.

- New OCMQs are generated by the OCMQ Steering Committee as needed.

- OCMQs may be removed by the OCMQ Steering Committee as needed.

OCMQ Tables and Figures Creation

- The CDS team creates OCMQ tables and figures as defined by the ST&F Integrated Guide (IG) and provides them to clinical reviewers.[3]

- OND Clinical reviewers may also generate OCMQ tables and figures using review software that contain OCMQs.

- The OND Clinical reviewer may request that the CDS customize the OCMQ tables and figures at any time.

OCMQ Tables and Figures Interpretation

- The OND Clinical reviewers evaluate the OCMQs presented in the ST&F package and incorporate them into their clinical review. When a safety issue is identified using an OCMQ, the reviewer should assess the individual terms within the OCMQ, other relevant grouping(s), and potential causality to fully evaluate the safety issue.

- Adverse reactions (ARs) identified by OCMQs can be included in labeling, as appropriate. The regulatory standard for including ARs in drug labels remains the same. Careful consideration should be given as to whether it is appropriate to list some or all of the individual AEs of the OCMQ or the name of the OCMQ in the AR table. The *OCMQ Labeling Quick Tips* document provides examples.

[3] Refer to the *Standard Safety Tables and Figures* (site to be launched in coordination with the publication of MAPPs 6025.8 and 6025.9).

REFERENCE

1. 21 CFR 312.32, *IND Safety Reporting.*
2. Draft Guidance for Industry: *Sponsor Responsibilities – Safety Reporting Requirements and Safety Assessment for IND and Bioavailability/Bioequivalence Studies* (June 2021).[4]
3. Guidance for Industry: *E2A Clinical Safety Data Management: Definitions and Standards for Expedited Reporting* (March 1995).
4. *Biomedical Informatics and Regulatory Review Science (BIRRS)* site (https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/biomedical-informatics-and-regulatory-review-science-birrs).
5. *OND Custom Medical Queries* site (site to be launched in coordination with the publication of MAPP 6025.8).
6. OCMQ Labeling Quick Tips, available on the internal *OND Custom Medical Queries* site.

DEFINITIONS

- ***Adverse Event (AE)*** – any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.[5]
- ***Adverse Reaction (AR)*** – an undesirable effect, reasonably associated with use of a drug, that may occur as part of the pharmacological action of the drug or may be lfunpredictable in its occurrence.[6] Adverse reaction implies a greater degree of certainty about causality than suspected adverse reaction, which means any adverse event for which there is a reasonable possibility that the drug caused the adverse event.
- ***Algorithmic OCMQ*** – OCMQ containing an algorithmic component that uses additional information to identify safety signals such as combinations of adverse event terms instead of a single term, laboratory data, concomitant medications, medical history, or timing information.

EFFECTIVE DATE

- This MAPP is effective upon date of publication.

[4] For the most recent version of a guidance, check the *Search for FDA Guidance Documents* webpage at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.
[5] Refer to 21 CFR 312.32, *IND Safety Reporting*.
[6] This adverse reaction definition is for the purposes of prescription drug labeling and *"…does not include all adverse events observed during use of a drug, only those adverse events for which there is some basis to believe there is a causal relationship between the drug and the occurrence of the adverse event."* (21 CFR 201.57(c)(7)).

CHANGE CONTROL TABLE

Effective Date	Revision Number	Revisions
06/13/2025	Initial	N/A

ATTACHMENT 1: Ground Rules for Creating OND Custom Medical Queries (V.3.2)

Narrow Category: Indicates that the OND Custom Medical Query (OCMQ) occurred.

- Adverse events (AEs) that are near synonyms of the OCMQ (e.g., Preferred Term PT Abdominal Discomfort in OCMQ Abdominal Pain, and PT Blood Glucose Increased in OCMQ Hyperglycemia)

- AEs that are subgroups of the OCMQ (e.g., PT Anaemia Neonatal in OCMQ Anemia).

- AEs that specify an etiology for the OCMQ (e.g., PT Uraemic Pruritus in OCMQ Pruritus).

- AEs that ensure the occurrence of the OCMQ (e.g., PT Aortic Rupture in OCMQ Hemorrhage).

Broad Category: Reasonably suggestive that the OCMQ may have occurred.

- AEs that may indicate the presence of the OCMQ (e.g., PT Osteopenia in OCMQ Osteoporosis).

- AEs that provide laboratory, radiologic, or other diagnostic test results reasonably suggestive of an OCMQ, including AEs with ambiguous results such as "abnormal" (e.g., PT Troponin I Increased in OCMQ Myocardial Infarction, and PT Blood Glucose Abnormal in OCMQ Hyperglycemia).

- AEs reasonably suggestive of the OCMQ, but not required by the OCMQ (e.g., PT Bronchospasm in OCMQ Hypersensitivity).

- AEs that indicate a "carrier" status for OCMQ that specify an infectious disease (e.g., PT Bacterial Disease Carrier in OCMQ Bacterial Infection).

AE Term Exclusion Rules:

- AEs that are neither a required component nor reasonably specific for the OCMQ are excluded (e.g., PT Nausea would not be included in OCMQ Migraine).

- AEs that provide the names of laboratory, radiologic, or other diagnostic tests without a result are excluded (e.g., PT Clostridium Test). AEs that provide test names without a result, but that would only be performed in the presence of disease, should be included if they otherwise qualify (e.g., PT Antipsychotic Drug Level in OCMQ Psychosis [Broad]).

- AEs that identify congenital, familial, or genetic disorders are excluded.[7]
- AEs that identify pregnancy, puerperium, and perinatal conditions are excluded.[8]

[7] While it is possible for such disorders to first become clinically apparent because of a drug effect during a clinical trial, such diagnoses in clinical trials are extremely rare and their manifestation as an adverse reaction to a drug rarer still. In addition, many of these diagnoses have heterogeneous manifestations and variable presentations that are difficult to categorize into OCMQs and are poorly characterized due to their infrequent occurrence. Any congenital, familial, or genetic disorders reported during a clinical trial can be identified using the MedDRA System Organ Class for these terms.

[8] Such conditions are quite rare in a typical clinical trial, and when they do occur should be carefully analyzed. For trials that specifically investigate pregnancy or breastfeeding, that allow these as part of their eligibility criteria, or that include neonatal or infant populations, the *Pregnancy, puerperium and perinatal conditions* MedDRA System Organ Class can be used to identify these terms for further analysis.